JMIR Research Protocols

Impact Factor (2023): 1.4
Volume 14 (2025) ISSN 1929-0748 Editor in Chief: Xiaomeng (Simone) Ma, PhDc, MS, BS

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Protocol

Impact of Remote Symptom Management on Exercise Adherence After Video-Assisted Thoracic Surgery for Lung Cancer in a Tertiary Hospital in China: Protocol for a Prospective Randomized Controlled Trial

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Abstract

Background: Regular pulmonary rehabilitation exercises are crucial for patients with lung cancer after surgery. However, poor adherence to outpatient exercises is difficult to address due to inadequate supervision. The integration of remote symptom management through electronic patient-reported outcomes (ePROs) offers a potential solution to improve adherence by enabling more effective monitoring and intervention.

Objective: This study aims to evaluate the impact of ePRO-based remote symptom management on enhancing adherence to outpatient pulmonary rehabilitation exercises following video-assisted thoracic surgery for lung cancer.

Methods: In this single-center, prospective, randomized controlled trial, 736 patients undergoing minimally invasive lung resection will be recruited. All patients will use a smartphone app for perioperative management, allowing periodic PRO measurement and recording of exercise participation. Upon discharge, patients will be randomly assigned 1:1 into either an intervention or control group. The intervention group will complete the Perioperative Symptom Assessment for Patients Undergoing Lung Surgery (PSA-Lung) scale on the day of discharge and postdischarge days 3, 7, 14, 21, and 28. Alerts will be triggered at the provider side if any of the 5 core symptoms (pain, cough, shortness of breath, sleep disturbance, and fatigue) scored ≥4, prompting remote symptom management. The control group will complete the PRO measures without triggering alerts. The primary outcome is the rehabilitation exercise adherence rate. Secondary outcomes include postdischarge pulmonary complication rate, 30-day readmission rate, trajectory of symptom severity changes, exercise participation rate, and patient satisfaction.

Results: The enrollment of study participants started in December 2023 and is expected to end in March 2025. The final comprehensive analysis of the results is planned for May 2025, after all data have been collected and thoroughly reviewed.

Conclusions: This study is among the first to investigate the feasibility and effectiveness of ePRO-based remote symptom management in enhancing rehabilitation adherence after video-assisted thoracic surgery for lung cancer. If successful, this approach could significantly influence postoperative care practices and potentially be adopted in similar settings.

Trial Registration: ClinicalTrials.gov NCT05990946; https://clinicaltrials.gov/study/NCT05990946

International Registered Report Identifier (IRRID): DERR1-10.2196/60420

(JMIR Res Protoc 2025;14:e60420) doi:10.2196/60420

KEYWORDS

thoracic surgery; rehabilitation medicine; patient-reported outcome measures; patient participation; telemedicine; eHealth; mobile phone

Introduction

Lung cancer remains a predominant cause of cancer-related morbidity and mortality worldwide. Specifically in China, the incidence rate reached 828,000 cases in 2016 [1]. Non–small cell lung cancer is the most prevalent subtype. With the increasing adoption of lung cancer screening, more patients are being diagnosed at early stages. Surgical resection is the gold standard for treating early-stage, non–small cell lung cancer, and the paradigm of enhanced recovery after surgery has been widely adopted in perioperative care [2].

While enhanced recovery after surgery effectively shortens inpatient stays, its benefits are often offset by inadequate outpatient management stemming from limited resources, which can adversely affect clinical outcomes and postdischarge quality of life [3]. One critical factor in postoperative recovery is adherence to pulmonary rehabilitation exercises. However, adherence rates are suboptimal due to insufficient supervision and guidance.

Following discharge, many patients face decreased exercise adherence rates, ranging from 50% to 70% according to studies focusing on patients with musculoskeletal disorders [4-6]. Several factors influence adherence, including self-efficacy, personal beliefs, sense of self-control, physical and psychological condition, clinical symptoms like pain, and perceived forgetfulness [7-11].

Moreover, many patients continue to experience symptoms such as coughing, pain, poor sleep, and breathlessness after discharge, which may substantially undermine their exercise adherence [12]. In the era of patient-centered care, remote symptom management through electronic patient-reported outcomes (ePROs) is emerging as a promising approach to improve outpatient quality of life and reduce postoperative complications [13-16]. By providing effective strategies for timely monitoring and managing patients' symptoms, ePRO-based interventions may help patients overcome barriers to exercise and enhance their self-efficacy and motivation, thus promoting exercise adherence [17].

There is a pressing need for research to investigate the impact of postoperative symptoms on exercise adherence and to evaluate whether ePRO-based remote symptom management can effectively improve adherence to outpatient rehabilitation exercises [18,19].

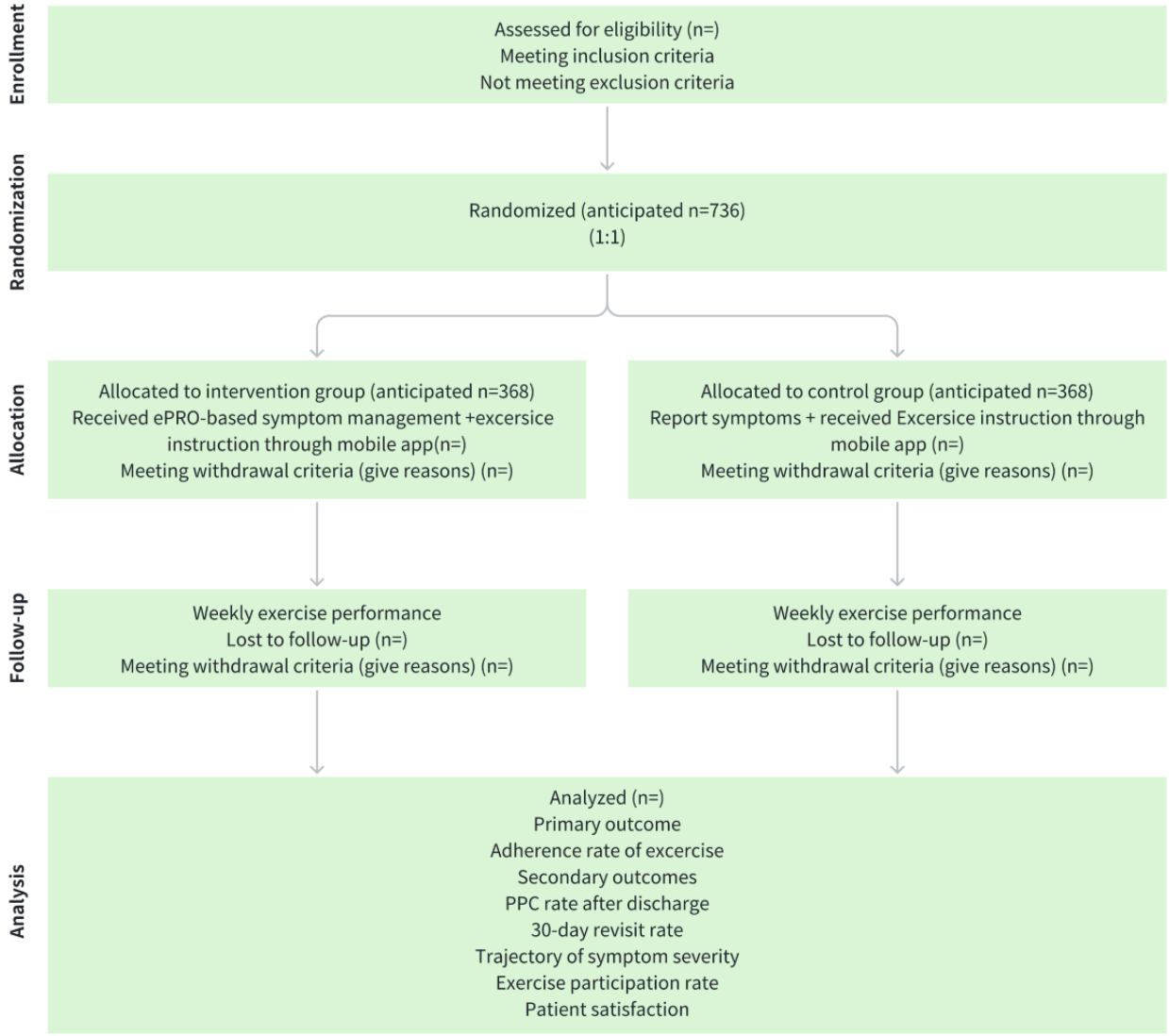
Therefore, this study aims to assess the feasibility and preliminary effects of remote symptom management based on ePROs on enhancing adherence to outpatient rehabilitation exercises after video-assisted thoracic surgery (VATS) for lung cancer. A prospective, randomized controlled trial study design is adopted to provide new strategies for rehabilitation management in patients with lung cancer. We hypothesize that remote symptom management based on ePROs can improve exercise adherence in patients with lung cancer after VATS compared with usual care.

Methods

Study Setting

This is a single-center, prospective, superiority, randomized controlled trial, consistent with the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) guidelines [20]. Participants will be recruited from the Department of Thoracic Surgery, Zhongshan City People's Hospital, Guangdong, China, which performs approximately 600 lung cancer surgeries annually. The findings will be reported based on the CONSORT (Consolidated Standards of Reporting Trials) guidelines [21]. The study flowchart is shown in Figure 1. This trial has been registered on ClinicalTrials.gov (NCT05990946), where detailed information about the study protocol, inclusion and exclusion criteria, interventions, outcomes, and ethical approval can be found. The trial registration process was completed before the enrollment of the first participant.

Figure 1. Flowchart of this parallel-group randomized controlled trial. ePRO: electronic patient-reported outcome; PPC: postdischarge pulmonary complication.



Eligibility Criteria

Inclusion criteria for the participants are (1) being aged 18-75 years; (2) undergoing VATS, including lobectomy or segmentectomy; (3) being able to use smart devices and completing electronic questionnaires; and (4) providing informed consent. The exclusion criteria are (1) conversions to open thoracotomy during surgery, (2) preoperative Eastern Cooperative Oncology Group score >1, (3) received neoadjuvant therapy, (4) previous thoracic surgery history, (5) unable to exercise due to physical impairments, (6) continuous systemic corticosteroid use within 1 month, (7) unresolved toxicity above grade 1, (8) significant medical history, (9) uncontrolled comorbidities, (10) postoperative length of stay >14 days, and (11) other unsuitable conditions in the investigator's judgment.

Participant Recruitment

Patient recruitment will commence before discharge, including preoperative patients awaiting scheduled surgery. Eligible patients will be randomly assigned before discharge after confirming they can properly operate the smartphone app. After discharge, patients will be reminded to use the app for symptom and exercise logging. The app provides an incentive for participating in the 4-week rehabilitation program between discharge and the first postoperative clinic visit.

Randomization and Allocation Concealment

Each potential participant will be assigned a unique 3-digit screening number in sequence. Eligible participants will be randomly allocated 1:1 to the intervention and control groups.

Randomization will be performed using a central Interactive Web Response System (IWRS), which is deployed on a third-party platform (Huawei Cloud) and was developed by the Shuyu app development team. The IWRS uses a block randomization algorithm to generate the allocation sequence and ensure balance between the treatment groups. After confirming eligibility, the study site will enter participant information into the IWRS and receive the allocation. Withdrawn participants will retain their randomization number without re-enrollment. The randomization code will be securely stored in the IWRS throughout the study.

Blinding

Due to the nature of interventions, blinding of participants and care providers is not feasible. However, data collectors and statisticians will be blinded to group allocation. The data collectors, who are research nurses, will be trained to administer questionnaires and collect data consistently according to the study protocol. They will collect data at baseline through in-person interviews and then weekly for 4 weeks after discharge through telephone interviews.

Interventions

Participants will use the app "Shuyu" (Module type: TH001, Developed by Shanghai CinoCore Health Technology Co) for perioperative management.

Preoperatively, nurses will instruct app use and provide education. The app will assign individualized exercises and prompt logging. Patients will complete baseline PRO measurements. The Perioperative Symptom Assessment for Lung Surgery (PSA-Lung) was used for PRO assessments. The PSA-Lung scale includes 7 symptom items (pain, coughing, shortness of breath, disturbed sleep, fatigue, drowsiness, and distress) and 2 functional items (interference of activity and walking). Each symptom's severity was rated between 0 (the absence of symptom) and 10 (the worst imaginable symptom). Similarly, functional items were also rated on a scale between 0 (no interference) and 10 (complete interference). The PSA-Lung scale development team has verified its reliability and validity in patients who undergo lung cancer surgery, and the research results suggested adequate reliability and validity. The relevant articles have been submitted for publishing, and the preliminary results were announced at the 28th Annual Conference of the International Society for Quality-of-Life Research [22]. Permission to use the PSA-Lung scale in this study has been obtained from the scale development team.

Postoperatively during hospitalization, nurses will guide app-based rehabilitation, doctors will supervise exercises and PROs, and patients will complete daily PROs without alerts.

Before discharge, the care team will evaluate if patients can properly operate the app. Eligible patients will be randomly allocated into groups by the nurse entering the patient's screening number and discharge date in the provider app. Based on the pregenerated randomization code from the central system, this process will automatically allocate patients into the intervention or control group, unlocking the corresponding outpatient module.

After discharge, the app continues to offer postoperative education and exercise logging, sending daily reminders at 9 AM and follow-ups at 5 PM if logs are incomplete. Weekly phone checks by staff will confirm exercise log accuracy. Noncompliance or inaccessibility after 3 phone attempts will result in protocol violation and withdrawal.

Reminders for PRO assessments are set for 9 AM on the day of discharge and on postdischarge days 3, 7, 14, 21, and 28. A follow-up reminder will be sent at 5 PM if the assessment remains uncompleted. These assessments must be completed on the specified days, and the analysis will include patients who have logged exercises but have not submitted PRO assessments. For participants who are unable to continue using the ePRO system, a manual follow-up plan will be implemented to collect PRO data through telephone or email on the day following the scheduled assessment days to avoid conflict with system reminders.

Comparison

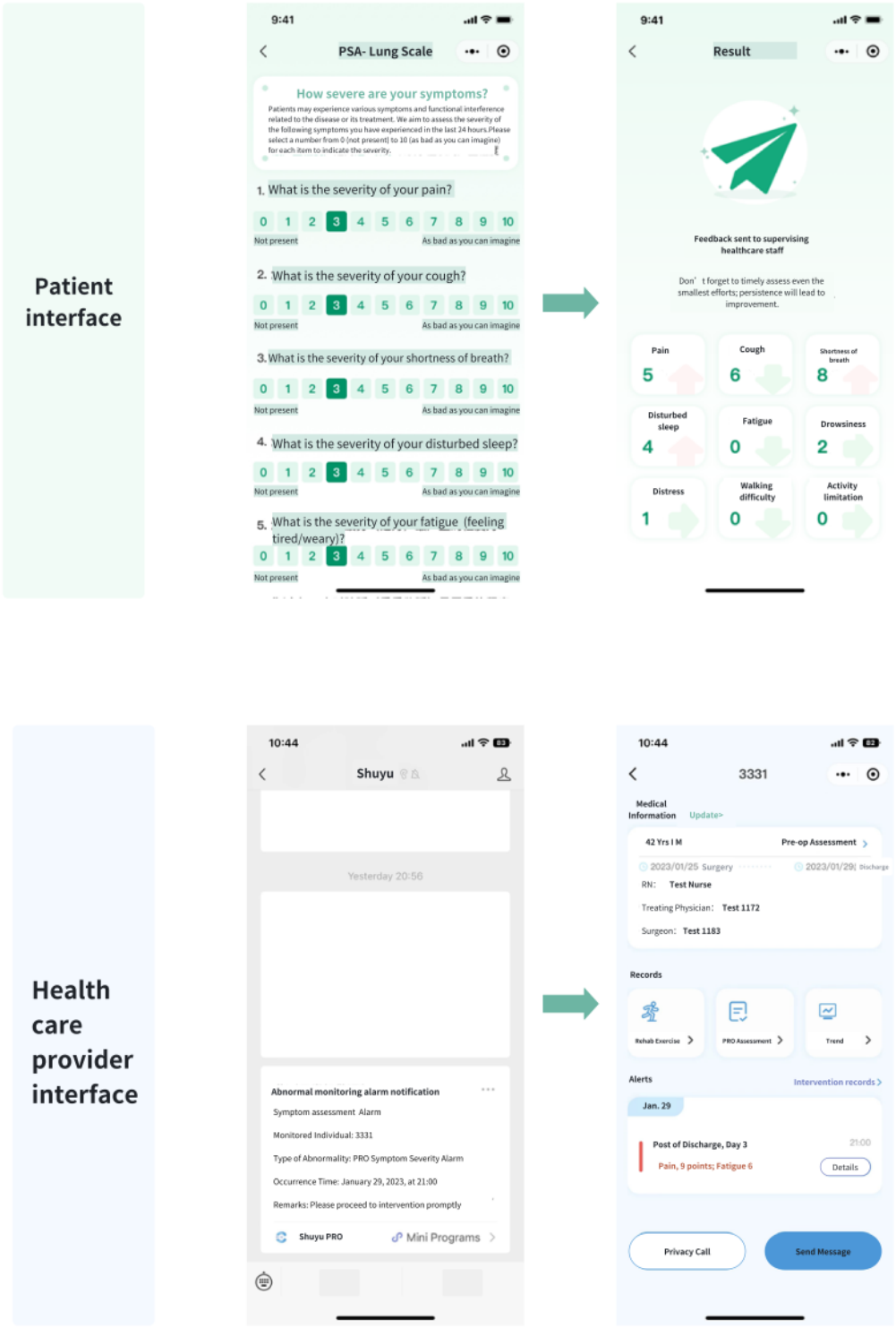
Intervention Group

The intervention group will be notified to complete the PRO measures on the designated days.

If any of the 5 core symptoms (pain, cough, shortness of breath, sleep disturbance, and fatigue) scored ≥4 in the ePRO questionnaire, alerts will be triggered on the provider end, prompting the assigned doctor and nurse to initiate remote guidance and intervention through the app through text or phone call within 24 hours following standardized procedures in the operation manual. Interventions will be based on PRO scores and include recommendations for self-management, medications, and clinic visits. In addition, patients who report any of the 5 core symptoms will immediately receive automated internet-based self-management suggestions generated by the system after submitting the PRO questionnaire.

The intervention will focus on the management of these 5 core symptoms since they were identified as critical symptoms for postoperative management in previous studies on remote PRO-based symptom management after lung cancer surgery in China [16]. Based on recommendations from the National Comprehensive Cancer Network and published studies, symptom scores ≥4 are considered moderate severity or above [23,24]. Therefore, a symptom score of 4 is set as the threshold for triggering alerts. Details of the patient self-reporting process and health care provider alert interface are shown in Figure 2.

Figure 2. Workflow of patient self-reporting via the shuyu app and healthcare provider alert interface.



Symptom management in the intervention arm will adhere to the latest guidelines and be standardized across providers through standard operating procedure manuals, as shown in Multimedia Appendix 1. In cases of severe symptoms, physicians may advise patients to temporarily pause or adjust their exercise plans to ensure safety.

Control Group

The control group will complete PRO measures on the same days without triggered alerts or self-management suggestions.

All patients, regardless of group assignment, will receive guidance on seeking medical attention through conventional means for severe symptoms. Severe symptoms are defined as individual symptom scores ≥6 on the PSA-Lung scale.

Withdrawal Criteria

Participants meeting the following withdrawal criteria will be removed from the analysis: (1) no primary lung cancer on pathology, (2) non-microscopically complete resection, (3) stage IV disease, (4) initiation of adjuvant therapy during follow-up, (5) severe protocol violation (nonadherence to instructions, random responses, etc), and (6) voluntary withdrawal.

Study Outcomes

Primary Outcome

The primary outcome is the rehabilitation exercise adherence rate over 4 weeks after discharge, defined as the proportion of patients completing the prescribed outpatient exercise regimen. Exercise completion will be ascertained based on patient self-reports through the app and verified through weekly phone follow-ups. Referencing exercise guidelines for cancer survivors from the American Cancer Society, ≥150 minutes of moderate to vigorous intensity physical activity per week (equivalent to 150 minutes of brisk walking) is considered adherent [25].

Secondary Outcomes

Secondary outcomes are listed in Textbox 1.

Textbox 1. Secondary outcomes and their measurement criteria.

- Postdischarge pulmonary complication (PPC) rate
  - Proportion of patients experiencing pulmonary complications within 30 days after discharge. Complications will be graded using the Clavien-Dindo classification [26], categorizing PPCs into 5 grades, as shown in Multimedia Appendix 2.
- 30-day revisit rate
  - Proportion of nonscheduled revisits within 30 days after discharge.
- Trajectory of symptom severity
  - Changes in symptom and interference scores on the electronic patient-reported outcome questionnaire from discharge to 30 days after discharge.
- Exercise participation rate
  - Number of days with exercise logged within 4 weeks after discharge. Any day with exercise logged is considered participation, regardless of whether the target duration is achieved.
- Patient satisfaction: score on the 4-item questionnaire including
  - Whether the app helped with rehabilitation and symptom control;
  - Overall satisfaction rating;
  - Whether the app caused daily life disruption; and
  - Likelihood of recommending the app to others. Each item is rated from 0 to 10.

Other Data

The study will record time intervals from alert to provider intervention in the app backend. Questionnaires and interviews will also survey provider acceptance of the app. Participant demographic information, tumor characteristics, clinical management, treatment outcomes, adverse events, and follow-up data will be collected at different time points. All adverse events will be evaluated and managed by thoracic surgeons.

Sample Size

The primary outcome is the rehabilitation exercise adherence rate, defined as the proportion of patients completing the prescribed exercise regimen. Adherence is defined as completing the prescribed exercise regimen, calculated from self-reported app data and verified through weekly follow-ups.

The sample size was calculated to detect a 10% difference in adherence rates between the intervention and control groups, with 80% power and a 2-sided significance level of .05. The control group adherence rate was assumed as 70% based on previous studies [27-30]. The 10% clinically important difference was determined through expert consultation, considering their practical experience and the potential impact on patient outcomes, despite limited direct literature support. The dropout rate was estimated as 20% from previous digital intervention trials (from 3.75% to 18.3%) [31-33]. Dropouts include discontinuation of app use and loss of follow-up.

Using a z test with a 10% proportion difference, 80% power, 5% type I error, and 20% dropout rate, the required sample size is 368 per group, 736 in total.

Data Analysis

Statistical analyses will be performed based on both the intention-to-treat principle and the per-protocol principle. The intention-to-treat population will include all randomly assigned participants, while the per-protocol population will include participants who provide baseline PRO data and measures for at least 2 additional time points, with at least 1 calculable weekly exercise duration logged. Participants meeting withdrawal criteria will be excluded from all analyses. Statistical inferences

will adopt 2-sided tests at a significance level of .05, with 2-sided 95% CI for estimation. The primary outcome, exercise adherence rate, will be compared between groups using the Pearson χ^2 test or Fisher exact test. Secondary outcomes will be analyzed as follows: PPC rate and 30-day revisit rate will be compared using χ^2 test or Fisher exact test; symptom severity trajectory, which involves repeated measurements, will be assessed using linear mixed effects models to account for within-subject correlation; exercise participation rate will be compared using Wilcoxon rank sum test; and patient satisfaction scores will be compared using the Student 2-tailed *t* test or Wilcoxon rank sum test. The time from alert to intervention and provider acceptance will be summarized descriptively. Baseline characteristics will be compared using 2-tailed *t* test, Wilcoxon rank sum test, χ^2 test, or Fisher exact test, as appropriate. Missing data will be handled through multiple imputation or maximum likelihood estimation methods.

Data Monitoring and Interim Analysis

A Data Safety Monitoring Board will be set up, including 1 clinical physician and 1 data manager, to conduct independent data monitoring. No interim analysis is planned considering the low-risk nature and short study duration.

Patient and Public Involvement Statement

Patients and the public will not be involved in the design, recruitment, or implementation of this study. Study results will be disseminated to applicants. As disseminating results to participants is not standard practice in China, we have no plans for participant-directed dissemination. Study participants will be informed that final results can be accessed through our future publications.

Ethics Considerations

The study protocol was approved by the Ethics Committee of Zhongshan City People's Hospital in December 2022 (approval K2022-285). All recruited patients will be required to give written informed consent. Any subsequent amendments to the protocol will be submitted for further review and approval. Study findings will be disseminated through peer-reviewed publications and conference presentations.

Results

The enrollment of study participants started in December 2023 and is expected to end in March 2025. An interim analysis is planned to assess the feasibility and preliminary effects of the intervention. The final comprehensive analysis of the results is planned for May 2025, after all data have been collected and thoroughly reviewed.

Discussion

Conclusions

This study primarily investigates the impact of outpatient symptom management on exercise adherence after minimally invasive lung surgery. Remote symptom monitoring based on ePROs provides an innovative approach to improve patient self-management and rehabilitation compliance. While previous digital interventions have focused on education and coaching, this study explores a new precision rehabilitation model that actively monitors patient-reported symptoms and provides timely medical feedback. Although symptom-related exercise interruptions may occur in both groups, the ePRO-based interventions are designed to help manage symptoms and provide personalized exercise guidance, which may potentially mitigate the impact of symptoms on exercise adherence.

Potential findings from this preliminary study include (1) providing initial evidence on whether ePRO-based remote symptom management can improve outpatient exercise adherence, which has been a neglected area in previous research; (2) demonstrating the feasibility and acceptability of implementing such a personalized symptom-exercise comanagement model in local patients; and (3) exploring its potential to reduce patient symptom burden and postoperative complications. The findings from this study will provide valuable insights into the barriers and facilitators of implementing ePRO-based symptom management in real-world settings, informing future efforts to expand and optimize outpatient care for postoperative patients. The planned analyses will also help elucidate the complex relationships between symptom alerts, symptom management, and exercise adherence in this context. Understanding these relationships is crucial for optimizing the design and implementation of integrated symptom-exercise management interventions for postoperative patients. If the findings support the feasibility and potential effectiveness of this innovative rehabilitation approach, it could inform future larger-scale studies and efforts to improve postoperative care for a broader patient population. The research framework and findings will contribute to advancing telehealth for patient-centered and digitally enabled care models.

Limitations

This study also has some limitations. First, the single-center design may limit generalizability. Second, the strict inclusion or exclusion criteria may restrict the eligible population, such as excluding patients unable to use smartphones or with poorer reading comprehension. Third, the eligibility criteria may cause selection bias and limit external validity, although stringent criteria and verification of exercise data are adopted. Further pragmatic trials in more heterogeneous populations are warranted to validate broader generalizability and effectiveness. Fourth, the lack of blinding for researchers and participants may introduce bias into the results. Fifth, the short follow-up precludes evaluation of potential long-term impacts on exercise habits.

In summary, this unblinded randomized controlled trial aims primarily to provide preliminary evidence on the effects of ePRO-based symptom management on outpatient exercise behaviors, evaluating the feasibility of this management approach. Larger studies in real-world diverse populations are needed to further validate its generalizability and effectiveness.

Acknowledgments

The authors acknowledge the efforts and software support of the Shanghai CinoCore Medical Technology Co., Ltd, especially thanks to Mr. Kaishen Chen, Ms. Jing Gao, Mr. Kun Wang, and Mr. Qi Yang. This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Data Availability

The data sets generated during and/or analyzed during this study are available in the ClinicalTrials.gov repository. The protocol will be published on an open-access repository.

Authors' Contributions

All authors contributed to the design of this protocol. XY and JS initiated the project. XY drafted the protocol and will be responsible for manuscript preparation. JS, YL, and CY contributed to the study design and methodology and will provide critical revision of the manuscript. QZ was involved in the statistical design and will be responsible for data management and analysis. WJ, GL, and YC will contribute to research coordination, ongoing patient enrollment, outpatient research follow-ups, and data collection. All authors have read, refined, and approved the final manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Standard operating manual for symptom intervention.
[PDF File (Adobe PDF File), 127 KB - resprot_v14i1e60420_app1.pdf]

Multimedia Appendix 2
Clavien-Dindo classification of surgical complications.
[DOCX File , 14 KB - resprot_v14i1e60420_app2.docx]

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Abbreviations

CONSORT: Consolidated Standards of Reporting Trials
ePRO: electronic patient-reported outcome
IWRS: Interactive Web Response System
PPC: postdischarge pulmonary complication
PSA-Lung: Perioperative Symptom Assessment for Patients Undergoing Lung Surgery
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials
VATS: video-assisted thoracic surgery

Edited by A Schwartz; submitted 12.05.24; peer-reviewed by X Wei; comments to author 10.09.24; revised version received 12.10.24; accepted 27.11.24; published 01.01.25.

Please cite as:
Su J, Ye C, Zhang Q, Liang Y, Wu J, Liang G, Cheng Y, Yang X
Impact of Remote Symptom Management on Exercise Adherence After Video-Assisted Thoracic Surgery for Lung Cancer in a Tertiary Hospital in China: Protocol for a Prospective Randomized Controlled Trial
JMIR Res Protoc 2025;14:e60420
URL: https://www.researchprotocols.org/2025/1/e60420
doi:10.2196/60420
PMID:39610048

Protocol

Effectiveness of the User-Centered "Healthcare CEO" App for Patients With Type 1 Diabetes Transitioning From Adolescence to Early Adulthood: Protocol for a Randomized Controlled Trial

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Abstract

Background: Young patients aged 16 to 25 years with type 1 diabetes (T1D) often encounter challenges related to deteriorating disease control and accelerated complications. Mobile apps have shown promise in enhancing self-care among youth with diabetes. However, inconsistent findings suggest that further evidence is necessary to confirm the effectiveness of app-based interventions.

Objective: This study aims to evaluate the effectiveness of the Healthcare CEO app in patients with T1D transitioning from adolescence to early adulthood.

Methods: A 2 arms, double-blind, randomized controlled trial will be conducted over a 9-month period, with strategies designed to enhance treatment fidelity. The study expects to enroll 96 patients with T1D, aged 16 to 25 years. Participants will be randomly assigned to either the experimental or control group through central randomization. The intervention will be implemented using the Healthcare CEO app, which consists of 11 interfaces. The research will compare differences in disease control outcomes, confidence in self-management, self-care behaviors, emotional distress, quality of life, and specific diabetes-related knowledge between the 2 groups at baseline and 3, 6, and 9 months after intervention. Additionally, changes within the experimental group will be analyzed before and after the intervention.

Results: The study was funded in August 2020. It was originally scheduled from August 2020 to July 2022 but was interrupted by the COVID-19 pandemic after enrolling 38 participants, with preliminary results anticipated for publication by November 2024. Recruitment resumed in August 2023, with findings expected to be finalized by July 2025.

Conclusions: The Healthcare CEO app is a comprehensive solution tailored specifically for individuals with T1D transitioning from adolescence to early adulthood. This innovative app has the potential to improve the quality of care for adolescents with T1D during this critical stage and may serve as valuable evidence in support of app-based intervention strategies.

Trial Registration: ClinicalTrials.gov NCT05022875; https://www.clinicaltrials.gov/study/NCT05022875

International Registered Report Identifier (IRRID): DERR1-10.2196/59871

(JMIR Res Protoc 2025;14:e59871) doi:10.2196/59871

KEYWORDS

type 1 diabetes; transition; mobile health; treatment fidelity; diabetes; user-centered; adolescence; teenager; app; adolescent patients; early adulthood

Introduction

Overview

Type 1 diabetes (T1D) is the most common type of diabetes among youth younger than 18 years [1]. The incidence of T1D has exhibited a decline in the 0-9 years age group and an increasing trend in the 10-14 years age group [2,3]. Notably, T1D accounts for approximately 0.59% of all diabetes cases in Taiwan, and its incidence in patients aged 19 years or younger is 5.17 out of 100,000 while its prevalence is 0.05%. The prevalence and incidence of T1D in patients aged 19 years or younger increased significantly from 2005 to 2014 [4]. With this increase, the demand for care during the transition phase between adolescence and early adulthood is also expected to increase [5]. Therefore, understanding the life experiences and health care needs of adolescents with T1D in this transition phase and comprehending the customization of interventions to meet these needs is crucial in T1D care.

Background

Encounters and Challenges of Patients With T1D in the Transition Phase From Adolescence to Early Adulthood

A transition phase is when an individual encounters significant life events or environmental changes. It is fraught with uncertainty and requires adaptation by learning new skills and strategies [6]. In nursing, the antecedents of the transition process are transition events that can be classified into 4 categories: developmental, situational, health‐illness, and organizational transitions [6]. Moreover, providing nursing support to patients in transition may contribute to role mastery and maintenance of physical and emotional well-being [7].

The encounters and challenges of patients with T1D transitioning from adolescence to early adulthood are wide-ranging and possess unique characteristics. The developmental transition from adolescence to early adulthood is often characterized by a rapid increase in height and body weight, as well as dramatic hormonal changes. Therefore, individuals with T1D in this transition commonly face the physiological challenge of maintaining stable blood glucose levels [5,8] and are at a high risk of poor disease control [9,10]. A study of individuals registered in the T1D Exchange Clinic Registry (a large-scale registry of patients with T1D in the United States) revealed that the mean hemoglobin A_{1c} (HbA_{1c}) level in 18- to 25-year-olds was 8.7% (SD 1.9%) [11], which is higher than the average. The inability to achieve optimum blood glucose control is one of the greatest stressors faced by patients with T1D and may even cause anticipatory nervousness, which in turn affects sleep quality [12]. Other key stressors include the quest for independence, the burden of disease-related self-care, and the implementation of disease self-management [13,14]. Challenges faced by young patients with T1D in situational transition include the deconstruction of peer relationships caused by education system transition, establishment of sexual relationships, worries regarding the health and genetic inheritance of offspring, and reconstruction of physician-patient relationships due to workplace changes or home relocation [13,15,16]. During health-illness transition, especially from late adolescence to early adulthood, patients often become hospitalized owing to acute complications such as ketoacidosis and hypoglycemia. The need for frequent blood glucose monitoring and the transition from hospitalization to discharge often causes disruptions to life routines [5,16,17]. Young patients with T1D often experience an organizational transition, from family-centered care to patient-centered care, at 16-25 years [18,19]. Difficulties faced during this transition period often include the lack of a comprehensive transition-phase care plan that meets patient requirements, negative health care–seeking experiences in adult care systems, termination of health insurance, and loss to follow-up [10,20,21]. In Taiwan, the pediatric care model is adopted for most patients with T1D transitioning from adolescence to early adulthood. Many patients consider the transition from pediatric to adult care unnecessary owing to trust in physician-patient relationships and the familiarity of medical environments. Moreover, approximately 25% of patients reported that physicians should engage in active discussions with patients and provide assistance for referrals to adult care [5].

Needs and Effectiveness of App-Based Interventions Among Patients With T1D in the Transition Phase From Adolescence to Early Adulthood

Support from health care providers and primary caregivers is crucial for patients with T1D in the transition phase [14,22]. Patients with T1D, their primary caregivers, and health care providers agree that the provision of technology-based care and the development of specific apps for T1D self-management are important health care needs that should be addressed [23,24]. Studies have shown that diabetes-related knowledge, diabetes-specific and general life stress, and emotional disorders can affect self-care behaviors, disease management effectiveness, and HbA_{1c} control among patients in the transition phase [25-28], with higher severity of emotional distress

associated with poorer HbA_{1c} control and quality of life (QoL) [29,30]. Therefore, app-based intervention measures should aim to address these factors.

Among the studies on the use of app-based interventions for youth with T1D or those in the transition phase, Goyal et al [31] and Veazie et al [32] reported that app-based interventions improved HbA_{1c} levels. Additionally, Frøisland et al [33] found that app-based interventions resulted in a better understanding of disease-related knowledge, whereas app usage seemed to positively affect diabetes self-care. However, some longitudinal studies have revealed that app interventions had no significant effects on HbA_{1c} levels [34,35], frequency of hypoglycemic events [31], diabetes-related QoL [31,34], self-perceived diabetes management ability, and diabetes-related emotional distress [35]. Although young patients with T1D generally provide positive ratings for the usability and feasibility of user-centered apps [35,36], these inconsistent results indicate that further evidence is necessary to support the effectiveness of app-based interventions.

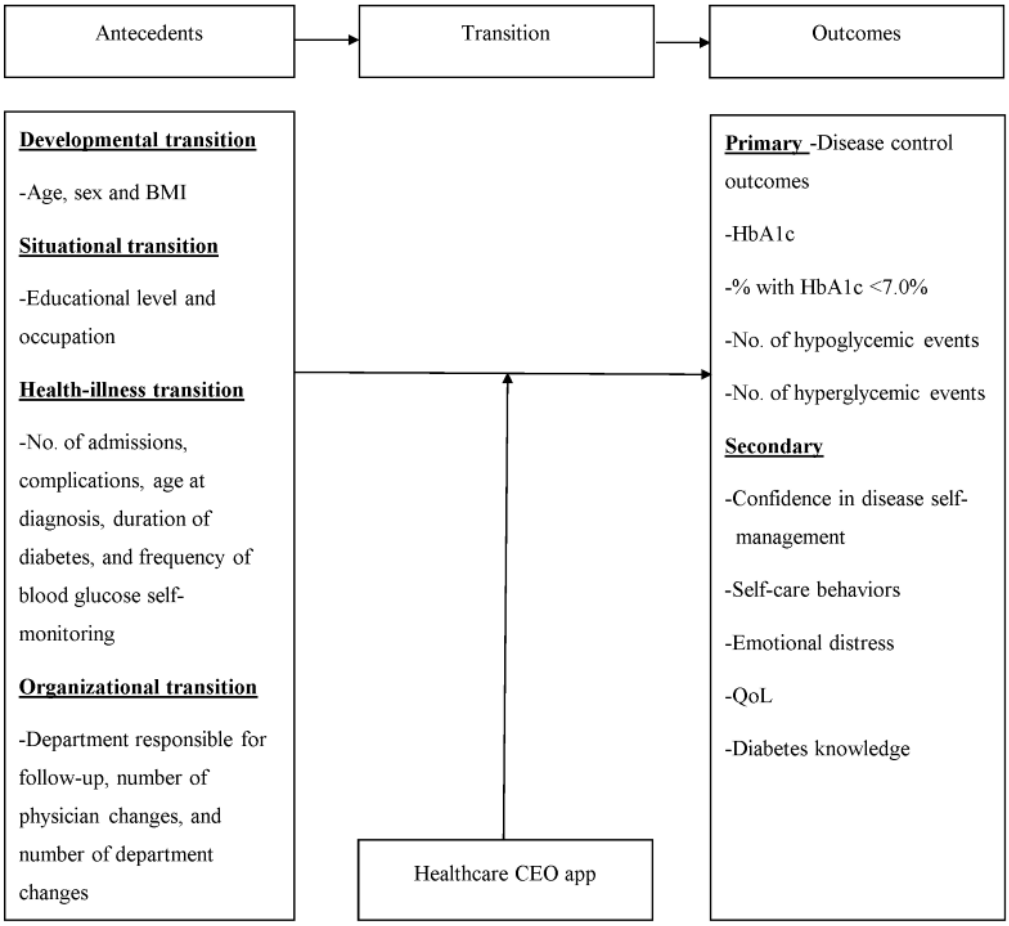
Knowledge Gaps

Currently, the available apps for diabetes management can be broadly classified into 5 categories: nutrition, physical activity, blood glucose monitoring, insulin titration, and insulin injection. Most apps merely possess a single function, although there is an increasing trend toward integration [37]. Additionally, the majority of Chinese-language apps provide general diabetes knowledge, which may not be applicable to adolescents or young adults, and do not cater to the specific needs of patients with T1D in the transition phase [5]. Furthermore, the effectiveness of such apps should be validated by long-term empirical evidence [24,38], and few studies have mentioned the adoption of strategies to enhance treatment fidelity [31,35]. Health apps developed for intervention should incorporate evidence-based content while fulfilling the needs and protecting the privacy of the target age groups to enhance effective disease self-management [39]. To address the specific needs of patients in the transition phase, we developed the Healthcare CEO app using a user-centered approach. This app targets challenges such as poor glycemic control; pressures related to self-care; effective disease self-management; and interpersonal issues, including the establishment of romantic relationships, concerns about the health and heredity of future generations, workplace adaptation, parent-child conflicts, and enhancing QoL. This study aims to present a comprehensive protocol for evaluating the efficacy of the Healthcare CEO app. This will involve a series of detailed analyses, including (1) comparing disease control outcomes, confidence in self-management, self-care behaviors, emotional distress, and QoL between the experimental and control groups, and (2) a comparison of differences in preintervention and postintervention disease control outcomes, confidence in self-management, self-care behaviors, emotional distress, and QoL in the experimental group.

Conceptual Framework of the Study

Based on the literature described above, the transition phase theory was used as the framework of this study [6,40]. According to the transition phase theory, antecedents that trigger transition can be classified into 4 categories: developmental, situational, health illness, and organizational transitions. The Healthcare CEO app will be used as an intervention measure for patients with T1D transitioning from adolescence to early adulthood, and the effectiveness of the intervention in improving disease control outcomes, confidence in disease self-management, self-care behaviors, emotional distress, and QoL will be investigated, as shown in Figure 1.

Figure 1. Conceptual framework of the study. HbA_{1c}: hemoglobin A_{1c}; QoL: quality of life.



Methods

Design

A 9-month, 2-arm, parallel-group, double-blind, randomized controlled trial will be conducted. Participants will be randomly assigned to the experimental or control groups, and treatment fidelity monitoring strategies will be adopted to enhance the consistency and fidelity of intervention measures.

Participants

Inclusion and Exclusion Criteria

Participants will be enrolled from the outpatient clinic and wards of the Department of Pediatric Endocrinology and Metabolism, at a medical center in Northern Taiwan. The inclusion criteria are as follows: (1) a confirmed diagnosis of T1D from an endocrinologist before the age of 16 years and a disease duration of >6 months; (2) aged 16-25 years; (3) mean HbA_{1c} level ≥7.5% one year before inclusion; (4) ability to communicate in Chinese or Mandarin; (5) owning a smartphone with internet access; (6) agreeing to voice recording while explaining the treatment process; and (7) signing the informed consent sheet prior to participation—for minors, a legal representative must provide consent and sign the informed consent sheet. Patients with T1D with concomitant metabolic diseases, chromosomal aberrations, major illnesses, and cognitive impairment will be excluded from the study because their health care needs during the transition phase may differ from those who experience T1D only.

Sample Size

The required sample size was estimated using the G*Power program (Heinrich-Heine-Universität Düsseldorf) for repeated measures with 2 groups, 9 measured variables, power of 0.80, α set at .05, an estimated Cohen effect size of 0.25, and a correlation coefficient of 0.5. The sample size for each group was calculated as 36. By allowing for a potential 25% dropout rate, as suggested by Goyal et al [31], a final sample size of 96 participants (48 participants in each group) was established.

Sample Accessibility

The cumulative number of patients in the transition phase, aged 16-25 years, at the study site is expected to exceed 300. For each enrolled participant, the study explanation and data collection process is expected to last approximately 1 hour. Based on our research team's qualitative research experience, the on-site interview length for each participant was 1-1.5 hour, whereas the refusal rate is expected to be approximately 10%. Therefore, each week, approximately 8 patients who fulfill the inclusion criteria will participate in the study. Thus, the number of valid samples expected each month is roughly 28-32.

Randomization and Blinding

Randomization of the participants will be performed by a statistician, using the central randomization method in SPSS (IBM Corp). During participant enrollment, participants will

be randomly assigned to the experimental or control groups in accordance with the instructions provided on the phone by the statistician; the participants and data collectors will be blinded to allocation. Blinding strategies include the following. First, the statistician will not be allowed to disclose the randomization results to others. Second, once a physician referral is received, the participant will be promptly taken to a private room. The data collection assistant will complete their duties and leave the room, and then 2 research assistants will come in and take over to administer the intervention phase. Third, participants of both the experimental and control groups will download the app, but the app content will differ. Fourth, to avoid differential demand characteristics, research assistants will emphasize to all participants that app usage is potentially beneficial for disease management.

Description of the Intervention

Overview

The Healthcare CEO app was developed guided by the user-centered information systems research framework and comprised 3 key cycles: Relevance, Rigor, and Design [41]. It was named after the self-expectations of patients in diabetes management, as patients with T1D often wished to become the "Chief Executive Officers" of their disease. The development and testing process of the Healthcare CEO app is detailed in published articles [42]. The app content was designed based on the results of previous qualitative and Delphi studies [5,23] and consisted of 11 interfaces (as shown in Figure 2): CEO's Profile; Health Tracking; CEO Knowledge Base; Barrier-free Communication; See Here: Diet and Exercise; Help Me, Detective!; CEO Chat Room; CEO's Secretary; Who's the Best CEO; SOS Calls; and Q&A. The evidence-based content aims to enhance disease knowledge among individuals in the transitional phase, improve self-care behaviors, and bolster confidence in disease self-management. These were combined with interpersonal communication skills training, to alleviate disease-related emotional distress, ultimately improving disease control outcomes and QoL. The content, objectives, and expected outcomes of each interface are detailed in Table 1.

Figure 2. Interfaces of the Healthcare CEO app. CEO: chief executive officer.

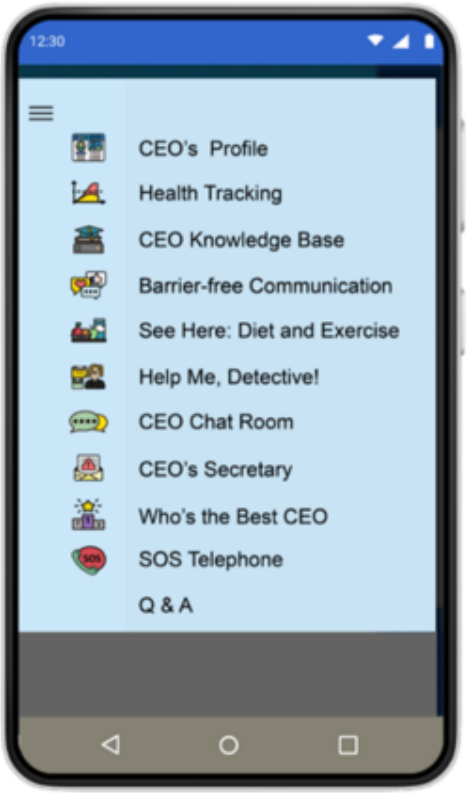


Table 1. Content of Healthcare CEO app.

Interface	Description of content	Purposes and expected outcomes
CEO's Profile	Personal and disease data, including the following: name, nickname, date of birth, occupation, duration of disease, hospital, and attending physician. The patient can select the data to be openly displayed.	1. Establish basic data 2. Review and confirm basic disease information through data entry
Health Tracking	Upload or enter data on blood glucose level, blood pressure, body weight, and insulin dosage. HbA_{1c}[a] targets can be set, and changes in HbA_{1c} can be analyzed and displayed as trends.	1. The status of HbA_{1c} control can be checked to enhance self-care motivation and confidence in disease self-management
CEO Knowledge Base	Basic and advanced knowledge of interest to patients with T1D[b] in the transition phase is provided in the e-book format. Examples of basic knowledge include the following: impact of secondary sex characteristic development on blood glucose; blood glucose control targets in T1D; and tips for dieting, exercise, and travel during puberty. Examples of advanced knowledge are as follows: matters related to sex, genetics, gestation, and employment among patients with T1D. Both a pretest and posttest must be completed to determine the learning effectiveness of each article before the next article can be accessed.	1. Patients can enhance T1D-related knowledge on a need basis 2. Patients can boost their confidence in disease management by accumulating disease-related knowledge. This will enhance self-care behaviors, disease control outcomes, and disease-related QoLc
Barrier-free Communication	Guidance for techniques in parent-child, peer, and workplace interactions is provided through video and e-book links. Questions and scenarios are designed to prompt patients to reflect on their communication methods and think about/enact their strategies for effective interaction.	1. Improve communication skills, enhance ability to deal with interpersonal difficulties, and reduce emotional distress
See Here: Diet and Exercise	Carbohydrate and calorie calculators and a food swap guide are provided. The calorie contents of preferred foods and calories burned in preferred exercises of patients in the transition phase are displayed in images. Patients can keep records using the handy checkbox interface or uploading photos.	1. Assist in disease management and self-care, which will in turn improve disease control outcomes and disease-related QoL
Help Me, Detective!	When the blood glucose level is not within the expected range or emergency complications occur, this interface allows for the recording of the time of event occurrence, uploading of blood glucose readings, photographs of the patient's diet, exercise, or patient condition during the event, and documentation of the treatment measures adopted. These data can serve as a reference for discussion with the physician during outpatient visits, and physician advice can be input into the interface to guide the handling of future emergencies.	1. By recording and analyzing the causes of acute complications, the patient may devise improvement measures to enhance disease control, which will gradually enhance confidence in disease self-management and improve disease control outcomes
CEO Chat Room	An optional second password can be set to achieve 2 levels of privacy protection, which may be very important to patients in the transition phase. Two chat rooms named the "insider chat room" and "outsider chat room" have been designed. The insider chat room is reserved for patients using the app, with 2 themed chats organized monthly. Patients may invite individuals whom they trust (eg, attending physicians, close friends, or primary caregivers) and can engage in heart-to-heart talk using the outsider chat room, to develop their interpersonal networks and exchange views and ideas.	1. Provide interpersonal support and enhance disease-related knowledge and management strategies through experience sharing, which will alleviate emotional distress and strengthen disease self-management ability
CEO's Secretary	This consists of 2 functions, namely "Reminders" and "Online consultations." (1) Reminders: When trends of exceedances related to blood glucose occur, such as excessively high postdinner blood glucose level for 3 consecutive days, noninput of health data for ≥3 days, fewer blood glucose measurements than the required number of measurements for 3 days, and on the day before a scheduled outpatient visit, patients and app administrators will receive notifications and text message reminding them to perform relevant tracking actions. Reminders can also be set based on the needs of the patients; (2) Online consultations: The timing and theme of online consultation sessions can be booked in advance. Online consultations involve the clarification of doubts related to disease care through interactions with health care professionals.	1. Assist in disease management and provide individualized knowledge to enhance disease-related knowledge and confidence in self-care, thereby alleviating emotional distress and improving disease-related QoL 2. Conditions for reminders can be set to reduce annoying reminders, to prevent resentment of app use

Interface	Description of content	Purposes and expected outcomes
Who's the Best CEO	One point is awarded every time the user performs data input on time, reads an article, devises a communication technique, and correctly enters data into the Help Me, Detective! interface, or enquires about online consultation. Ten points are awarded when the target HbA_{1c} level is reached. The patients with the highest number of points are listed weekly. At the end of each month in our study, the top 3 patients with the highest number of points will each receive an NT $300 (approximately US $9.24) voucher. Moreover, at the end of the study, the top 3 patients with the highest number of points will receive an NT $1000 (approximately US $30.79) voucher.	1. Enhance motivation and effort in self-care
SOS calls	Patients can set up 3 contact numbers to call for help quickly when necessary.	1. Assist in disease management and self-care, thereby improving disease control outcomes
Q&A	Patients who may be unaccustomed to asking questions in the chat room can have their queries answered via the provided email account.	1. Assist in disease management and self-care to improve outcomes

[a]HbA_{1c}: hemoglobin A_{1c}.

[b]T1D: type 1 diabetes.

[c]QoL: quality of life.

Experimental App Intervention

The complete Healthcare CEO app will be used to intervene in the experimental group. Two trained research assistants will supervise each other to guide the participants in the following aspects, according to the standard treatment manual: (1) account setup; (2) viewing of operation guidance videos; (3) demonstration of all app functions, getting participants to perform app operations, and clarifying doubts about app usage; (4) explaining troubleshooting methods; (5) providing contact information of app administrators; and (6) setting a HbA_{1c} control target. Between every 2 rounds of data collection, the research assistants will contact the participants to check if they have encountered issues or difficulties when using the app, although they will not exchange disease care-related information. After the completion of data collection, the app will be remotely uninstalled by the administrators at the backend.

Control App Intervention

Participants in the control group will only install the "CEO's Profile" and "Health Tracking" interfaces of the Healthcare CEO app. In addition to explanations for the account setup and the use of the 2 interfaces, the research assistants will not provide any app-related information to the control participants. The status and difficulties of app use will also not be tracked. After the last round of data collection, the full version of the Healthcare CEO app will be provided to the control group participants, according to their preferences. The app will be remotely uninstalled at the backend by the administrators after 9 months.

Measures

Overview

All survey questionnaires will be accessed via QR codes and answered online, with all fields set as mandatory to prevent nonresponses. The tools to be used in this study are as follows.

Demographic Questionnaire

This self-designed questionnaire has been developed based on the conceptual framework of this study. It includes questions on age, sex, BMI, educational level, occupation, number of hospital stays, complications, age at diagnosis, duration of diabetes, frequency of blood glucose self-monitoring, department responsible for follow-up, number of physician changes, and number of department changes.

Primary Outcomes

These include HbA_{1c} levels, percentage with HbA_{1c} <7.0%, and the number of hyperglycemic and hypoglycemic events.

HbA1c

HbA_{1c} will be recorded as a percentage; data will be obtained through venous blood analysis.

Percentage With HbA1c <7.0%

The percentage of HbA_{1c} readings below 7.0% for each participant will be calculated.

Hyperglycemic Events

The number of events with blood glucose >200 mg/dL or "high" on the glucometer or diagnosed ketoacidosis will be calculated for each participant.

Hypoglycemic Events

The number of events with blood glucose <60 mg/dL or "low" on glucometer or diagnosed hypoglycemia will be calculated for each participant.

For hyperglycemic and hypoglycemic events, during the data collection period, the blood glucose readings will be downloaded from the blood glucose meters of the participants, and the number of hyperglycemic and hypoglycemic events will be calculated. Considering that changes in blood glucose levels may be tracked only after adopting treatment measures, 2 researchers will perform a manual inspection of the data simultaneously. Only the first recorded reading, among all

readings taken within the same measurement period, will be analyzed.

Secondary Outcomes

Perceived Diabetes Self-Management Scale

The original questionnaire was developed by Wallston et al [43]. It consists of 8 items scored on a 5-point Likert scale ranging from 1 (strongly disagree) to 5 (strongly agree), of which items 1, 2, 6, and 7 are reverse scored. The total score ranges from 8 to 40, with higher scores indicating higher confidence in diabetes self-management. Lin et al [44] translated the scale into Chinese to assess 168 patients with T1D and type 2 diabetes (T2D). The translated questionnaire has content validity, Cronbach α, and test-retest reliability values of 0.75, 0.93, and 0.97, respectively.

Self-Care Behavior Assessment Scale

This scale was originally developed in Chinese by Wang [45] to measure self-care behaviors of adolescents with T1D. It comprises 7 dimensions: pharmacological treatment–insulin injections; healthy diet–diet control; blood glucose monitoring–self-monitoring; physical activity and exercise–regular exercise; problem-solving–risk reduction; healthy coping–psychological and social adaptation; and stress adaptation. A total of 39 items are scored on a 5-point Likert scale ranging from 1 (not achieved at all) to 5 (completely achieved), of which items 26 to 35 are reverse scored. The total score ranges from 39 to 195, with higher scores indicating better self-care behaviors. Cronbach α and the content validity value are 0.87 and 0.92, respectively.

Diabetes Distress Scale

The original scale was developed by Polonsky et al [46]. The Chinese version consists of 17 items across 4 subscales: emotional burden, physician-related distress, regimen-related distress, and diabetes-related interpersonal distress. Items are scored on a 4-point Likert scale ranging from 1 (no distress) to 4 (severely distressed), with higher scores indicating more severe emotional distress. Cronbach α and test-retest reliability values of the Diabetes Distress Scale are 0.89 and 0.81, respectively [47].

Diabetes Quality of Life

The original scale was developed for use in the Diabetes Control and Complications Trial and translated into Chinese by Cheng et al [48]. The Chinese version consists of 42 items with the following subscales: satisfaction, impact, and diabetes-related worry. Each item is scored on a 5-point Likert scale, with 1 and 5 representing “very dissatisfied” and “very satisfied” in the satisfaction subscale, “never” and “always” in the impact subscale, and “never worried” and “always worried” in the diabetes-related worry subscale, respectively. Higher scores are indicative of a higher QoL. The Cronbach α and test-retest reliability values of the scale and subscales are within the ranges of 0.76-0.92 and 0.94-0.99, respectively.

Diabetes Knowledge Questionnaire

The original questionnaire was developed by Garcia et al [49]. The Chinese version comprises 24 items that are answered “Yes,” “No,” or “I don’t know”; 1 point is awarded for each correct answer. The total score ranges from 0 to 24 points, with higher scores indicating more excellent knowledge of diabetes. In a study that adopted the 24-item Diabetes Knowledge Questionnaire (DKQ) for assessing 108 patients with T2D, the results indicated reliability and Cronbach α values of 0.78 and 0.89, respectively [50]. Currently, the DKQ is used chiefly for patients with T2D. However, when we sequentially inspected all items of the DKQ to determine its applicability to patients with T1D, it was found that the correct answer for Item 6, “If I am diabetic, my children have a higher chance of being diabetic,” needs to be changed to “No,” and for Item 13, “Medication is more important than diet and exercise to control my diabetes,” needs to be changed to “Yes.” In contrast, the remaining items and answers remain applicable to patients with T1D and are considered essential knowledge among such patients. Therefore, the DKQ will be used in this study following the above-mentioned modifications.

App Use Data

During the data collection period, the administrators will also download app-use data at the backend. Such data include log-ins to the Healthcare CEO app, the number of e-books read in the CEO Knowledge Base, the number of online consultations with the CEO’s Secretary, and the content of the chats in the CEO Chat Rooms.

Data Collection

Three research assistants with a background in health care, who have a basic understanding of T1D, have undergone training, and are not involved in the provision of health care, will be responsible for the data collection. Attending physicians of patients with T1D will provide referrals of patients who meet the inclusion criteria. One research assistant in charge of data collection will then approach the patients to explain the purposes of the study and the research process. Patients who agree to participate will subsequently fill out the informed consent sheet and undergo the preintervention test (T0) in an undisturbed environment. The second research assistant will obtain the randomization results from the statistician by phone and assist participants in downloading the Healthcare CEO app onto their smartphones based on their group assignment. The third research assistant will check and remind the second research assistant of the intervention steps to ensure the accuracy and completeness of the intervention. Considering that HbA_{1c}, the critical indicator of blood glucose control, is measured once every 3 months, the time points for the postintervention data collection for both groups are set at 3 months (T1), 6 months (T2), and 9 months (T3) after the intervention.

Treatment Fidelity

Overview

To monitor the faithfulness and fidelity of the intervention process and enhance intervention effectiveness evaluation, we formulated strategies for the inspection of treatment fidelity in the 5 areas proposed by Bellg et al [51] at the National Institution of Health Behavior Change Consortium.

Treatment Design

A standard treatment manual was formulated to explain the purpose of the study, the processes, and the details. Standardized interaction content of the interventions was established.

Training Provider

Research assistants received 16 hours of standardized training in accordance with the roles they will serve in the study. The standard training sessions attended by all research assistants included treatment of patients with T1D in the transition phase, research ethics, and 2 observational visits to the outpatient clinic for familiarization with the study settings. Individual training sessions included data collection techniques or the development, methods of use, and troubleshooting of the Healthcare CEO app. In addition, during the data collection process for the first 10 participants, the research assistants will be accompanied by senior researchers to confirm their techniques and abilities in participant inclusion and ensure faithfulness in the implementation of the intervention measures, and strategies for improvement will be provided after observation.

Delivery of Treatment

An intervention step checklist has been formulated and will be provided to research assistants for the sequential inspection and confirmation of the level of completion and completeness of the intervention measures. Another assistant will inspect the fidelity and faithfulness of the intervention process using an intervention process checklist and perform voice recordings of the entire treatment process for researchers to conduct random analyses, evaluations, and feedback.

Receipt of Treatment

Participants will be asked to perform operations in the app and discuss and clarify any doubts that they may have. An intervention content checklist will be provided to the participants after the completion of the intervention to confirm that they have received the complete intervention and determine their level of understanding and app use abilities.

Enactment of Treatment Skill

To ensure that participants are capable of using the app in everyday life, the following will be carried out: weekly monitoring of the frequency of app content usage and the level to which app usage has been correctly completed, documenting usage issues and suggestions highlighted by participants during routine telephone follow-up, and downloading and analyzing app use data during each round of data collection.

Data Analysis

Statistical Analysis

The intention-to-treat principle will be used for the data analysis; that is, all participants will be included in their initially assigned groups for analysis, regardless of whether they withdraw from the study for any reason or are lost to follow-up. Data will be analyzed using IBM SPSS 26.0 for Windows, with differences considered statistically significant at $P<.05$. Demographic and disease status data, including age, gender, BMI, age at diagnosis, disease duration, and HbA_{1c}, along with metrics on the app usage to evaluate treatment fidelity, such as the log-ins to the app, frequency of use for each interface, number of e-books read in the CEO Knowledge Base, and number of online consultations in CEO's Secretary, will be presented through descriptive statistics. This will include frequency distributions, percentages, means, SDs, and maximum and minimum scores. Homogeneity in the essential attributes of the 2 groups will be compared and analyzed using inferential statistics, such as the chi-square test and ANOVA. Owing to the longitudinal nature of this study, repeated data measurements will be taken. Dependencies may exist among the data at different time points, and data loss may also occur. Using generalized estimating equation models, repeated measurements can be simultaneously included in the regression analysis. Through the variance correction process, consistent estimates of the regression parameters and their variance can be provided to correct for dependencies, and participants with missing values can still be included in the analysis [52]. Therefore, a generalized estimating equation will be used for data analysis to compare the differences between the experimental and control groups at both preintervention and postintervention time points, as well as the differences in the scores of the experimental group before and after intervention.

Healthcare CEO App Chat Room Data Analysis

Chats in the CEO Chat Rooms will first undergo thematic categorization, beginning with a review of the chat content to gain an initial understanding. Relevant patterns will then be identified and labeled through initial coding, and similar codes will be grouped to form broader themes. These themes will be reviewed and refined for relevance and consistency with the data, and each theme will be clearly defined. Finally, the frequency of each identified theme will be calculated.

Ethical Considerations

The study will follow the Declaration of Helsinki and has received approval from the Ethics Committee of the Chang Gung Foundation Institutional Review Board (submission reference: 202100050B0; March 9, 2021). It will uphold key ethical principles, including informed consent, with participants receiving comprehensive information about the study. For minors, consent will be obtained from a legal guardian simultaneously, and efforts will be made to minimize any undue influence from guardians or family members to guarantee voluntary participation. Participants may withdraw at any time without impacting their medical care. The study prioritizes participant safety through self-reported questionnaires and a mobile app that poses no risks. Justice is maintained by ensuring equal medical care for all participants, with the control group accessing the app after the study. Privacy is protected with data secured in locked storage and coded identifiers used in publications to ensure anonymity. Participants will receive a voucher worth NT $300 (approximately US $9.34) for each completed questionnaire as an appreciation for their time and effort.

Validity and Reliability

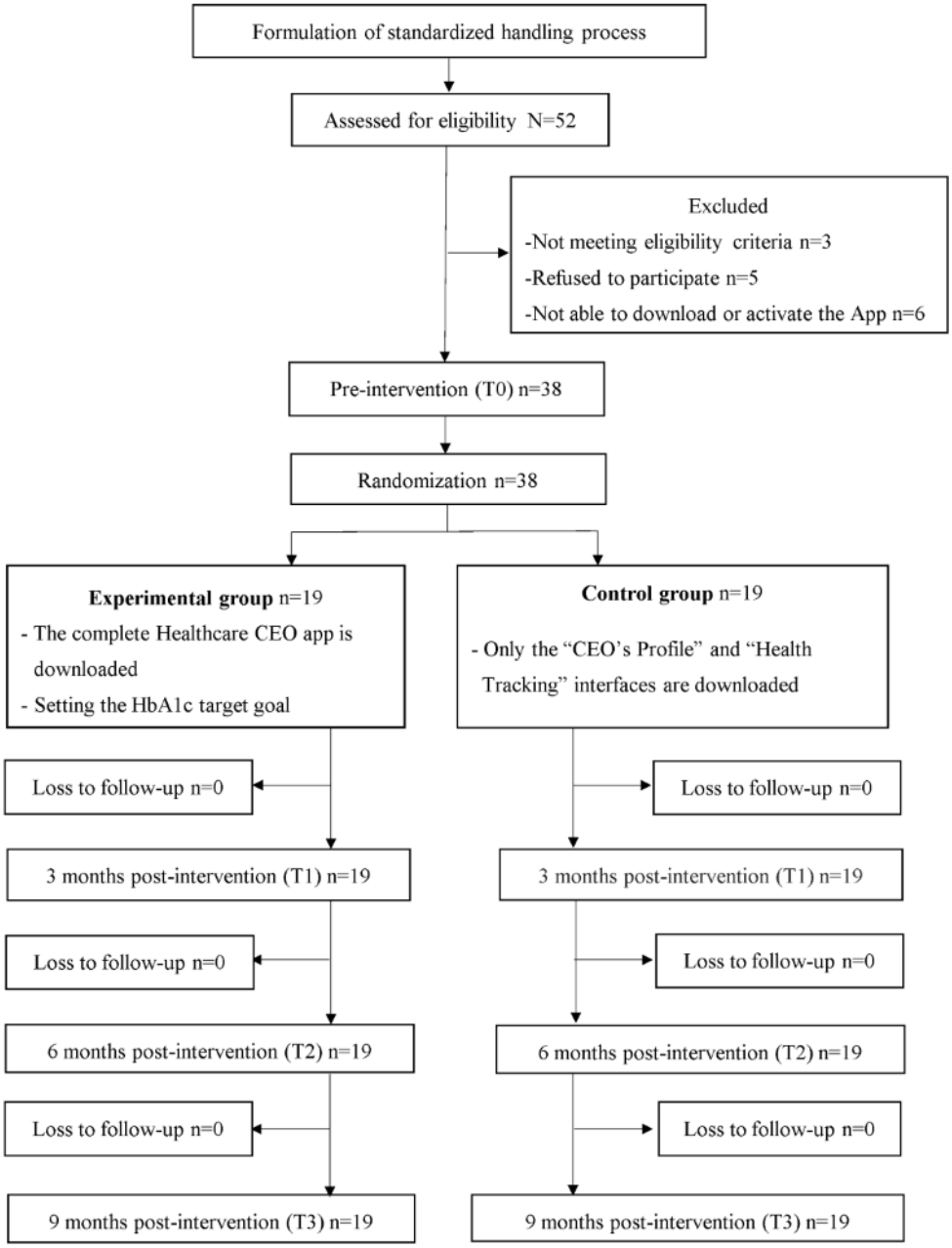
The study design and participant enrollment process were formulated in accordance with the recommendations of the CONSORT (Consolidated Standards of Reporting Trials)

statement. We also formulated strategies based on the National Institution of Health Behavior Change Consortium guidelines to monitor the faithfulness and fidelity of the intervention process. The research tools used in this study also exhibit good validity and reliability. In the measurement of the primary outcome variables, this study differs from previous works on diabetes management apps in that "% with HbA_{1c} <7.0%" data will be calculated for the first time for analysis. This allows for greater objectivity and rigor in evaluating the effectiveness of the Healthcare CEO app.

Results

After a comprehensive review, the National Science and Technology Council, Republic of China (MOST 109-2314-B-182-057-MY2), and Chang Gung University (NMRPD1K1021) provided financial support for this research project. The project was initially scheduled to run from August 1, 2020, to July 31, 2022. However, owing to the widespread impact of the COVID-19 pandemic, the study was abruptly halted after the enrollment of 38 participants. Details of the recruitment and randomization processes can be found in the CONSORT flowchart (Figure 3). We anticipate that the preliminary results will be compiled and submitted for publication by November 2024. The recruitment of participants resumed in August 2023, with findings expected to be finalized by July 2025. At present, each experimental and control group includes 13 participants.

Figure 3. CONSORT (Consolidated Standards of Reporting Trials) flowchart of preliminary results of the trial. HbA_{1c}: hemoglobin A_{1c}.



Discussion

Principal Findings

The Healthcare CEO app distinguishes itself as one of the few evidence-based, multifunctional integrated apps specifically designed for individuals aged 16-25 years managing T1D. This study uses a double-blind, randomized controlled trial intervention, with anticipated outcomes aimed at enhancing disease knowledge, improving self-care skills, and strengthening self-efficacy in disease management. Additionally, training in effective communication skills is intended to reduce interpersonal and emotional distress, enhance QoL, and ultimately improve glycemic control outcomes. The strengths and limitations of this study are elaborated in the following sections.

Strengths

The 6 major aspects of diabetes self-management are physical activity, nutrition, blood glucose testing, medications or insulin injections, health feedback, and education. However, existing diabetes management apps focus only on 2 to 3 of these aspects on average. App developers should work closely with health care providers and patients to ensure that the developed apps address patients' health care needs [53]. Our app differs from the majority of commercially available apps in that it contains the following distinctive features: (1) the app content has been designed based on a series of empirical studies [5,23,42] to ensure that it fulfills the needs of the users; (2) the app contains diverse content across 11 interfaces instead of being limited to 2 or 3 aspects; (3) the See Here: Diet and Exercise interface allows for easy and convenient recording of carbohydrate and calorie intake and exercise intensity; (4) the CEO Knowledge Base contains specific content targeted at patients in the transition phase, which is divided into basic and advanced knowledge, for perusal on a need basis; (5) themed discussions can be organized in the CEO Chat Rooms interface, during which users can discuss their needs and expert suggestions can be provided; (6) an SOS Calls function is provided for users transitioning from the dependence to independence phases, so that they can seek help from trusted individuals when needed; and (7) a points system, in which points can be exchanged for gift vouchers, is used to reward users for app use. With the above features and added emphasis on enhancing treatment fidelity, we anticipate that our results will indicate high effectiveness in diabetes self-management among patients with T1D in the transition phase due to our app-based intervention.

Limitations

This study design has several limitations. First, the app usage may be limited by an unstable internet connection, which could impact the effectiveness of our app-based intervention. Second, in addition to providing gift vouchers to enhance the motivation and efforts of the participants, we also factored in an allowance during sample size estimation to minimize the effects of participant withdrawals. Third, because of the nature of the study, the researchers cannot be blinded during the study implementation, which may lead to potential biases. To address this issue, researchers must adhere to strict intervention principles to minimize the impact on the study results. Finally, the Healthcare CEO app was developed and will be evaluated based on Taiwanese participants with T1D in the transition phase. Therefore, caution will have to be exercised, and cultural differences will be considered when interpreting the study results.

Conclusions

Patients with T1D transitioning from adolescence to early adulthood are in extreme need of support from health care providers and primary caregivers. The Healthcare CEO app developed in this study differs from current commercially available apps in that the functions desired by transitioning adolescent patients, as indicated by the empirical results obtained from previous qualitative and quantitative studies, have been integrated into the app to the best of our ability. In other words, this app is the first multifunctional app targeted at the needs of patients with T1D in the transition phase from adolescence to early adulthood. Our study protocol consisted of strategies formulated to enhance the treatment accuracy of the intervention measures. Such strategies make it possible to increase the objectivity of intervention effectiveness evaluation. The findings can serve as a reference for further applications to the clinical care of patients in the transition phase.

Acknowledgments

The authors thank all participants and acknowledge funding support from the National Science and Technology Council, Republic of China (MOST 109-2314-B-182-057-MY2), and Chang Gung University (NMRPD1K1021).

Data Availability

The datasets produced or analyzed in this study can be obtained from the corresponding author upon reasonable request.

Authors' Contributions

YTC, PKT, CW Chen, CLH, FSL, and PM contributed to the conception of the study. YTC, HYY, CW Chang, and CW Chen contributed to the study design. YTC and PKT performed statistical planning and data analysis. YTC, HYY, PKT, and CLH performed implementation and process evaluation planning. YTC, HYY, and FSL performed data collection. YTC, HYY, and PM contributed to the manuscript writing. YTC, HYY, PKT, CW Chen, JGE, CW Chang, CLH, FSL, and PM performed the article review.

Conflicts of Interest

None declared.

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Abbreviations

CONSORT: Consolidated Standards of Reporting Trials
DKQ: Diabetes Knowledge Questionnaire
HbA1c: hemoglobin A_{1c}
QoL: quality of life
T1D: type 1 diabetes
T2D: type 2 diabetes

Edited by A Schwartz; submitted 28.04.24; peer-reviewed by LC Chang, WY Lin, JJ Lin; comments to author 21.10.24; revised version received 06.11.24; accepted 25.11.24; published 13.01.25.

Please cite as:
Chiang YT, Yu HY, Tsay PK, Chen CW, Chang CW, Hsu CL, Lo FS, Moons P
Effectiveness of the User-Centered "Healthcare CEO" App for Patients With Type 1 Diabetes Transitioning From Adolescence to Early Adulthood: Protocol for a Randomized Controlled Trial
JMIR Res Protoc 2025;14:e59871
URL: https://www.researchprotocols.org/2025/1/e59871
doi:10.2196/59871
PMID:

Protocol

Digital Health Intervention (SANGYAN Podcast) to Enhance Knowledge Related to COVID-19 and Other Health Conditions: Protocol for an Implementation and Evaluation Study

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Abstract

Background: Podcasts are an unconventional method of disseminating information through audio to the masses. They are an emerging portable technology and a valuable resource that provides unlimited access for promoting health among participants. Podcasts related to health care have been used as a source of medical education, but there is a dearth of studies on the use of podcasts as a source of health information. This study will provide new perspectives by implementing the SANGYAN podcast, which contains information about COVID-19 and other health conditions.

Objective: The study aims to determine the usefulness and effectiveness of the SANGYAN podcast as a digital health intervention to address misinformation related to COVID-19 and other health conditions among individuals in Chennai, Tamil Nadu, India.

Methods: An implementation and evaluation study will be conducted with 500 participants from the Panimalar Medical College Hospital & Research Institute (PMCHRI) and Rural Health Training Centre in Chennai. Among individuals aged 18 years and older, those residing in the selected urban and rural settings who visit the outpatient department of the PMCHRI and Rural Health Training Centre will be recruited. For participants who consent to the study, their sociodemographic details will be noted and their health literacy will be assessed using the Rapid Estimate of Adult Literacy in Medicine scale. Once the participants have listened to the podcast, the usability, acceptance, and user satisfaction of the podcast will be assessed. Descriptive analysis will be used for continuous variables, and frequency analysis will be used for categorical variables. Bivariate analysis will be conducted to understand the correlation of sociodemographic features in response to perception, usefulness, acceptance, and user satisfaction of the podcast. All analysis will be performed using SPSS (version 24), and the results will be reported with 95% CIs and $P<.05$.

Results: As of December 2024, the SANGYAN podcast has been launched for voluntary usage in the PMCHRI.

Conclusions: The finding from this research project will aid in the development and implementation of data-driven, evidence-based, and human-centered behavior change interventions using podcasts to address public health challenges among populations living in diverse settings. This would also help in enhancing the acceptability of podcasts as a source of health-related information.

International Registered Report Identifier (IRRID): DERR1-10.2196/41175

(JMIR Res Protoc 2025;14:e41175) doi:10.2196/41175

KEYWORDS

podcast; human-centered behavior; pandemic; coronavirus; intervention; digital health; usefulness; effectiveness; usability

Introduction

Background

The term "podcast," coined in 2004, is derived from the terms iPod and broadcast. It was chosen as the word of the year by the New Oxford American Dictionary in 2005 [1,2]. It is an unconventional means of distributing information to the general public via audio. Podcasting is a relatively new portable technology. It has established itself as a reliable channel for knowledge and information exchange. Podcasts are classified under Web 2.0 tools among other tools such as wikis and blogs, which comprise the latest generation of web-based collaboration [3]. Technology-enabled approaches to managing lifestyle have begun to emerge with the increased development and use of electronic media. Public health practitioners are now using mobile health technology to deliver health-related interventions [4]. However, there are hurdles to offering web-based interventions since they often need research participants to have a mobile phone, a certain level of education, and the capability of properly comprehending textual material [5]. The development of audio or video material for an audience that wants to listen to what they want, when they want, where they want, and how they want is the heart of podcasting [6].

India has reported a significant shift in the number of podcast users over the years. A report states that India holds the third-largest podcast user population after China and the United States, with over 57.6 million users [7]. Podcasting is becoming increasingly popular due to its ability to communicate health-related data and information for educational reasons [3]. Podcasting represents a largely untapped conduit for promoting health information to the general public with internet access and those who are not comfortable seeking face-to-face knowledge, treatment, and guidance. The COVID-19 pandemic played a significant role in increasing the consumption of podcasts by 29.3% in India [8]. Podcast use in entertainment, lifestyle, health, society, and culture is widespread according to a Spotify report. While in regard to health care [9-11], podcasts in India have seen increasing use in medical education and training, but not in other aspects of health care [12]. There is a dearth of research showing the use of podcasts to address misinformation, especially in an Indian context. A medium like a podcast provides screen-free alternatives even during the COVID-19 pandemic's restrictive environment. Podcasts are becoming increasingly popular among the younger population as a source of entertainment, self-improvement, and awareness.

Why Use a "Podcast" to Deliver Public Health Intervention?

According to user control theory, allowing flexibility boosts learning as compared to traditional instruction such as print. Podcasting may be more effective than the web because such a platform can decrease cognitive load [13]. Podcasts can encourage users' positive knowledge, attitude, and practice by allowing them to listen to the podcast anywhere, anytime. Podcasts promote knowledge dissemination by allowing podcast channel owners to communicate knowledge even when movement is restricted (eg, during a pandemic). The most prominent reason for the podcast boom is the connection between the host and listener. Podcast technology is a valuable resource that provides unlimited access for promoting health among participants. It also plays a significant role in public health and global health, where challenging and critical situations demand simple, effective, and concise information delivery. Numerous studies have examined the acceptability or feasibility of this modality for learning; however, limited studies have focused on podcast use for knowledge sharing [14]. Also, journals such as The *New England Journal of Medicine* [13] and *Lancet* [15] currently use podcasts to support medical and nonmedical information dissemination.

Need for the Study

The COVID-19 pandemic has shown that misinformation spread via social media and other digital platforms is a more significant threat to global public health than the virus itself [16]. Studies show that female individuals are more likely to accept misinformation than male individuals. A higher education level also decreases the possibility of accepting misinformation. Thus, older people with a higher level of education are less likely to accept misinformation [17,18].

This research will provide new perspectives through implementing the SANGYAN podcast, which contains information about the COVID-19 pandemic and other health conditions. The research project's findings will directly benefit individuals and researchers in developing tailored intervention models aimed at addressing misinformation.

Study Objectives

The study aims to determine the usefulness and effectiveness of the SANGYAN podcast as a digital health intervention to address misinformation related to COVID-19 and other health conditions among individuals in Chennai, Tamil Nadu, India.

Methods

Study Design and Population

An implementation and evaluation study will be conducted at the outpatient department of the Panimalar Medical College Hospital & Research Institute (PMCHRI) and Rural Health Training Center (RHTC) in Chennai. The participants will be recruited through convenience sampling in a paper-based format, by the researchers or trained data collection team from the RHTC and PMCHRI. A total of 500 individuals (250 each from the PMCHRI and RHTC) will be enrolled for the study. The data will be collected at a single time point by administering the study questionnaire to the eligible study participants. For participants who consent to the study, their sociodemographic details will be noted and their health literacy will be assessed

using the Rapid Estimate of Adult Literacy in Medicine (REALM) scale. Once the participants have listened to the podcast, the usability, acceptance, and user satisfaction will be assessed.

The eligible study participants will comprise individuals (1) aged 18 years and older, (2) residing in the selected urban and rural settings who visit the outpatient department of the PMCHRI and RHTC, and (3) consenting to participate in the study. Individuals with any mental or physical challenges that might affect their ability to participate in the study will be excluded.

Variable Assessment

Sociodemographic Profile

Sociodemographic data will be gathered, including participants' age, gender, income level, education level, employment status, occupation, region of residence, marital status, parenthood, and religion.

Health Literacy

The REALM scale is one of the most widely used tools to measure health literacy. Statistically, the REALM scale appears to provide a highly reliable data [19]. The study will use this scale as a screening instrument to assess an adult patient's ability to read common medical words. It is designed to assist medical professionals in identifying patients with poor literacy skills [20].

Use of Podcast or Other Mediums for Health Information

This measure will help us gather data on prior use of podcasts or other sources by participants to gather health data.

Usability

A Likert-scale System Usability Scale (SUS) survey will assess user acceptance. The SUS is a 10-item questionnaire with 5 response options, ranging from strong agreement to strong disagreement on a scale of 0 to 4, for each question. The total score will be calculated by adding the converted responses for each user and multiplying that total by 2.5. This will restore the range of possible values to 0-100 instead of 0-40 [21].

Client Satisfaction Questionnaire-8

The Client Satisfaction Questionnaire-8 (CSQ-8) is an 8-item measure of client satisfaction with services. The items for the CSQ-8 were selected on the following basis: ratings on information seeking by participants for a number of items that could be related to client satisfaction and a subsequent factor analysis. The CSQ-8 is unidimensional, yielding a homogenous estimate of general satisfaction with services [22].

SANGYAN Podcast

The SANGYAN podcast comprises audio content that will be delivered over a network via a free subscription.

The steps for developing the SANGYAN podcast are as follows: (1) file production, (2) podcast publication, (3) podcast delivery, and (4) podcast playback. File production involves planning, writing, recording and editing content, and file compression. Recording requires hardware like a recording microphone, and editing requires software like Audacity (The Audacity Team) and Premiere Adobe Pro (Adobe). The feed would be a simple XML file that lists the location of the podcast's COVID-19 episodes. The meta-tagging will have file information like the producer details, date of publication, title, and description of each episode. The RSS feed then will be posted to the web server of SMAART Rapid Tracker [23]. The podcast is hosted by the Foundation of Healthcare Technologies Society with a team of researchers that curate evidence-based content. Listeners will be able to subscribe, access, and download the podcast file.

Data Collection, Data Entry, and Quality Assurance

Data will be collected using a structured questionnaire. The questionnaire will be presented to the participants in the local Indian dialects to help increase the usefulness and generalizability of the study data. Data collection and data entry will be performed by a team of data collectors and data management personnel. To ensure efficiency and high-quality data collection and processing, the following data management protocol is in place: a clearly defined study manual, a well-trained team of data collectors, weekly meetings with the research team, weekly data checks, maintenance of study participants contacts, and data instrument logs.

Expected Outcomes

The proposed research study will help explore the usability and acceptability of a health-related podcast. Further, it will help evaluate the SANGYAN podcast's usability as well as satisfaction toward information delivery through a podcast. The results of the study will help design and develop a podcast platform that can deliver health educational information to facilitate podcast acceptance in varied settings. The expected study outcomes include the acceptability of using a digital health podcast to obtain tailored and evidence-based health information related to COVID-19 and other health conditions.

Data Analysis Plan

The gathered data will be presented in tables comprising the recorded characteristics of all variables. These tables will serve the purpose of data quality control to find inconsistencies in the data patterns and outliers or any missing data. Descriptive analysis will be conducted to report the means and SDs of the continuous variables (such as SUS scores), and frequency analysis will be conducted for the categorical variables (such as CSQ-8 scores and data on the use of podcasts and other mediums for health information). Bivariate analysis will be conducted to understand the correlation of sociodemographic features in response to perception, usefulness, acceptance, and user satisfaction of the podcast. All analysis will be performed using SPSS (version 24; IBM Corp), and the results will be reported with 95% CIs and $P<.05$.

Project Timeline and Milestones

A detailed study timeline is presented in Table 1.

Table 1. Project timeline and milestones.

Task	Month														
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Review of the literature, initial designing, and planning of the study	✓														
Development of study proposal and ethical approval	✓														
Approval of the study proposal	✓														
Development of survey items and the questionnaire	✓														
Review and revision of the questionnaire by the research team		✓													
Recruitment and training of the data collector team		✓													
Recruitment of the target sample		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		
Data analysis														✓	
Results write-up and preparation of the manuscript														✓	
Dissemination														✓	✓

Ethical Considerations

This study (protocol PMCHRI-IHEC-056) gained approval from the PMCHRI Institutional Human Ethics Committee (Central Drugs Standard Control Organization Registration ECR/1399/Inst/TN/2020) in February 2022, with approval PMCH&RI/IHEC/2021/078 (dated February 18, 2022).

The institutional review board–approved informed consent form will be administered by the research team to the eligible individuals for the study. The research team will explain the study, the time commitment necessary, and the advantages of the study results to participants. Those willing to participate and give their consent will be enrolled in the study. Written informed consent will be obtained in both English and local Indian dialects. The data gathered will be stored securely, ensuring data privacy and confidentiality. No compensation will be provided.

Dissemination

The study's findings will be disseminated through peer-reviewed publications and national and international conference presentations. Results will also be disseminated to the local community health leaders, state officials, and policy makers for data-driven, evidence-based, and informed decision-making.

Results

As of December 2024, the SANGYAN podcast has been launched for voluntary usage in the PMCHRI.

Discussion

Podcasts are rapidly being used as a tool for information distribution by a wide range of organizations and associations, including medical and dentistry schools, research institutes, and scientific journals. There is a need for robust strategies to boost podcast acceptability and provide community-specific information on misconceptions about public health concerns. The study would help assess the acceptability of podcasts as a source to obtain tailored and evidence-based health information.

The study findings will elucidate the association of the acceptance and usability of podcasts with various sociodemographic factors such as education level, gender, and occupation, for which there is a dearth of data in the Indian context. The findings will also provide insight into people's awareness of podcasts and other digital sources of health information prior to the study.

The rollout of the protocol may see some limitations, in that it is a one-time implementation of the SANGYAN podcast and adherence is not assessed. Another limitation could be in its implementation within a limited geographical setting; thus, future studies regarding the usability, acceptance, and adherence can be carried out at a larger scale across various states in India.

Studying the spread of misinformation (or infodemics) in India remains critical considering the booming use of social media in the wake of the COVID-19 pandemic. India, along with 132 member states of the United Nations, has endorsed fighting infodemics especially during COVID-19 [24]. This study relevant to this endorsement, as the study findings will contribute to the development and implementation of data-driven, evidence-based, and human-centered behavior change interventions using podcasts to address public health challenges among populations living in diverse settings. Further, this study would aim to expand the use of the SANGYAN podcast as source of evidence-based health information for the public.

Data Availability

The data supporting this study's findings are available on request from the corresponding author.

Authors' Contributions

All authors have contributed to the study's design, development of the questionnaire, and preparation of the manuscript and have approved the manuscript for publication.

Conflicts of Interest

None declared.

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Abbreviations

CSQ-8: Client Satisfaction Questionnaire-8
PMCHRI: Panimalar Medical College Hospital & Research Institute
REALM: Rapid Estimate of Adult Literacy in Medicine
RHTC: Rural Health Training Centre
SUS: System Usability Scale

Edited by A Mavragani; submitted 18.07.22; peer-reviewed by J Griffith, W Evans; comments to author 01.02.23; revised version received 21.02.23; accepted 22.02.23; published 20.01.25.

Please cite as:
Joshi A, Mohan SK, Pandya AK, Grover A, Saggu SR, Revathi SK, Sharma S
Digital Health Intervention (SANGYAN Podcast) to Enhance Knowledge Related to COVID-19 and Other Health Conditions: Protocol for an Implementation and Evaluation Study
JMIR Res Protoc 2025;14:e41175
URL: https://www.researchprotocols.org/2025/1/e41175
doi:10.2196/41175
PMID:

Protocol

LoVE4MUM Mobile App to Prevent Postpartum Depression: Protocol for a Pilot Randomized Controlled Trial

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Abstract

Background: Postpartum depression remains a significant concern, posing substantial challenges to maternal well-being, infant health, and the mother-infant bond, particularly in the face of barriers to traditional support and interventions. Previous studies have shown that mobile health (mHealth) interventions offer an accessible means to facilitate early detection and management of mental health issues while at the same time promoting preventive care.

Objective: This study aims to evaluate the effectiveness of the Leveraging on Virtual Engagement for Maternal Understanding & Mood-enhancement (LoVE4MUM) mobile app, which was developed based on the principles of cognitive behavioral therapy and psychoeducation and serves as an intervention to prevent postpartum depression.

Methods: This single-blinded, pilot randomized controlled trial includes 64 mothers recruited from the postnatal ward and randomized using a 1:1 ratio to receive either postpartum care (treatment as usual) or postpartum care (treatment as usual) plus the self-guided LoVE4MUM mobile app. The primary outcome is the effectiveness of the mobile app at improving postpartum depression. Secondary outcomes are changes in the mental health literacy score and negative automatic thoughts, which are collected using a self-reported questionnaire.

Results: Patient recruitment began on September 1, 2024. As of January 1, 2025, recruitment was successfully completed, with a total of 72 participants enrolled: 36 in the intervention group and 36 in the control group . The final results are anticipated to be available by March 2025, and publication is expected by the end of 2025.

Conclusions: By examining the LoVE4MUM app alongside standard postpartum care, this pilot randomized controlled trial seeks to offer preliminary evidence on the potential of mHealth tools to improve maternal mental health as well as to reduce postpartum depression symptoms. The findings are expected to contribute to the future development of effective, accessible, and scalable interventions for mothers.

Trial Registration: ClinicalTrials.gov NCT06366035; https://clinicaltrials.gov/study/NCT06366035

International Registered Report Identifier (IRRID): PRR1-10.2196/63564

(JMIR Res Protoc 2025;14:e63564) doi:10.2196/63564

KEYWORDS

postpartum depression; mHealth intervention; mobile phone; prevention; self-guided; virtual engagement; engagement; maternal; protocol; randomized controlled trial; postpartum; depression; maternal; well-being; mobile health; preventive care; mobile app; mental health literacy; postpartum care

Introduction

The global pooled prevalence of postpartum depression (PPD) was as high as 34% in a recent systematic review [1]. In Malaysia, the National Morbidity and Health Survey 2022 reported that 11.2% of mothers had depression [2] and an alarming 90% were unaware of their symptoms. Moreover, PPD results in detrimental consequences not only for the mother but also for the baby and their future bonding and relationship [3,4].

Meeting the increasing demand for mental health care is particularly challenging. These challenges encompass issues such as a lack of privacy, limited access to mental health experts, insufficient knowledge, and cultural stigma [5-8]. Consequently, mothers do not receive the necessary assistance that they require [5]. Mobile health (mHealth), a component of eHealth [9], has emerged as a crucial means to provide accessible health care solutions, especially with the advent of technologies like smartphones, web-based platforms, and text messaging [10,11]. These tools have become helpful for offering health care services and making health care more flexible, private, and readily available. This is particularly relevant in countries with high mobile internet penetration rates, such as Malaysia where rates of mobile internet coverage reached 128% in 2021 [12].

Interventions for depression range from pharmacotherapy to psychotherapy as well as lifestyle modifications [13]. Over the years, service delivery has evolved with the use of smartphone apps, web-based applications, and text messaging services to deliver therapeutic content [14,15]. Psychotherapies such as cognitive behavioral therapy (CBT) [16-18], mindfulness [19], and psychoeducation [20,21] using these technologies have previously been reported. A systematic review found that mHealth interventions can significantly improve depressive symptoms, highlighting their potential as accessible and cost-effective treatment options [22]. Additionally, more recent reviews concurred that mHealth interventions can effectively reduce PPD, as evidenced by improvements in Edinburgh Postnatal Depression Scale (EPDS) scores among these mothers [23,24].

Women in the perinatal period are less likely to seek help for mental health issues than women at other life stages due to lower postpartum mental health literacy [25]. Mental health literacy has evolved from being defined merely as knowledge and beliefs about mental disorders to attitudes toward these disorders and efficacy in seeking help [26,27]. Kutcher et al [27] highlighted that poor mental health literacy leads to underutilization of mental health services, noting the critical role of help-seeking attitudes. mHealth platforms can boost mental health literacy by offering resources that heighten awareness of mental health issues, treatments, and self-care. For example, Chan et al [28] showed that mHealth is effective at enhancing mental health knowledge, attitudes, and behaviors, thus bridging the educational gap and reducing stigma. A systematic review emphasized the need for interventions to improve mental health literacy among perinatal women, due to a widespread lack of awareness about PPD symptoms, hesitance toward seeking professional help, a preference for informal support, and numerous other obstacles to accessing care, which are further compounded by marked stigma surrounding mental health issues [29].

Within the CBT framework, our thought processes are usually framed by our beliefs, which have a profound impact on how we feel and act in response to life's challenges [30]. Past experiences shape beliefs that can distort interpretations of events, leading to emotional disorders. In stress-triggering situations like the postpartum period, these beliefs trigger automatic negative thoughts and worsen depressive symptoms, underscoring the need to target these thoughts through depression management. By altering negative thought processes and maladaptive behaviors into more positive emotional outcomes, CBT offers improvements for depression management [31,32]. In addition, digital interventions, including exercises, thought diaries, and educational materials, facilitate the identification, confrontation, and modification of these negative cognitive patterns. A study demonstrated that smartphone-based CBT interventions could significantly reduce negative automatic thoughts and improve cognitive restructuring skills for users [33]. Mental health experts also advocate for short-term preventive CBT interventions, tailored for perinatal concerns, as a robust therapeutic strategy [34-36].

CBT's traditional reliance on mental health professionals is challenged by cost and availability barriers. Due to health care personnel limitations, Mohammad-Alizadeh-Charandabi et al [37] highlighted the shortcomings of midwife-led phone interventions due to inconsistent quality and time constraints. In contrast, Niksalehi et al [38] effectively deployed structured automatic text messages with optional phone support, significantly enhancing depression scores and showcasing the potential of accessible, self-guided support. Complementing this, Carona et al [39] introduced a low-intensity, self-guided CBT program as an effective firstline intervention to help perinatal women, resulting in more improved depression scores in the intervention group than in the control group. Another study that used internet-based CBT [40] reported significant differences between the intervention and control groups.

It is noteworthy that the majority of studies on mHealth interventions were conducted in urban and academic settings in high-income countries [14]. Therefore, the generalizability of the outcomes is limited to the local population and might not apply to other settings such as Malaysia, which has a diverse cultural and religious background. Furthermore, these technologies frequently lack a user-centered design [41] and are primarily developed in western countries, which impacts their adaptability and sustainability in local contexts [14]. To culturally tailor appropriate mHealth interventions, meticulous development is required, engaging not only health care professionals to shape evidence-informed intervention priorities but also patients to enhance the effectiveness and widespread adoption of these interventions [42].

Initiatives in Malaysia include the TIARA MURNI project [43], which involves health care workers for its delivery. However, there is a notable absence of self-guided mental care solutions for mothers during the postpartum period especially in the Asian setting. This highlights an opportunity to improve mental health care access especially in areas with limited resources [38,44,45].

This study protocol intends to assess a user-centered, self-guided mental health app and compare it with standard postpartum care. It aims to determine the app's preliminary effectiveness at improving depression and mental health literacy and addressing negative thoughts among mothers in the postpartum period.

Methods

Type and Design

This study is a single-blind, pilot randomized controlled trial with participants randomized using a 1:1 ratio.

Study Location

The study includes postpartum mothers located in the postnatal ward of tertiary hospitals in the Selangor state of Malaysia. According to the Department of Statistics Malaysia, Selangor has the highest birth rate in the country, with a total of 95,211 live births in 2019 [46]. The National Morbidity and Health Survey 2022 survey indicated that urban mothers have a higher risk of depression. Considering Selangor's birth statistics and status as a highly urbanized state, we considered it to be the ideal location for our research. We selected 2 hospitals from urban locations using a computerized random number generator.

Ethics Approval and Ethical Considerations

Approval to conduct the study was obtained from the Medical Research and Ethics Committee, Ministry of Health Malays (ref number 24-00924-HPO, dated April 04, 2024). Written informed consent was obtained from all participants prior to their involvement in the study. Participants are fully informed of their right to opt out at any time without any consequences. All participant data are anonymized to ensure privacy and confidentiality. No identifiable information is collected nor stored during the study. Protective measures, including secure data storage, were implemented to safeguard participant information. Participants are compensated MYR 10 (US $2.15) for each questionnaire returned, to acknowledge their time and effort. Participation is entirely voluntary, without any form of coercion.

Recruitment

Mothers were recruited from the obstetric wards by the investigators. Mothers received comprehensive information about the study, including its aims, procedures, risks, and benefits. Sufficient time was given to ensure informed consent was obtained in the ward. Those agreeing to participate were enrolled in the pilot randomized controlled trial, and reasons for refusal were documented.

Patients were screened for eligibility based on the study criteria. Mothers (1) scoring between 9 and 11 on the EPDS, (2) who had access to a smartphone, (3) who possessed home wireless internet or could access internet connectivity, (4) who planned to continue routine postpartum care in the government primary health facility, and (5) who were literate in both English and Malay were included in the study. Mothers (1) with a history of drug abuse; (2) who had been diagnosed with depressive illness in the current pregnancy; (3) who were undergoing treatment for depression, bipolar disorder, or any other psychiatric disease at the time of participation; and (5) whose infant experienced intrauterine death or death immediately after birth were excluded from the study.

Randomization and Blinding

Participants were randomized (1:1) into 2 groups (ie, intervention and control groups). The researchers were blinded to the randomization process. Randomization was conducted by an independent assistant using a prearranged sealed opaque envelope. The envelopes contained a QR code linking to either a mobile app (the intervention group) or a WhatsApp communication channel (the control group). Both groups continue to receive treatment as usual (TAU) postpartum care.

Intervention Group

The intervention group receives TAU postpartum care and the Leveraging on Virtual Engagement for Maternal Understanding & Mood-enhancement (LoVE4MUM) mobile app intervention.

The LoVE4MUM app represents an innovative self-guided approach to postpartum mental health care and offers a comprehensive, tailored intervention for maternal mental health during the postpartum period. It is available in English and the local Malay language. It was developed using a prior rigorous research process that included in-depth interviews with mothers who had symptoms of PPD and guidance from a multidisciplinary expert panel including clinical psychologists, psychiatrists, obstetricians, family health specialists, public health specialists, and epidemiologists with further input from previous literature [13,47-50]. This app-based intervention is grounded in psychoeducation, intrapersonal therapy, and CBT principles.

The app was validated by a panel of 4 experts. The content underwent detailed item-by-item validation to ensure its relevancy and clarity. In this face validation process, the majority of the items garnered unanimous approval, which was reflected in a content validity index and kappa coefficient of 1.00. Nevertheless, items 12 and 16 had content validity index and kappa scores <0.7, necessitating their revision to enhance relevancy within the module content. Additionally, item 18 was modified to provide better clarity. The expert panel reviewed the revisions and subsequently approved the finalized module. See Multimedia Appendix 1 for details of the validation process.

A linguistic expert translated the content into the Malay language to ensure that it was culturally and contextually appropriate. The app was developed on a self-developed website platform using a mobile phone interface. Snippets of the mobile app are available in Multimedia Appendix 2 and Multimedia Appendix 3.

The app is structured around 5 main modules that provide flexible and accessible support over a 6-week period. It does not require sequential module completion and allows for personalized pacing. Each module targets critical aspects of postpartum mental well-being and is delivered in several formats including video, infographics, notes, and worksheets. Each module takes approximately 20 minutes to 30 minutes to complete. Automated reminders incorporated into the app and

linked to users' emails encourage regular user engagement with app. The modules are described in Table 1.

Table 1.

Module	Module description	Skills learned	Worksheet
Module 1: Learn to Love Yourself	This module emphasizes self-care, establishing goals, and navigating social comparisons while addressing typical challenges like managing expectations, hospital admissions, and handling baby feeding and care. It aims to empower mothers to prioritize their well-being.	Self-care practices, goal formulation, effective communication for seeking help, and strategies for tackling common issues	Setting goals and listing things you love
Module 2: Understanding Postpartum Depression	This module offers foundational knowledge about postpartum depression, aiming to increase awareness and reduce stigma.	Identifying postpartum depression, seeking help, treatment options, and assertive communication with partners and family	—[a]
Module 3: Addressing Unhelpful Thinking	This module integrates cognitive behavioral therapy (CBT) concepts, guiding mothers to recognize and question negative thinking and understand how thoughts influence behaviors.	Identifying unhelpful thinking habits and mechanisms to improve thought patterns	Encourages describing specific situations and working on improving the associated thoughts
Module 4: Mood Tracker	This module engages mothers in monitoring their mood and provides strategies for mood improvement.	Identifying emotions, identifying healthier responses, and learning how to perform deep breathing	—
Module 5: I Need Help Now	This module guides users in accessing immediate calming techniques, help, and essential information for assertive communication with health care providers.	Calm breathing, communication with health providers, and information on seeking help	—

[a]Not applicable.

All data in the mobile app are stored in a password-protected, secured data cloud handled by the app developer. To register to use the app, participants must create a password that is requested after every time they sign in. Only administrative personnel have access to the encrypted password data.

Control Group

Both groups receive TAU postpartum care during the study. According to The Malaysian Perinatal Care Manual (fourth edition), at least 5 postnatal home visits and 1 clinic visit are conducted for normal cases, and the frequency increases for high-risk mothers and babies [51,52]. Routine postnatal care services include lactation consultation in the ward and postnatal visits by health care workers at home. Each postnatal check should assess the mother's overall, psychological, and emotional health, asking about any concerns, and evaluate the baby's well-being, feeding, and development to promptly identify any issues [53]. Participants are advised that they are free to withdraw from the study at any point for any reason.

Measurements

The study uses a questionnaire delivered online (Google form) and divided into 3 outcome measurement tools.

Primary Outcome Measurement

The EPDS is a 10-item questionnaire extensively used to assess postnatal depression in both international and local contexts. It uses a 4-point Likert scale for responses, with higher scores indicating greater depressive symptoms. The scale has been translated into the Malay language [54], where a score of 11.5 was the optimum cut-off for 72.7% sensitivity, 95% specificity, and a positive predictive value of 80%. In our study, participants with an EPDS score ≥12 are categorized as having postpartum depressive symptoms.

Secondary Outcome Measurements

Postpartum Depression Literacy Scale (PoDLiS)

The Postpartum Depression Literacy Scale (PoDLiS) is a 31-item, self-administered questionnaire developed by Mirsalimi et al [55] to assess the understanding of PPD. It evaluates 7 attributes of PPD literacy, including recognition, knowledge of risk factors and causes, self-care activities, available professional help, attitudes toward recognition and help-seeking, and information sources. Responses are scored on a 5-point scale, with attribute scores calculated by averaging related item scores. The Malay version of PoDLiS has acceptable reliability, with a Cronbach α of 0.73.

Automatic Thought Questionnaire (ATQ)

The Automatic Thought Questionnaire (ATQ), which is available in the Malay language [56], assesses the frequency of negative automatic thoughts linked to depression and anxiety. This 17-item scale asks respondents to rate the occurrence of specific negative thoughts over the past week on a scale from 1 to 5. Higher total scores indicate more frequent negative thinking. The scale's internal consistency ranges from 0.83 to 0.93 [56]. The total score ranges from 17 to 85, with a higher score reflecting a higher frequency of negative thinking.

Data are conducted at baseline, 1 week postpartum, and 6 weeks postpartum using the Google form, which is delivered via either the mobile app or a Whatsapp number. The self-reported survey takes approximately 15 minutes to 20 minutes to complete. All answers are automatically storied in the Google drive, and only

the research team has access to the data. The schedule of enrollment, interventions, and assessments is summarized in Multimedia Appendix 4 and Multimedia Appendix 5.

Sample Size

Based on the recommendations of Whitehead et al [57], for a pilot trial with 90% power and a 2-sided significance level of 5%, the suggested sample size per treatment arm based on previous literature with a medium effect size (0.43) [58] is 25. Hence, a total of 72 participants (36 participants per arm) was required after taking into consideration a 30% nonresponse rate.

Statistical Analysis

Data will be analyzed using SPSS version 26, and significance is set at $P<.05$. Intention-to-treat analysis will be used. Categorical variables will be presented as the frequency and percent values, while continuous data will be presented as mean (SD). Baseline between-group comparisons will be conducted using Pearson chi square and Fisher exact tests for categorical data. Meanwhile, independent *t* tests will be used for continuous data. Repeated measures ANOVA will be used for within-group (time effect) and between-group (treatment effect) comparisons at 6 weeks. The mean difference and its corresponding 95% CI will be reported, with the significant level set at $P<.05$.

Risk Management

All participants were informed that the intervention serves as a supplementary self-help program and does not replace professional health care services. They are strongly encouraged to seek advice from their doctors or general practitioners regarding any concerns related to their mental or general health. Participants who experience symptoms of depression during the pilot trial are urged to promptly consult health care professionals and inform the research team of their condition. These measures allow for the appropriate management of any adverse effects and ensure the well-being of participants throughout the study.

For those screened and found ineligible for the trial, comprehensive support information was provided through a brochure containing information on PPD, immediate assistance, and emergency contact details. These individuals are also advised to consult their health care providers if they have concerns about their mental health. Specifically, mothers with an EPDS score ≥12 were excluded and referred to specialists for further evaluation and intervention in line with the Malaysian guideline for managing PPD.

Moreover, all participants continue to receive postpartum care by attending health care professionals at the Malaysia's Ministry of Health facilities, with care adhering to the standards set forth in the Perinatal Care Manual (fourth edition) [51].

Results

Participant recruitment began on September 1, 2024. As of January 1, 2025, recruitment was complete, resulting in a total of 72 participants enrolled: 36 in the intervention group and 36 in the control group. Data analysis and results are anticipated to be available by March 2025. The trial results are expected to be published by the end of 2025.

Discussion

Overview

PPD is influenced by a combination of intrapersonal, environmental, and physical factors that necessitates multifaceted interventions. The LoVE4MUM app represents a potential intervention for PPD prevention and uses an innovative approach that integrates the complexity of PPD with the unique cultural and societal contexts of Malaysia. The app combines psychosocial interventions, including CBT components, to address negative automatic thoughts and improve mental health literacy through engaging, educational content. The authors anticipate that participants receiving the LoVE4MUM app will demonstrate improvements in depressive symptoms, as measured by EPDS, compared with those receiving only standard postpartum care. Previous studies highlight the potential of mobile apps to improve mental health in perinatal populations [59]. Several reviews on mHealth interventions have revealed significant reductions in EPDS scores among postpartum mothers using mobile apps [23,60-62]. The LoVE4MUM app is designed to provide culturally relevant content. It also considers the barriers postpartum mothers in Malaysia face, such as limited access to face-to-face care and social stigma surrounding mental health.

The COVID-19 pandemic amplified the global prevalence of PPD, with rates within middle-income countries increasing from 20.8% before the pandemic to 34% during the pandemic [1,63] . This surge emphasizes the urgent need for remote health care solutions. The LoVE4MUM app leverages this shift by offering a self-guided platform that empowers mothers to engage in self-care from the convenience of their smartphones, circumventing the limitations of in-person care.

Lin et al [64] demonstrated that digital interventions promoting psychological empowerment and hedonic well-being are effective at driving these behavioral changes. In line with these findings, the LoVE4MM app encourages mothers to engage in activities that enhance their well-being while offering tools for cognitive restructuring. This approach is particularly crucial in a cultural context like Malaysia, where mental health stigma may prevent mothers from seeking professional therapy. Compared with the control group, we expect that mothers using the app will have improved EPDS scores; better scores for mental health literacy, as measured by the PoDLiS tool; and reductions in automatic negative thoughts.

Additionally, mHealth interventions alleviate depressive symptoms by improving social support [65,66]. Enhancing environmental support through assertive communication enables mothers to seek effective help from spouses and family members, reducing stress and improving mental health [67-69]. Similar to the CareMom app, which demonstrated a significant reduction in depressive symptoms through communication exercises, assertive requests within the CBT framework in the LoVE4MUM app are expected to improve emotional well-being during the postpartum period [70].

Anto et al [71] and Hartnup et al [72] showed that postpartum mothers often experience social risk and pressure through social

media, which can exacerbate stress by promoting unrealistic comparisons and idealized identities of motherhood. Many mothers feel pressured to project a “perfect” image, leading to feelings of inadequacy and increased mental strain. By addressing these concerns, the LoVE4MUM app emphasizes the importance of self-compassion and reinforces a supportive, nonjudgmental digital environment, encouraging mothers to focus on doing their best rather than striving for perfection, which is crucial for improving mental well-being in this vulnerable period.

The strength of this pilot trial lies in its integration of validated measurement tools—EPDS, PoDLIiS, and ATQ—which offer a comprehensive view of maternal mental health. We expect the LoVE4MUM app's CBT-based interventions to demonstrate the success seen in similar applications, such as the CareMom, MumMoodBoster, Sunnyside, and Mother and Babies Course apps, which have successfully used structured exercises and personalized feedback to reduce depressive symptoms [18,70,73-76].

Nevertheless, certain challenges remain. First, the reliance on self-reported measures may introduce bias, as participants may underreport symptoms due to stigma or discomfort. Second, as demonstrated with other mHealth interventions like the Happy Mother app, user engagement can be inconsistent, and low adherence rates may diminish the overall effectiveness of the intervention[77]. To address this, the LoVE4MUM app incorporates strategies to enhance user engagement, such as push notifications, scripts, and personalized feedback. Another critical aspect to consider is the influence of cultural factors on app engagement and perception, which may affect how Malaysian mothers interact with the app. Ensuring that the app’s content is culturally sensitive and tackles common misconceptions about PPD will be essential in maximizing its impact. Moreover, as a pilot trial, the sample size may not allow for definitive conclusions, and the study’s findings should be interpreted as preliminary evidence of the app's potential.

Conclusion

The LoVE4MUM app represents a promising, scalable solution to address PPD among Malaysian mothers. If successful, this app could serve as a model for culturally adapted digital interventions that empower mothers to manage their mental health, ultimately reducing the prevalence and impact of PPD. Future studies will be necessary to further refine the app’s features and evaluate its long-term impact on maternal mental health outcomes.

Acknowledgments

The authors would like to express gratitude for the support of the Department of Public Health Medicine, Faculty of Medicine University Kebangsaan Malaya and the Director General of Health Ministry of Malaysia for the approval for the publication of this manuscript.

Data Availability

The data sets generated or analyzed during this study are available from the corresponding author on reasonable request.

Authors' Contributions

SSK, IBI, SS, and NA contributed to the conception, design, and methods. SSK and IBI drafted the manuscript. IBI, SS, and NA provided study supervision and critically revised the paper. All authors revised and approved the final version of the manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Expert validation of LoVE4MUM module content.
[PNG File , 302 KB - resprot_v14i1e63564_app1.png]

Multimedia Appendix 2
Snippets from LoVE4MUM mobile app login interface.
[PNG File , 460 KB - resprot_v14i1e63564_app2.png]

Multimedia Appendix 3
Snippets from LoVE4MUM mobile app module Postpartum Depression.
[PNG File , 795 KB - resprot_v14i1e63564_app3.png]

Multimedia Appendix 4
Patient visit schedule.
[PNG File , 25 KB - resprot_v14i1e63564_app4.png]

Multimedia Appendix 5
Consolidated standard of reporting trials flow diagram of the LoVE4MUM pilot trial.
[PNG File , 130 KB - resprot_v14i1e63564_app5.png]

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Abbreviations

ATQ: Automatic Thought Questionnaire
CBT: cognitive behavioral therapy
EPDS: Edinburgh Postpartum Depression Scale
LoVE4MUM: Leveraging on Virtual Engagement for Maternal Understanding & Mood-enhancement
mHealth: mobile health
PoDLiS: Postpartum Depression Literacy Scale
PPD: postpartum depression
TAU: treatment as usual

Edited by A Schwartz; submitted 24.06.24; peer-reviewed by A Eisingerich; comments to author 06.09.24; revised version received 05.10.24; accepted 12.12.24; published 27.01.25.

Please cite as:
Kamarudin SS, Idris IB, Sharip S, Ahmad N
LoVE4MUM Mobile App to Prevent Postpartum Depression: Protocol for a Pilot Randomized Controlled Trial
JMIR Res Protoc 2025;14:e63564
URL: https://www.researchprotocols.org/2025/1/e63564
doi:10.2196/63564
PMID:

Protocol

Increasing Access to Mental Health Supports for 18- to 25-Year-Old Indigenous Youth With the JoyPop Mobile Mental Health App: Study Protocol for a Randomized Controlled Trial

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Abstract

Background: Transitional-aged youth have a high burden of mental health difficulties in Canada, with Indigenous youth, in particular, experiencing additional circumstances that challenge their well-being. Mobile health (mHealth) approaches hold promise for supporting individuals in areas with less access to services such as Northern Ontario.

Objective: The primary objective of this study is to evaluate the effectiveness of the JoyPop app in increasing emotion regulation skills for Indigenous transitional-aged youth (aged 18-25 years) on a waitlist for mental health services when compared with usual practice (UP). The secondary objectives are to (1) evaluate the impact of the app on general mental health symptoms and treatment readiness and (2) evaluate whether using the app is associated with a reduction in the use (and therefore cost) of other services while one is waiting for mental health services.

Methods: The study is a pragmatic, parallel-arm randomized controlled superiority trial design spanning a 4-week period. All participants will receive UP, which involves waitlist monitoring practices at the study site, which includes regular check-in phone calls to obtain any updates regarding functioning. Participants will be allocated to the intervention (JoyPop+UP) or control (UP) condition in a 1:1 ratio using stratified block randomization. Participants will complete self-report measures of emotion regulation (primary outcome), mental health, treatment readiness, and service use during 3 assessments (baseline, second [after 2 weeks], and third [after 4 weeks]). Descriptive statistics pertaining to baseline variables and app usage will be reported. Linear mixed modeling will be used to analyze change in outcomes over time as a function of condition assignment, while a cost-consequence analysis will be used to evaluate the association between app use and service use.

Results: Recruitment began September 1, 2023, and is ongoing. In total, 2 participants have completed the study.

Conclusions: This study will assess whether the JoyPop app is effective for Indigenous transitional-aged youth on a waitlist for mental health services. Positive findings may support the integration of the app into mental health services as a waitlist management tool.

Trial Registration: ClinicalTrials.gov NCT05991154; https://clinicaltrials.gov/study/NCT05991154

International Registered Report Identifier (IRRID): DERR1-10.2196/64745

(JMIR Res Protoc 2025;14:e64745) doi:10.2196/64745

KEYWORDS

mental health; youth; Indigenous; First Nations; eHealth; mHealth; JoyPop; protocol; mobile mental health app; mobile app; Canada; mobile health; emotion regulation

Introduction

Background

Transitional-aged youth refer to individuals aged roughly 15-26 years who are transitioning from childhood to adulthood, a time of developing independence and increased challenges [1]. In Canada, mental health difficulties among transitional-aged youth have increased across the past decade and during the COVID-19 pandemic [2,3]. Indigenous individuals within this age range experience a greater burden of mental health difficulties compared to their non-Indigenous peers [4,5], partly attributed to distal factors such as a family history of residential school attendance [6] and more proximal factors such as experiences of childhood adversity [7]. Stressors such as substance use, loss of culture, racism, socioeconomic status, and family instability also impact the well-being and mental health of Indigenous youth [8].

Mental health services are less accessible for youth living in remote and rural locations [9]. For instance, there is less use of outpatient-based mental health care and psychiatry services and higher rates of emergency department visits and hospital admissions for mental health-related reasons in Northern Ontario, a region of many different Indigenous communities [10]. In general, long wait times in Northern Ontario are similar to those experienced in other regions of the province [10]; however, wait times for counseling and therapy are particularly long in Thunder Bay compared to many other communities, with an average of 348 days [11]. Services that consider and incorporate culture are even more sparse. Long wait times for services not only delay care and contribute to prolonged distress and suffering but also affect interest and engagement in services once they are offered [12,13].

Mobile health (mHealth) innovations can increase access to mental health support. Specifically, smartphone apps can be an effective medium for improving mental health symptoms and quality of life [14,15] and for youth specifically [16]. Knowledge gaps exist, however, with respect to app effectiveness for those on a waitlist for services and for Indigenous youth. For instance, a recent review of waitlist interventions for youth did not include any app-based interventions [17]. Further, until recently, app evaluation studies seldom included Indigenous youth in the evaluations [18]. A review published in 2024 highlights several initial evaluations of apps with Indigenous youth that were focused on a variety of health-related outcomes, with a few of these focused on general mental health or coping and well-being [19]. Most of this research has been conducted with Indigenous populations outside of Canada, whose cultural values related to well-being may differ [20]. While there are apps geared toward Indigenous populations in Canada [21], they have not been evaluated among treatment-seeking youth, and some are primarily informational in nature or used for data collection only [22,23]. More research is needed to test the effectiveness of apps for addressing mental health among Indigenous youth [24].

In collaboration with an Indigenous-led agency informed by Anishinabek culture and located in Northern Ontario (Dilico Anishinabek Family Care; Dilico), in this study, the JoyPop app will be evaluated as a tool for supporting the mental health needs of Indigenous youth currently waiting for mental health services. The app was developed by researchers in collaboration with youth and service providers [25], and input from these stakeholders continues to inform its implementation and evaluation [26,27]. The app was designed to promote resilience to stress and adversity [25], targeting emotion regulation as part of this goal since it is linked to strengthening resilience [28]. Rather than targeting specific mental health diagnoses, focusing on emotion regulation is also in line with recommendations that apps target “transdiagnostic factors” to make the best use of resources [24], since difficulty with emotion regulation is common among different mental health concerns [29,30]. To accomplish this goal, app features include a mood rating feature to promote emotional awareness [31], breathing exercises to help with relaxation [32], relaxing sounds to help with sleep [33], a game and art feature helpful for distracting oneself from stressful situations [34,35], a journal focused on positive topics to promote well-being [36], and connection to one’s support network and professional helplines, if needed [37].

An initial evaluation of the JoyPop app showed that app use was associated with improvements in emotion regulation and depressive symptoms for transitional-aged youth starting university [38], who shared that they valued the opportunity to build awareness and regulation of emotions [39]. Another study conducted with an Indigenous community in Southern Ontario identified the potential utility of the app for youth in the community while also gathering knowledge on how cultural values were connected to the app features [26,27]. Prior to developing the current protocol, a pilot study was also conducted with Dilico and another local organization, in which youth identified benefits of using the app related to coping and mental health [40]. Service providers also expressed positive feelings about the app’s ease of use and how the app could be helpful for youth who are on the waitlist for services (eg, by increasing their comfort levels before services begin) [40].

In sum, it is important to identify beneficial transdiagnostic mental health supports for Indigenous transitional-aged youth in Northern Ontario. Considering past findings with the JoyPop app have been promising [26,27,38-40], a larger scale randomized controlled trial is warranted to more robustly evaluate its effectiveness. Providing this intervention while youth are on a waitlist for services may help reduce disengagement and the need to seek other services during this time.

Objectives

The objectives of the study are in response to the goals and needs identified by the community partner, Dilico. Specifically, the primary objective is to determine the effectiveness of the JoyPop app compared to usual practice (UP) in improving emotion regulation among Indigenous transitional-aged youth (aged 18-25 years) who are awaiting mental health services. We hypothesize that youth receiving the app will show improvement in emotion regulation (small to medium effect) greater than that observed for youth receiving only UP.

The secondary objectives are to (1) compare change in mental health difficulties and treatment readiness between youth in each condition to better understand the app's broader impact as a waitlist tool and (2) conduct an economic analysis to determine whether using the app while waiting for mental health services reduces other health service use and associated costs.

Methods

Overview of Study Design

This protocol was developed in collaboration with Dilico management and frontline staff to answer research questions of importance to the organization and the youth they serve. It was designed according to the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) statement [41] (see Multimedia Appendix 1 for completed checklist). A pragmatic, parallel-arm randomized controlled superiority trial design will be used. Participants will be randomly assigned to the control (UP) or intervention (UP+JoyPop) condition in a 1:1 ratio using stratified block randomization. UP will involve waitlist monitoring practices at the study site, which include regular check-in phone calls to obtain any updates regarding functioning. In addition to UP, participants allocated to the intervention condition will receive the JoyPop app for 4 weeks and be asked to use it at least twice daily. Outcome measures will be administered to participants in both conditions during 3 assessments (first [baseline], second [after 2 weeks], and third [after 4 weeks]).

Setting and Participants

Data collection will take place at Dilico Anishinabek Family Care, an Indigenous-led organization that provides culturally informed child welfare, mental health and addictions, and health services to Anishinabek children and adults. Programs and services are provided at individual, family, and community levels. This self-governed organization is situated in Fort William First Nation in Northern Ontario.

Youth will be informed about the study by waitlist case managers and with flyers and letters mailed and emailed to them. Youth will be eligible for trial participation if they are on the waitlist for mental health services at Dilico and between the ages of 18-25 years.

Study Procedure

Table 1 describes participant progression through the study. A research assistant will contact interested youth by phone, text, or email to provide a brief description of the study. If a youth is interested and meets eligibility criteria, the research assistant will schedule their study orientation (as part of the baseline assessment). The research assistant will obtain informed consent during this orientation. As part of the informed consent process, youth will be made aware of local support services they can access should they experience distress during the study. They will also be made aware of the possibility that they are assigned to the control group so that they can make an informed decision about participation in light of this possibility.

Table 1. Participant timeline.

	–1	T1	T2	T3
Activity/assessment	Pre-study screening	Orientation/baseline assessment	2 Weeks/second assessment	4 Weeks/third assessment
Eligibility screen	✓			
Informed consent and condition allocation		✓		
Intervention (UP+JoyPop; or UP only)				
Outcomes measured: emotion regulation, mental health, treatment readiness, and service usage		✓	✓	✓
Outcome measured: app quality				✓—intervention group only
Control group participants given access to app				✓

Following consent, participants will complete the baseline assessment measures. They will be encouraged to respond as honestly and accurately as possible and not how they think researchers might want them to. Any participant that endorses suicidal thoughts during the first assessment will see an onsite counselor who will conduct a risk assessment and intervene as needed. Following completion of the assessment measures, the research assistant will access the allocation envelope from the locked filing cabinet, open it to determine the allocation, inform the participant, and proceed with associated study tasks. Participants allocated to the intervention condition will be supported in accessing and learning about the app. All participants will return to Dilico after 2 and 4 weeks to complete the second and third assessments. Once they have finished the

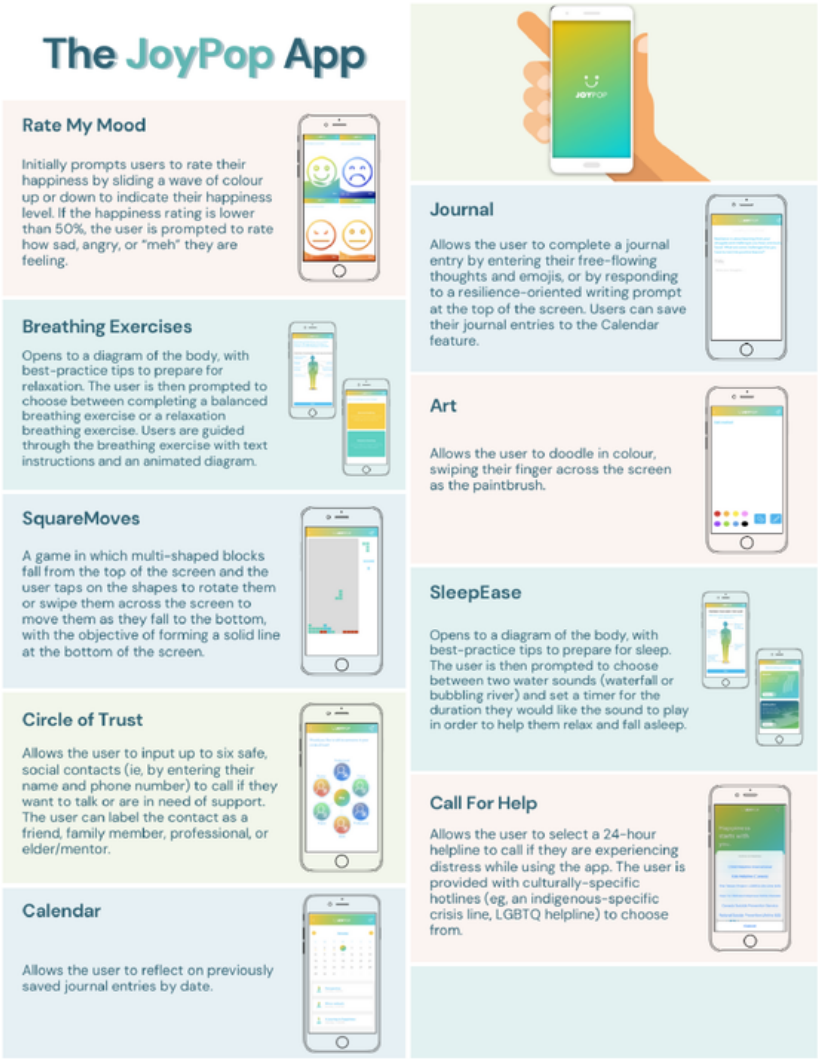
study at the end of their third assessment, participants in the control condition will learn about and receive access to the app.

To promote retention, participants will receive reminders about upcoming assessments via text and email. To incentivize completion [42,43], participants will receive cash compensation (CAD $20 [US $13.89] for baseline assessment; CAD $25 [US $17.36] for second assessment (after 2 weeks); CAD $30 [US $20.83] for third assessment (after 4 weeks); and an additional CAD $25 [US $17.36] if all assessments are completed). We will arrange transportation (taxis, bus fare) if required for participants. Promising retention rates were observed using these methods in a pilot study [44].

Description of Intervention and Control Conditions

Participants in the intervention condition will be able to use the JoyPop app by downloading it onto their own device (if suitable). Participants who do not have an iPhone will be given a refurbished one containing only the app to use for the duration of the study. Participants will be asked to use the app at least twice daily for 4 weeks. The JoyPop app has features that allow participants to rate their mood, engage in relaxation exercises (ie, breathing), prepare for sleep, journal, play a Tetris-like game, create art, and reach out to their support system or suitable helplines. Figure 1 further describes these features. Internet connection is not required to use the app.

Figure 1. JoyPop features. LGBTQ: lesbian, gay, bisexual, transgender, and queer/questioning.



To promote engagement, youth will receive an email and SMS text message twice per day (at 8 am and 8 pm) reminding them to use the app. Outside of recommending using the app near the start and end of their day, we will not instruct or prescribe participants to engage with the app for any specific duration or pattern. Our intention is to evaluate the effects of using the app under real-world conditions in which users choose when and how often to use the app. Prior research suggests youth do use the app for the majority of the 4-week period [38,39]. Youth will also receive the usual waitlist management practice (UP).

Participants allocated to the control condition will only receive the UP. We chose this comparator to assess whether the JoyPop app could be a complementary support for individuals waiting for mental health services. This comparison creates the opportunity to test whether those who receive the app experience improved outcomes compared to those who do not receive it, representing "true" change after accounting for the regression to the mean phenomenon likely to affect both groups [45]. The use of a control condition addresses the limitations of our

previous research in which all participants received the app [38].

Randomization and Blinding

Stratified block randomization will be used to randomize participants to the control or intervention condition in a 1:1 ratio. An independent researcher outside of the research team will create the randomization sequence using a computer-generated sequencing tool [46] and then place allocations into numbered, opaque, sealed envelopes. These will be stored in a locked filing cabinet and only accessed by the research assistant who is with the participant.

To protect against bias, the principal and coinvestigators and the statistician conducting the analyses will be blinded to conditions. Trial participants cannot be blinded given the nature of this trial in which they are actively using the app or not. Research assistants will also not be blinded, as the condition assignment determines study procedures such as showing the participant how to use the app and providing them with the correct measures.

Outcomes

The primary outcome is change in emotion regulation from the baseline assessment to the second assessment (after 2 weeks) and to the third assessment (after 4 weeks). Secondary outcomes are changes in mental health symptoms, readiness for treatment, and service usage from the baseline assessment to the second assessment and to the third assessment.

Measures

Descriptive Measures

During the baseline assessment, participants will complete a demographics measure asking about their age, ethnicity, family composition, highest level of education, gender, sex at birth, sexual orientation, and living situation. Demographic variables that could change over time (ie, gender, sexual orientation, family composition, and living situation) will be reassessed at subsequent assessments. We will also measure symptom presentation during the baseline assessment using a modified version of the *DSM-5* (*Diagnostic and Statistical Manual of Mental Disorders* [Fifth Edition]) Self-Rated Level 1 Cross-Cutting Symptoms Measures (DSM-5-CCSM) [47] to characterize symptoms across 12 psychiatric domains (ie, depression, anger, irritability, mania, anxiety, somatic symptoms, inattention, suicidal ideation, psychosis, sleep disturbance, repetitive thoughts and behaviors, and substance use). One item pertaining to past suicide attempts was removed at the request of Dilico partners. Using the DSM-5-CCSM measure, respondents will report how much (or how often) they have been bothered by symptoms during the past 2 weeks. Items are rated on a 5-point scale (from 0=none at all to 4=severe or nearly every day) with the exception of items related to suicidal ideation and substance abuse, which are rated as either "Yes" or "No." In a sample of adults receiving mental health services, most items in this measure except for the mania items have good test-retest reliability (intraclass correlation range=0.53-0.97) [48]. The measure also has good internal consistency (α=0.96) and criterion validity in terms of severity of impairment across life domains (r=0.84) in a community sample [49]. App usage data will be recorded in the JoyPop app with a timestamped record created each time the participant uses a feature.

Primary Outcome Measure

Emotion regulation will be measured with the Difficulties in Emotion Regulation Scale-Short Form (DERS-SF) [50,51], an 18-item self-report measure that asks respondents how often statements regarding their emotions have applied to them over the previous 2 weeks. Items are rated on a 5-point scale (ranging from 1="almost never" to 5="almost always"). Total scores range from 18 to 90, and subscale (strategy use, nonacceptance of emotion, impulsivity, ability to maintain focus on goals, awareness of emotions, and clarity of emotions) scores range from 3 to 15, with higher scores indicating greater difficulty regulating emotion. The DERS-SF demonstrates convergent validity via associations with symptoms of emotional disorders (eg, r=0.66 with the Beck Depression Inventory) [51,52]. In our pilot sample of Indigenous youth from Dilico, internal consistency for the total score ranged from α=0.87 to α=0.91 [53].

Secondary Outcome Measures

Mental health difficulties will be assessed with 2 measures: the Depression, Anxiety, and Stress Scale 21 (DASS-21) [54] and the Strengths and Difficulties Questionnaire (SDQ) [55,56]. The DASS-21 is a 21-item self-report measure that asks respondents how much specific statements regarding psychological distress applied to them over the past week. Items are rated on a 4-point scale (from 0="never" to 3="almost always"). Total scores range from 0 to 63, and subscale scores range from 0 to 21, with higher scores indicating greater distress. In clinical samples, this measure demonstrates convergent validity via correlations with other mental health measures (eg, r=0.85 between the Anxiety subscale and Beck Anxiety Inventory; r=–0.66 between the Depression subscale and Mental Health Questionnaire) [57,58]. In our pilot sample, internal consistency ranged from α=0.95 to α=0.96 across subscales. The SDQ is a 25-item self-report measure that asks respondents how true various statements have been for them. Items are rated on a 3-point scale (from 0="not true" to 2="certainly true"). Total scores range from 0 to 40, and subscale (emotional problems, conduct problems, hyperactivity, peer problems, and prosocial behavior) scores range from 0 to 10, with higher scores indicating greater difficulty (except for the prosocial scale for which the reverse applies). The SDQ has satisfactory internal consistency (α=0.80) and validity via its association with clinical diagnoses [56,59]. In our pilot sample, internal consistency was variable [53]; thus, we will ensure adequate psychometric performance in this study with a larger sample prior to analyses.

Treatment readiness will be assessed with the 4-item treatment readiness subscale of the Motivation for Youth's Treatment Scale (MYTS) [60]. Items are rated on a 5-point scale (from 1="strongly disagree" to 5="strongly agree"), with the total subscale score calculated as the mean of item scores; higher scores indicate greater readiness. Groups with prior mental health service use and higher symptom severity tend to have

higher average scores [60]. In our pilot sample, internal consistency ranged from α=0.80 to α=0.90.

Service usage will be assessed with 5 items generated by the research team that ask respondents how many times they accessed various health care services (ie, walk-in clinic, family doctor or nurse practitioner, emergency department, mental health counselor, and mental health hotline or phone support) over the previous 2 weeks.

Statistical Analyses

Descriptives

We will describe the sample by calculating means and frequencies across demographic variables such as gender. We will also calculate mean scores on the DSM-5-CCSM to describe presenting mental health across 12 psychiatric domains. We will report internal consistency estimates and correlations between all measures to provide an indication of their reliability and convergent validity in the sample, given a lack of prior validation with Indigenous samples. With respect to app use among the intervention group, we will calculate the average frequency and duration of app use both in general and for each feature.

Primary Outcome

We will calculate the change in overall emotion regulation using the DERS-SF total score and the change in specific domains via the DERS-SF subscale scores. An independent statistician will use linear mixed modeling to test whether the change in emotion regulation is greater for those in the intervention condition relative to those in the control condition by including an interaction term between time and group [61]. We will evaluate the final sample to determine whether it is also feasible to analyze gender and baseline mental health symptoms as subgroup effects via interaction terms [62,63]. Analyses will be conducted with an intent-to-treat approach. Missing data will be handled with full information maximum likelihood estimation, which is recommended for avoiding bias in parameter estimates [64,65].

Secondary Outcomes

We will calculate change in mental health using total scores from the DASS-21 and SDQ, while we will calculate change in specific domains using the DASS-21 and SDQ subscale scores. We will calculate change in treatment readiness using the treatment readiness subscale from the MYTS as described. Similar to the primary outcome analyses, linear mixed modeling will be used to test whether the change in mental health symptoms and treatment readiness is greater for those in the intervention condition relative to those in the control condition by including an interaction term between time and group [61]. Covariates of gender and baseline mental health symptoms will again be included. With respect to service usage, we will estimate the costs of services used among participants in each condition and conduct a cost-consequence analysis to determine the incremental costs or savings associated with receiving the app [66].

Sample Size

We calculated the required sample size for a 2 (between subjects; treatment condition) by 3 (within subjects; time) mixed design, roughly estimating the statistical power needed for the planned linear mixed model for the primary outcome under the assumption of compound symmetry. We used parameters of f=0.2 (small to medium effect), =0.05, and power=0.95, resulting in a suggested sample size of 66 to achieve necessary power. We estimate 60% retention throughout the study (40% attrition) based on our initial research [53]; as such, an initial sample of 110 will be recruited.

Ethical Considerations

Ethics Approval

The study protocol (version 1) was approved on December 16, 2022, by the Research Ethics Board at the Thunder Bay Regional Health Sciences Centre (file #100157). This Research Ethics Board acts as the Board of Record for clinical research projects led by Lakehead University researchers. The Research Advisory Committee at Dilico reviewed and approved all procedures. All participants will provide informed consent and will be made aware that they will receive counseling regardless of their choice to participate. Any required amendments would be reviewed by the Research Ethics Board, and participants would be informed by phone or email if such amendments directly impacted their experience in the study. We would also update the ClinicalTrials.gov registry (NCT05991154).

Mitigation of Harms

The risk of harm due to study participation is minimal. Participants may withdraw at any time by contacting the research team via phone or email. Any concerns or adverse events experienced or reported by participants to a research assistant would be reported immediately to the principal investigator (author ARM). The research team also meets weekly and will discuss any issues or concerns as they arise. All serious adverse events will be reported to the Thunder Bay Regional Health Sciences Centre Research Ethics Board using the Research Ethics Local Serious Adverse Event Reporting Form.

As described earlier, we will provide participants with contact information for local support services during the orientation, including walk-in counseling services and a local crisis line. Additionally, if recent suicidal thoughts are endorsed, an onsite counsellor will conduct a risk assessment with the participant and intervene as needed. As part of this risk assessment, the participant and counsellor will discuss whether continued study participation is recommended. Finally, as participants are on the waitlist for mental health services, they will be offered counseling services at some point following study completion (exact timing based on waitlist at the time).

Data Management and Confidentiality

Practices related to confidentiality follow the Canadian Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans [44] and ethical guidelines at the Thunder Bay Regional Health Sciences Centre and Lakehead University. During recruitment, names and contact information of potential participants will be kept in a list only accessed by the research

team. Once enrolled, the research assistant will assign each participant an ID number; both self-report and app data will contain only this ID number and no identifying information. The list connecting participant IDs to their names and contact information will be deleted upon study completion. The research assistant leading the orientation will inform participants about confidentiality and its limits during the informed consent procedure, including the procedure for notifying a staff member if recent suicidal ideation is endorsed; we will also provide this information in the information letter that is given to participants.

With respect to data management, a research assistant will enter responses from the hard-copy measures into a version of the measures hosted by Survey Monkey. Survey Monkey has SOC 2-accredited data centers [67] with physical security, including 24×7 monitoring, cameras, visitor logs, entry limitations, as well as dedicated cages for Survey Monkey hardware. Data in transit is encrypted using secure TLS cryptographic protocols. Usage data from the JoyPop app will be stored on a password-protected server within Canada and encrypted during transmission. In accordance with the Ownership, Control, Access, and Possession (OCAP) standards set by the First Nations Information Governance Centre [68], all data will be stored at Dilico; electronic measures and app data will be stored on a password-protected computer while hard-copy data will be stored in a locked filing cabinet. Data will not be shared with the public or outside third parties. Data will be retained for at least 7 years after study completion following Lakehead University policy.

Oversight and Monitoring

Author ARM, as the principal investigator, will oversee all trial activities and hold weekly meetings with research assistants to discuss the day-to-day running of the trial. Author ARM will consult with coinvestigators and meet on a quarterly basis to discuss the trial status and plan for future trial activities. Author ARM will also meet with collaborators from the local community partner (Dilico) to discuss ongoing implementation of the trial. Retention will be discussed on an ongoing basis with further strategies implemented if needed.

Results

This research is funded through a Brain Canada—2021 Future Leaders in Canadian Brain Research grant, which began in October 2022. Recruitment began September 1, 2023, and is ongoing. As of July 2024, two participants have completed the study and attended all assessments. When the trial is complete, our community partner, Dilico, will review the findings via their research advisory committee, which is in line with OCAP principles [68]. Pending approval by the committee, results will be disseminated through academic conferences and publications as well as media interviews to reach the broader community. We will also share a summary of findings with participants who selected that they would like to receive this, as well as with staff at Dilico who are interested in the information. Pending positive results, avenues for future funding to support scalability will also be discussed with community partners.

Discussion

Overview

The current research will explore the impact of the JoyPop app on emotion regulation, mental health, and treatment readiness among Indigenous youth waiting for mental health services. Positive change among these variables and demonstrated cost-effectiveness associated with using the app would support adopting the app into routine waitlist management practices within the current partner organization. The degree and magnitude of findings within this clinical sample of Indigenous youth will be compared to prior work within a non-clinical sample in which use was associated with positive change in emotion regulation and depression symptoms [38]. We will also compare findings to another trial studying the effectiveness of the app among younger Indigenous youth [69] and another with non-Indigenous youth [70]. Such comparisons will allow identifying how to best use the JoyPop app as a supportive tool. Finally, positive findings would also be consistent with a growing emphasis on transdiagnostic approaches to mental health care. Specifically, findings may increase our knowledge about the link between emotion regulation and various mental health–related difficulties among Indigenous youth [29].

Dissemination of Findings

When the trial is complete, our community partner, Dilico, will review the findings via their research advisory committee, which is in line with OCAP principles [68]. Pending approval by the committee, results will be disseminated through academic conferences and publications. We will also create infographics and videos to be shared broadly through team members' networks, on social media, and through public presentations, which we will invite youth from the study to help develop and participate in. We will use media interviews to reach the broader community. We will share a summary of findings with participants who selected that they would like to receive this, as well as with staff at Dilico who are interested in the information. Pending positive results, we will discuss further scalability and potential integration of e-mental health solutions into services with the community partner, such as seeking funding to conduct a hybrid implementation/effectiveness study. We will also share findings with decision makers from other organizations who are similarly seeking solutions to meet youth mental health needs.

Strengths and Limitations

Study strengths include the randomized controlled trial design, methods to promote retention and uptake of the intervention (eg, reminders and provision of phones and transportation), and evaluation of diverse outcomes, including both clinical outcomes and an analysis of service usage to understand the broader impact of the app within the health care system. The experimental design specifically improves upon the limitation of non-randomized earlier work [38]. An inherent study limitation is that participants are not blinded to condition assignment. A further limitation is that although the study was designed with few requirements surrounding app usage to allow for a more naturalistic examination, it is possible that in potential future nonresearch clinical settings, participants may engage

with the app to a lesser extent when they are not actively involved in attending research sessions.

Given the nature of the intervention, an additional consideration is whether implementing an app-based intervention may contribute to problematic mobile device use. While this is an important consideration, the app does differ from social media and communication apps, which some research indicates are among those identified as the most "addictive" [71]. Future research, however, could evaluate whether accessing an app such as JoyPop encourages greater smartphone use overall. Future research could also incorporate scales assessing the risk of smartphone app addiction [eg, 72].

Conclusions

Transitional-aged youth in Canada experience a heightened burden of mental health difficulties relative to adult populations, and Indigenous youth in this age range may be especially at risk [4,5]. Individuals who live in more remote or rural locations, such as in Northern Ontario, have less access to mental health care, which has negative impacts on well-being and engagement in future services [10,12]. This study, conducted in partnership with Dilico Anishinabek Family Care, will speak to whether adopting the JoyPop app as part of routine waitlist management practices may benefit Indigenous youth mental health and reduce additional service use during the waiting period. While an app is unlikely to remedy all mental health symptoms, it may be a useful tool for helping youth build skills and readiness in advance of formal counseling services.

Acknowledgments

This study was funded through a Brain Canada—2021 Future Leaders in Canadian Brain Research grant (ARM). The study was also supported through a Tier 1 Canada Research Chair in Addictions and Mental Health (SHS) and in-kind contributions by Dilico Anishinabek Family Care. ARM is the principal investigator and led the design of the study and protocol, while ASN, ET, FS, JVO, and SHS provided substantial contributions to the study design. ARM, ASN, AO, ET, FS, JVO, and SHS sought funding for the study. CD, ET, FS, KS, and TB provided guidance regarding implementing the study locally and recruiting and retaining participants at the local site. TN led the trial coordination and data collection with supervision from ARM and support from ET and IM. AM drafted the manuscript. ARM provided supervision and revisions on the manuscript. All authors reviewed and approved the final manuscript.

We would like to thank Dilico staff whose knowledge and experiences have informed the study design and who have supported the onsite implementation of the trial. We also thank the youth who have participated in our research and shaped the ongoing design of the JoyPop app and associated research projects.

Conflicts of Interest

The majority of the authors have no conflicts of interest to declare. The principal investigator (ARM) recently acquired intellectual property ownership rights for the JoyPop app (in June 2024). Prior to this time, intellectual property rights were owned by another researcher or institution. ARM did not own any intellectual property rights when applying for funding for this study, when creating the protocol, or when initiating the study. To mitigate any risk related to ARM's new intellectual property ownership rights, ARM will not be involved in collecting or analyzing the data, will be blinded to participant condition assignment, and will consult with coinvestigators throughout the study.

Multimedia Appendix 1
SRIRIT (Standard Protocol Items: Recommendations for Intervention Trials) checklist.
[PDF File (Adobe PDF File), 90 KB - resprot_v14i1e64745_app1.pdf]

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Abbreviations

DASS-21: Depression, Anxiety, and Stress Scale 21
DERS-SF: Difficulties in Emotion Regulation Scale-Short Form

Dilico: Dilico Anisinabek Family Care
DSM-5: Diagnostic and Statistical Manual of Mental Disorders (Fifth Edition)
DSM-5-CCSM: DSM-5 Self-Rated Level 1 Cross-Cutting Symptoms Measures
mHealth: mobile health
MYTS: Motivation for Youth's Treatment Scale
OCAP: Ownership, Control, Access and Possession Standards
SPIRIT: Standard Protocol Items: Recommendations for Intervention Trials
SDQ: Strengths and Difficulties Questionnaire
UP: usual practice

Edited by A Schwartz; submitted 29.07.24; peer-reviewed by A Eisingerich, Y Chu; comments to author 27.08.24; revised version received 13.09.24; accepted 29.11.24; published 30.01.25.

Please cite as:
MacIsaac A, Neufeld T, Malik I, Toombs E, Olthuis JV, Schmidt F, Dunning C, Stasiuk K, Bobinski T, Ohinmaa A, Stewart SH, Newton AS, Mushquash AR
Increasing Access to Mental Health Supports for 18- to 25-Year-Old Indigenous Youth With the JoyPop Mobile Mental Health App: Study Protocol for a Randomized Controlled Trial
JMIR Res Protoc 2025;14:e64745
URL: https://www.researchprotocols.org/2025/1/e64745
doi:10.2196/64745
PMID:

Protocol

Effect of an Internet-Based Pilates Telerehabilitation Intervention in People With Multiple Sclerosis: Protocol for a Randomized Controlled Trial

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Abstract

Background: Physical activity (PA) has been recommended in multiple sclerosis (MS) to maintain good physical fitness and mental health, reduce the severity of symptoms and risk of relapse, and improve quality of life. Pilates has been suggested as an ideal PA to manage physical, cognitive, and psychological symptoms of MS and a useful method to maintain and improve balance and gait.

Objective: This paper presents the protocol for a study that aims to evaluate the efficacy on the physical domain (specifically balance and gait) of a home-based, self-managed PA intervention delivered through the MS-FIT exergame (HELAGLOBE Società a responsabilità limitata). In addition, measures of cognitive performance, quality of life, and well-being will be considered.

Methods: This is a 2-arm, multicenter, randomized controlled trial with 3 assessment points (baseline, 12 weeks postintervention, and 6 weeks follow-up). People with MS with mild disability, low risk of falling, preserved cognitive functions, and low anxiety and depression are potential eligible participants. The experimental group (MS-FIT) will self-administer the MS-FIT exergame at home in addition to their leisure-time physical activities. MS-FIT is an internet- and Pilates-based tool that uses the Microsoft Kinect Sensor V2. Participants in the control group will only have access to their leisure-time physical activities. Participants in the MS-FIT group will train at home with MS-FIT for 12 weeks and will be required to perform the exercises for a total of 30 minutes/day for at least 3 days/week. The primary outcome is the Timed Up and Go, a test designed to assess walking. We will also administer additional tests for motor function (visual analog scale 0-10, Timed 25-Foot Walk, Ambulation Index, 2-minute walk test, Twelve Item Multiple Sclerosis Walking Scale, Nine-Hole Peg Test), cognition (Brief International Cognitive Assessment for Multiple Sclerosis), fatigue (Modified Fatigue Impact Scale), quality of life (Multiple Sclerosis Quality of Life-54), well-being (Psychological Well-Being Scales), and PA (International Physical Activity Questionnaire and Minnesota Leisure Time Physical Activity Questionnaire). Acceptance and satisfaction with the intervention received (Client Satisfaction Questionnaire and an adapted version of the Tele-healthcare Satisfaction Questionnaire – Wearable Technology) and subjective impressions of changes in performance (Patients' Global Impression of Change) will also be assessed.

Results: Recruitment for the trial started on March 16, 2022, and the first participant was randomized the same day. Data analysis and results are expected to be published in 2025.

Conclusions: Pilates has proven beneficial in several neurological diseases such as MS. With this study, we will provide evidence for the use in clinical practice of a digital tool for self-administered Pilates exercises at home as a complement to rehabilitation and for the continuity of care in MS.

Trial Registration: ClinicalTrials.gov NCT04011579; https://tinyurl.com/2p9n4d2t

International Registered Report Identifier (IRRID): DERR1-10.2196/58026

(JMIR Res Protoc 2025;14:e58026) doi:10.2196/58026

KEYWORDS

exergame; MS-FIT; Pilates; Kinect; multiple sclerosis; exercise; physical activity; leisure time physical activity; Timed Up and Go

Introduction

Multiple sclerosis (MS) is a chronic inflammatory neurodegenerative disease with autoimmune demyelinating lesions of the central nervous system and one of the most common causes of neurological disability in young adults. Clinically, MS progressively worsens over time, leading to cumulative physical disability, cognitive deficits, and neuropsychiatric and behavioral symptoms [1]. Physical impairments lead up to 85% of people with MS to complain of ambulation difficulties after typically 10-15 years of disease, and, after 20 years, over 66% of people with MS do not retain the ability to walk [1]. Several factors, such as weakness, spasticity, cerebellar ataxia, fatigue, and impaired attention, can cause imbalance and gait disorders [2,3]. They prevent people from performing daily activities properly and regularly, with negative effects on work status and social relationships. Rehabilitation is the main option to enhance recovery from disabling symptoms such as spasticity, ataxia, sensory loss, fatigue, pain, mood, and cognitive disorders [4]. More recently, people with MS have been recommended to engage in regular physical activity (PA).

PA, including leisure-time physical activity and exercise, comprises any bodily movement produced by skeletal muscles' contraction that results in a substantial increase in energy expenditure over resting levels [5]. Increasing PA and reducing sedentary behavior are general recommendations to improve health outcomes for all people with chronic diseases [6]. For people with MS, PA maintains good physical fitness and mental health, prevents or reduces the severity of symptoms and the risk of relapses, and improves quality of life [7-9]. Based on current evidence and experts' opinions, recent MS guidelines recommend "at least 150 minutes/week of exercise and/or 150 minutes/week of lifestyle PA" throughout the disease course [10]. However, Klaren et al [11] report that people with MS do not engage in sufficient PA amounts, with only approximately 20% of people with MS meeting recommended levels of moderate or vigorous daily activity compared with 40% of healthy participants. Although a recent survey study reported higher rates among people with MS, only 60% of the total sample met recommendations, with the lowest rate shown in the severely disabled group [12]. Furthermore, the benefits of PA may be limited if not incorporated into a structured, personalized, and supervised program.

Various mind-body fitness modalities, such as Pilates, yoga, Tai chi, and Qigong, are widely used by people who seek to achieve physical and mental health outcomes [13,14].

Pilates has been suggested as an ideal approach to managing physical, cognitive, and psychological symptoms of MS [15] and a popular alternative method for maintaining and improving balance and gait performance [16], as in other neurological conditions [17-19]. Indeed, it is a precise and controlled form

of exercise that uses the body's stabilizing muscles and is based on the principles of concentration, control, centering, flowing movement, precision, and breathing. If followed correctly, they can improve flexibility, strength, core stability, muscle control, breathing, and posture, and increase body awareness with less ground impact and joint stress [20,21]. The research findings support the therapeutic use of Pilates in the management of MS because it is a safe, active treatment method (few adverse effects) with high adherence (low dropout rate), and it can improve important meaningful functions (eg, balance, gait, physical-functional capacities, and cognition) [22].

A possible perspective for delivering Pilates interventions could benefit significantly from the proliferation of exergames and new technologies for telerehabilitation [23]. Playing exergames is a form of whole-body physical exercise [24] that requires users to complete assigned tasks aimed at improving physical fitness and promoting an active lifestyle [25]. Furthermore, exergames have been demonstrated to be comparable with traditional therapies, may be more enjoyable and acceptable, and may improve the engagement of people with MS in PA [26]. Exergame-based telerehabilitation solutions represent an efficient alternative method to overcome barriers that prevent people with MS from accessing regular long-term rehabilitation interventions (ie, transportation and working time) and to provide effective treatments in a setting, matching the patient's circumstances (eg, at home), priorities (eg, during lunch break), and capabilities (eg, physical impairment) [27].

Recently, MS-FIT (HELAGLOBE Società a Relazioni Limitate), a Kinect-based playable exergame implementing Pilates exercises, has been developed by an Italian network of experts in the field of MS rehabilitation for future use in research and clinics [28]. It has been customized for people with MS, allows tailoring the intervention in order to potentiate the effects of an ongoing program, and has been conceived to be developed for asynchronous telerehabilitation purposes.

The aim of this study, promoted by the Italian Multiple Sclerosis Foundation, is to test in people with MS the efficacy on the mobility domain measured with the Timed Up and Go (TUG) test of a self-managed home intervention delivered through MS-FIT in addition to leisure-time physical activities, in comparison with leisure-time physical activities alone. Measures of balance, gait, upper limb functioning, PA, cognition, quality of life (QoL), well-being, acceptability, satisfaction with use, and adherence to the intervention will also be considered. In addition, a blood sample will be collected to investigate if genetic polymorphisms that are considered potential regulators of neural plasticity could influence the response to the proposed intervention [29].

Based on previous findings [30], we expect that the intervention, in addition to leisure-time physical activities, will be associated with a primary outcome of mobility (TUG) compared with leisure-time physical activities alone that are expected to worsen due to disease progression. Similar changes between groups are expected in secondary outcomes; furthermore, based on our previous findings [28], we expect high acceptability, satisfaction-to-use, and adherence to the MS-FIT intervention.

If results are positive, MS-FIT could be proposed in combination with rehabilitation to potentiate the effect of the rehabilitation intervention and ensure continuity of care for people with MS.

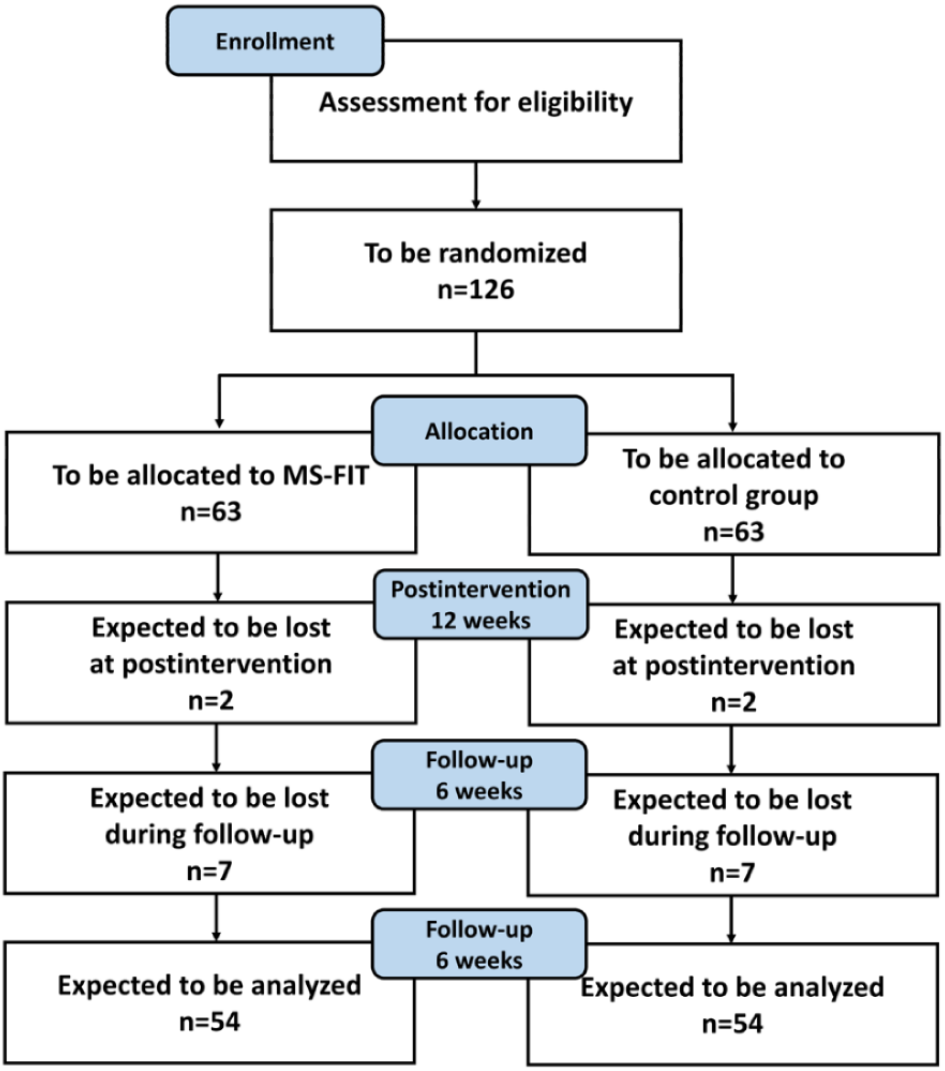
Methods

Study Design

We are conducting a multicenter 2-arm, superiority randomized controlled trial (RCT) with 3 assessment points (baseline, T0; postintervention at 12 weeks, T1; and follow-up at 6 weeks, T2). Participants will be allocated to the intervention (MS-FIT) or control group in a 1:1 ratio by simple randomization.

Participants in the MS-FIT group will have access to the MS-FIT exergame for at-home self-administration [28] (Multimedia Appendix 1) in addition to their leisure-time physical activities. Participants in the control group will have the possibility to perform only their leisure-time physical activities. Exercise will not be allowed and rehabilitation treatments, except for speech therapy, sphincter rehabilitation, and psychological support, must be suspended. The study design is illustrated in Figure 1.

Figure 1. Study design.



Setting

Participants will be recruited among those followed by 14 Italian neurorehabilitation centers; specifically, at the Italian Multiple Sclerosis Society Rehabilitation Services of Genoa and Padua, the Multiple Sclerosis Center of IRCCS (Istituto di Ricovero e Cura a Carattere Scientifico) Foundation "Carlo Besta" Neurological Institute (Milan), the Vita-Salute San Raffaele University (Milan), the Department of Neuroscience, Rehabilitation, Ophthalmology, Genetics, Maternal and Child Health (DINOGMI) of the University of Genoa, the Neurology Unit of IRCCS Neuromed (Pozzilli), the Department of Medical Science and Public health of the University of Cagliari, Department of Translational Biomedicine and Neurosciences (DiBraiN) of the University A. Moro (Bari), the IRCCS Fondazione Don Carlo Gnocchi ONLUS (Milan), the Uosi Multiple Sclerosis Rehabilitation of the IRCCS Istituto delle Scienze Neurologiche of Bologna, Department of Advanced Medical and Surgical Sciences (DAMSS) of the University of Campania Luigi Vanvitelli (Naples), the Department of Neurosciences of the S. Camillo-Forlanini Hospital (Rome), the Department of Medical and Surgical Sciences and Advanced Technologies "G.F. Ingrassia" (DGFI) of the University of Catania, and the IRCCS Centro Neurolesi "Bonino-Pulejo" (Messina).

The assessments will be carried out in person at the several centers. The intervention with MS-FIT will be performed at home.

Recruitment, Enrollment, and Randomization

People with MS along with mild disability, low risk of falling, preserved cognitive functions, and low anxiety and depression as reported in medical records are potential eligible participants. They will be contacted by telephone by the study manager of the related center (Multimedia Appendix 1), who will explain the study process in detail to ensure that patients understand the entire clinical trial; they will receive detailed information, including the purpose, procedures, follow-up content, data storage, benefits, and risks of the study, and will be given adequate time to consider participation. They will be informed that for the entire period of participation in the study, only leisure-time physical activities will be allowed, but not exercise and rehabilitation. They will also be informed verbally that their participation is voluntary and that they can withdraw their consent at any time without giving reasons and without depriving themselves of any treatment and care or other disadvantages.

Patients who agree to participate will be scheduled for a screening visit with a therapist (Multimedia Appendix 1). First, they will be asked to sign the written informed consent (Multimedia Appendix 2) after carefully reading and understanding the information about the study procedures and data security measures (including information on how to contact the study team in case of questions) provided to them. This approach is compliant with the General Data Protection Regulation and has been approved by the ethics committees.

After consent, recruited patients will proceed to the screening evaluation, where inclusion and exclusion criteria are assessed, and they will immediately receive feedback on whether or not they can participate in the study. Enrolled patients will be randomized by the study manager through the electronic case record form (eCRF) (Multimedia Appendix 1) into one of the 2 groups (ie, MS-FIT and control) and informed of the result of the assignment.

Eligibility Criteria

Eligibility criteria were selected to ensure optimal fitness of the study sample with respect to the subsequent implementation of the MS-FIT intervention in the health care setting, to minimize the impact of confounding variables (eg, rehabilitation outcomes), and to ensure comparability with other studies on similar interventions.

Inclusion Criteria

The study includes people with a diagnosis of MS according to McDonald's criteria [31] and aged ≥18 years; all disease courses are eligible (relapsing-remitting, primary progressive, and secondary progressive) [32]. Patients will be included if their disability level based on the Expanded Disability Status Scale (EDSS) [33] is between 2 and 4. Indeed, we expect that in people with MS with a lower EDSS, the proposed intervention might not be effective and other forms of PA based mainly on exercise should be considered. For people with MS with a higher EDSS, Pilates could be recommended as a complement but not as a replacement for rehabilitation; also, for this reason, we considered it unethical to include patients who should suspend their treatments for the aims of the study. Furthermore, asynchronous telerehabilitation tools for self-administered balance training should be proposed when the patient's ability to maintain balance safely is preserved (eg, pregnant women will be excluded until after giving birth). In any case, we included patients with preserved balance evaluated with the Berg Balance Scale score >46 [34].

To ensure the ability to use the MS-FIT exergame, normal cognitive functioning determined by a Mini-Mental Status Examination score >24 [35] is required; a Hospital Anxiety and Depression Scale score <10 in the 2 subsets of anxiety and depression [36] could prevent a loss of adherence due to mood disorders.

Exclusion Criteria

The study excludes individuals who have received at least 1 rehabilitation treatment (except speech therapy, sphincter rehabilitation, and psychological support) in the last month before being contacted. Other exclusion criteria are visual deficits that could compromise the use of the MS-FIT exergame and relapses in the last 3 months. Participants with relapses during the period of involvement in the study will be considered dropouts.

All hardware and software components will be provided to the participants in the MS-FIT group; training provided by the study manager will ensure ease of use. For this reason, technology will not be an exclusion criterion.

Intervention

All participants will be allowed to continue their leisure-time physical activities.

Participants in the MS-FIT group will receive the MS-FIT exergame [28]. They will be required to train at home with MS-FIT for 12 weeks by performing the exercises for a total of 30 minutes/day for at least 3 days/week.

While gaming, participants will choose their favorite and most useful exercises; the difficulty of the exercise will increase based on the user's performance. In this way, the exercise selection and the reward structure will ensure the personalization of the intervention.

Before starting the intervention, each participant will be trained in the use of the tool by the study manager.

Participants in the control group will not receive MS-FIT; however, as a reward for their participation, we will offer them the MS-FIT intervention at the end of their study involvement.

All participants will be assessed at T0, T1, and T2.

Assessment

The assessment will consist of clinical tests measuring the domains most relevant to MS. The primary outcome will always be administered first; the order of the secondary outcomes will be randomized across participants; however, the same order will be maintained for the individual participant. We assume that the administration of all tests will take, on average, about 60 minutes.

Multimedia Appendix 3 summarizes when the different outcome measures should be collected.

Primary Outcome

The primary outcome of the study is TUG [37], commonly used to measure dynamic balance and to assess activity limitations by examining the patient's ability to ambulate and perform transfers. The TUG was originally created to predict the risk of falling in geriatric patients.

At the "go" signal, the participant must rise from a chair, walk 3 m, turn around, return to the chair, and sit down as quickly but safely as possible. The participant starts with the back against the chair and the arms resting on the armrests and is timed from the moment he or she lifts the pelvis from the chair until he returns with the pelvis on the chair [34]. The participant wears his or her regular footwear and uses his or her customary walking aid (none, cane, or walker); however, due to the eligibility criteria adopted in this study, participants will not

use assistive devices for walking. No physical assistance is given.

Secondary Outcomes

Secondary outcomes will evaluate the effects of the intervention on the following:

1. Motor function: visual analog scale (VAS; 0-10) for balance subjective disability improvement [38], Timed 25-Foot Walk (T25FW) [39], Ambulation Index [40], 2-minute walk test (2MWT) [41], Twelve Item Multiple Sclerosis Walking Scale (MSWS-12) [42,43], and Nine-Hole Peg Test (9HPT) [44].
2. Cognition: Brief International Cognitive Assessment for Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS), which consists of the Symbol Digit Modalities Test (SDMT), the California Verbal Learning Test-II (CVLT-II), and the Brief Visuospatial Memory Test-Revised (BVMT-R) [45].
3. Fatigue: Modified Fatigue Impact Scale (MFIS) [46,47].
4. QoL: Multiple Sclerosis Quality of Life-54 (MSQoL-54) [48,49].
5. Well-being: Psychological Well-Being Scales (PWB) [50,51].
6. PA: International Physical Activity Questionnaire (IPAQ) [52,53], the Minnesota Leisure-Time Physical Activity Questionnaire [54] which provides a general evaluation of the total energy expenditure in leisure time physical activity.
7. Perceived intervention effect: 7-point Patients' Global Impression of Change (PGIC; from 1="no change or worse" to 7="a great deal better") scale.

Technology

Furthermore, acceptance of the used technology will be evaluated with an ad-hoc questionnaire on patients' expectations; satisfaction with the intervention will be evaluated with the Client Satisfaction Questionnaire (CSQ-8) [55,56] and the Tele-healthcare Satisfaction Questionnaire (TSQ-WT) [57].

Blood Sample

If the participant consents, a peripheral blood sample will be collected at T0 in vacutainer tubes containing ethylenediaminetetraacetic acid. According to previous studies [29], participants will be divided into subgroups with respect to polymorphism. All blood samples will be genotyped for a total of 55 genetic polymorphisms of 23 potential regulators, such as Homer1, AKT1, RAPTOR, D2R, GAPD, CHAT, p53, BRCA2, LIG4, XRCC5, CYP3A4, NBS1, MDM2, CNR1, ATTn, CNR2, GRIN1, GRIN2B, TRPV1, FAAH, COMPT, and BDNF.

For example, CNR1 region containing AAT repetitions will be amplified by polymerase chain reaction from genomic DNA; sequencing products will be purified using a rapid, high-performance dye-terminator removal kit and will be subjected to electrophoresis; AAT repetitions will be counted on the resulting electropherograms (short AAT: homozygous or heterozygous for an allele with ≤11 repeats of AAT triplets; long AAT: homozygous for an allele with ≥12 repeats of AAT triplets). For the TRPV1 and FAAH, the iPLEX Gold technology and MassARRAY high-throughput DNA analysis will be performed.

The blood sample will be collected early in the morning after awakening (8:00 AM). To synchronize the sample with lifestyle variables, participants were requested to avoid excessive physical activity in the last 3 days before blood sampling, to sleep for 7-8 hours the night before the study, to avoid starvation, and to have a normal breakfast in the morning [29]. The samples will be analyzed in the center of DC.

Other Measures

Adherence to the intervention will be provided by the number of sessions actually performed as automatically recorded by the MS-FIT tool and the number of dropouts.

Safety will be assessed by the number of potential issues (ie, number of falls). The severity of adverse events will be graded according to the Common Terminology Criteria for Adverse Events v 4.0 on a 5-point scale (grade 1, mild discomfort; grade 2, moderate discomfort; grade 3, severe inability; grade 4, life-threatening or disabling; grade 5, death) and reported in detail on the eCRF. A grade higher than grade 2 will be considered as a condition for dropout.

We will also collect information on the pharmacological treatments (specific and nonspecific for MS) followed by participants, comorbidities, and the type of PA practiced during participation in the study.

Criteria for Premature Withdrawal

In addition to withdrawal of consent at any time, the study manager at each site may also consider as criteria for premature withdrawal any medical conditions that could jeopardize the safety of the patient if she or he continues the study, changes in the disease treatment during the study, and noncompliance of the participants to the study procedures.

Sample Size

The sample size was calculated by referring to the TUG change after a Pilates intervention found by Kalron et al [30] in a group of people with MS. The authors found no difference between the group receiving the Pilates intervention and the control group receiving an intervention of physical therapy. The Pilates group improved the TUG performance by about 1.8 seconds, which is clinically relevant for people with MS. Considering a variability of about 3.4 seconds, a power of 80%, a significance level (2-sided) of 5%, and a potential loss of 15% of patients at follow-up, the estimation of the necessary sample size consists of approximately 63 participants for the experimental group (a total of 126).

Data Collection and Management

Data entry, including quality checks and double entry validation, will be performed through eCRF (Multimedia Appendix 1). Missing data from the unit record will be compared with the corresponding handwriting case record form and corrected accordingly.

Statistical Analysis

Descriptive statistics will be used to evaluate differences between the 2 groups of participants. The study hypotheses will be tested using an intention-to-treat analysis, where all consenting patients who were randomized during the accrual period will be included in the analysis.

Continuous data will be summarized using count, mean, median, SD, and IQRs, whereas categorical measures will be described using frequencies. The assumption of normality will be tested with the Shapiro-Wilk test. Pre-post effects within groups will be investigated using the paired *t* test or the Wilcoxon matched-pairs signed-rank test. Between-group proportions will be compared by chi-square or Fisher exact test, while between-group comparisons for continuous variables will be done using either the unpaired 2-sided *t* test or the 2-sided Wilcoxon 2-sample test for nonnormal data. Correlations will be computed using Pearson or Spearman coefficients.

The primary analysis will be performed by comparing mean changes from T0 to T1 in the primary and secondary study outcomes. In particular, the MS-FIT group will be compared with the control group with analyses of covariance. The model includes change as the dependent variable, with the intervention group as the main effect and baseline and number of sessions as additional covariates. Finally, generalized estimating equation models will be performed to assess the persistence of the intervention effect; here the mean effect of the intervention at the time points T0, T1, and T2 on all outcomes, adjusted for the baseline value, will be evaluated between the 2 groups.

Differences in the outcome measures between subgroups defined by different polymorphisms will be analyzed using the analysis of variance or the Kruskal-Wallis test, as appropriate.

Statistical analysis will be performed using STATISTICA 7.1 software (StatSoft GmbH). Significance will be recognized for $P<.05$.

Ethical Considerations

This trial is conducted in accordance with the protocol (version 1, July 27, 2018), the Declaration of Helsinki, and good clinical practice. It has been approved by the Ethics Committee of San Martino Hospital (134/2018) and registered before patient enrollment at ClinicalTrials.gov (NCT04011579).

Any change to this protocol must be agreed upon by all the study investigators. Each amendment must be signed by the principal investigator at each site, and amendment forms will be submitted to the local Ethics Committee for approval. The amendment will be updated in the clinical trial registry.

Participants will be asked to sign the written informed consent, and their data will be deidentified. Participants will not receive any compensation for participating in the study.

A formal audit process at the end of the study is proposed for this trial.

Patient and Public Involvement

Patients and the public were not involved in the design, conduct, reporting, or dissemination plans of our research, although patient feedback was an important source for the development and improvement of the MS-FIT tool investigated in this trial [28]. Published results will be disseminated to study participants upon request.

Dissemination

The results of this RCT study will be disseminated. Dissemination includes communication and promotion of the project activities and results to participants, people with MS, and their stakeholders (eg, caregivers, health care professionals, and the scientific community). Dissemination activities will begin at launch and will continue throughout the duration of the study. Specific activities include dissemination through materials such as flyers and videos to be distributed through the internet, social networks, forums, or at local, national, and international events, and specific meetings with end users; dissemination through presentation of results in national and international peer-reviewed scientific journals; dissemination through presentation of research results at major national and international health care conferences and annual meetings; and dissemination through the ClinicalTrials website registry.

Results

Recruitment for the trial started on March 16, 2022, and the first participant was randomized on the same day. As of March 2022, we enrolled 126 participants who received a T0 visit; up to now, 108 received a T1 visit and 103 received a T2 visit. Data analysis and results will be published in early 2025.

Discussion

Summary

Cumulative data suggest that the Pilates method has proven beneficial in several neurological diseases and may be a PA tool for people with MS. A recent review [22] in MS showed that Pilates improves balance, gait, physical-functional conditions (muscle strength, core stability, aerobic capacity, and body composition), and cognitive functions; in contrast, fatigue, QoL, and psychological function did not show a clear improvement. Furthermore, high adherence (average adherence ≥80%) and few adverse effects were reported. For these reasons, future research is needed to develop clinical protocols that can maximize the therapeutic effects of Pilates for people with MS. In this context, novel devices and technologies for home-based interventions could provide solutions to overcome limitations due to urban barriers (eg, transportation), daily activities (eg, working time), and clinical conditions (eg, level of disability) and to ensure continuity of care. Therefore, practicing Pilates at home through eHealth tools could help people with MS to regularly engage in PA and to successfully maintain their physical, cognitive, and emotional status.

Here, we describe the RCT protocol designed to test the efficacy of a home-based PA intervention delivered through the MS-FIT exergame on balance and gait. In addition, we will also assess the effects on cognition, QoL, and well-being.

The present RCT protocol was designed taking into account previous studies in the MS scientific literature in terms of the

number of weeks of intervention, weekly frequency, session duration, outcomes, setting, and control group [22]. Because only one study evaluated long-term monitoring after the intervention [58] and it is unclear whether the obtained results are maintained, as an additional element of novelty, we propose to schedule a follow-up assessment in order to define whether the effects of Pilates persist.

Limitations

The first limitation of this study is that we will only have evidence of the effectiveness of a Pilates exergame for people with MS with mild disability. However, even people with MS at more advanced disease stages benefit from regular PA to maintain fitness, prevent pain and secondary complications of inactivity, and treat or reduce symptoms. Thus, as specific prescriptions should be tailored to clinical conditions, a dedicated trial for patients with a higher level of disability should be considered. Second, due to the discontinuation of the Kinect Sensor V2 adopted in MS-FIT, for the successful translation of the exergame into clinical practice, a new compatible commercial sensor will be identified, and the app will be adapted; Microsoft Azure Kinect and Mentor Age (Wita Società a responabilità limitata) are valid and comparable systems already taken into account by other researchers [28,59,60]. Third, although the MS-FIT tool was not developed to pursue rehabilitation purposes, it would be helpful to analyze the MS-FIT intervention as a complement to the work of health care professionals and evaluate if it is able to potentiate the effect of a rehabilitation intervention, possibly also in people with MS with a higher level of disability. Finally, direct evidence, such as MRI acquisition, will not be considered to reveal which microstructural changes are due to the MS-FIT intervention.

Future Directions and Conclusions

MS-FIT is a usable and accepted digital health tool for telerehabilitation implementing Pilates exercises and aims at supporting the self-administration of Pilates training at home. This study will provide evidence for the use of the MS-FIT tool in clinical practice as a complement to rehabilitation and for the continuity of care of people with MS. However, a feasibility protocol involving patients with moderate disability (EDSS between 4 and 6) should be designed and tested, followed by a multicenter trial that assesses the effectiveness of the tool and paves the way for more extensive use in MS.

Acknowledgments

The authors would like to thank the Italian Multiple Sclerosis Foundation and Roche Società per Azioni (Società per azioni) for supporting this study.

Data Availability

The data sets generated and analyzed during this study will be available from the corresponding author on reasonable request.

Conflicts of Interest

AT, MP, PC, LL, EC, MR, LS, GT, LP, FP, ES, EP, MAB, and GB have no conflicts of interest to disclose. MI is coeditor for MSJ; she has received honoraria for participation in advisory boards from Biogen, Bristol Myers Squibb, Merck, Novartis, Roche, Sanofi, and Janssen. DC is an advisory board member of Almirall, Bayer Schering, Biogen, GW Pharmaceuticals, Merck Serono, Novartis, Roche, Sanofi-Genzyme, and Teva and received honoraria for speaking or consultation fees from Almirall, Bayer Schering, Biogen, GW Pharmaceuticals, Merck Serono, Novartis, Roche, Sanofi-Genzyme, and Teva; he is also the principal investigator in clinical trials for Bayer Schering, Biogen, Merck Serono, Mitsubishi, Novartis, Roche, Sanofi-Genzyme, and Teva; his preclinical and clinical research was supported by grants from Bayer Schering, Biogen Idec, Celgene, Merck Serono, Novartis, Roche, Sanofi-Genzyme, and Teva. DP received advisory board membership, speaker's honoraria, travel support, research grants, consulting fees, or clinical trial support from Almirall, Biogen, BMS-Celgene, Sanofi-Genzyme, Merck Serono, Novartis, Roche, and Alexion. PG is an advisory board member of Biogen, Bayer-Shering, Roche, Merck-Serono, Novartis Pharma, Sanofi-Genzyme, Teva; he received honoraria for speaking or consultation fees from Biogen, Bayer-Shering, Roche, Merck-Serono, Novartis Pharma, Sanofi-Genzyme, Teva, Almirall, Sandoz; he is the principal investigator in Phase I, II and III clinical trials for Biogen, Bayer-Shering, Roche, Merck-Serono, Novartis Pharma, Sanofi-Genzyme, Teva; he received research funds from Biogen, Bayer-Shering, Roche, Merck-Serono, Novartis Pharma, Sanofi-Genzyme.

Multimedia Appendix 1
Description of the digital tools used in the study and of the personnel involved in the study activities.
[DOCX File , 24 KB - resprot_v14i1e58026_app1.docx]

Multimedia Appendix 2
Original Italian version of the information sheet and its English translation.
[DOC File , 74 KB - resprot_v14i1e58026_app2.doc]

Multimedia Appendix 3
The collection of the outcome measures occurs at different time points depending on the considered measure.
[DOCX File , 25 KB - resprot_v14i1e58026_app3.docx]

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Abbreviations

2MWT: 2-minute walk test
9HPT: 9-Hole Peg Test
BICAMS: Brief International Cognitive Assessment for Multiple Sclerosis
CSQ-8: Client Satisfaction Questionnaire
eCRF: electronic case record form
EDSS: Expanded Disability Status Scale
IPAQ: International Physical Activity Questionnaire
IRCCS: Istituto di Ricovero e Cura a Carattere Scientifico
LTPA-Q: Leisure Time Physical Activity Questionnaire
MFIS: Modified Fatigue Impact Scale
MS: multiple sclerosis
MSQoL-54: Multiple Sclerosis Quality of Life-54
MSWS-12: 12-Item Multiple Sclerosis Walking Scale
PA: physical activity
PGIC: Patients' Global Impression of Change

PWB: Psychological Well-Being Scales
QoL: quality of life
RCT: randomized controlled trial
T25FW: Timed 25-Foot Walk
TSQ-WT: Tele-healthcare Satisfaction Questionnaire – Wearable Technology
TUG: Timed Up and Go
VAS: visual analog scale

Edited by A Schwartz; submitted 04.03.24; peer-reviewed by A Batrakoulis, S Monjezi, V Loerzel; comments to author 25.06.24; revised version received 30.08.24; accepted 25.11.24; published 03.02.25.

Please cite as:
Tacchino A, Ponzio M, Confalonieri P, Leocani L, Inglese M, Centonze D, Cocco E, Gallo P, Paolicelli D, Rovaris M, Sabattini L, Tedeschi G, Prosperini L, Patti F, Sessa E, Pedrazzoli E, Battaglia MA, Brichetto G
Effect of an Internet-Based Pilates Telerehabilitation Intervention in People With Multiple Sclerosis: Protocol for a Randomized Controlled Trial
JMIR Res Protoc 2025;14:e58026
URL: https://www.researchprotocols.org/2025/1/e58026
doi:10.2196/58026
PMID:

Protocol

Swasthya Pahal (Health for All) Using a Sustainable, Multisector, Accessible, Affordable, Reimbursable, and Tailored Informatics Framework in Rural and Urban Areas of Chennai, Tamil Nadu: Protocol for a Quantitative Study

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Abstract

Background: Noncommunicable diseases (NCDs) require a longer period of care, for which health care systems must acquire technologically advanced solutions to enhance patient care. Swasthya Pahal (health for all) is an innovative, interactive, multilingual, stand-alone, internet-enabled computer-based program that aims to improve the self-management of NCDs.

Objective: This study aims to enhance the self-management of chronic NCDs (diabetes, hypertension, high cholesterol, and obesity) by determining the usefulness, acceptance, and effectiveness of the Swasthya Pahal program in hospital and community settings in both rural and urban areas of Chennai, Tamil Nadu. This objective can be met by generating risk factor profiles of individuals enrolled and enhancing their self-management of NCDs using a portable health information kiosk that uses the Sustainable, Multisector, Accessible, Affordable, Reimbursable, and Tailored (SMAART) model.

Methods: A quantitative study will be conducted on a convenient sample of 2800 individuals from selected hospital and community settings in rural (n=1400) and urban areas (n=1400) in Chennai, Tamil Nadu. Data will be collected on sociodemographics, health behaviors, and clinical status, as well as knowledge, attitudes, and practices. Objective assessments such as weight, blood pressure, and random blood sugar levels will be measured. In addition, the usefulness, acceptance, and effectiveness of the Swasthya Pahal program will be determined.

Results: Results will be summarized using descriptive analysis. Appropriate bivariate and multivariate regression analysis will be performed to determine the predictors of the outcome variables of usefulness, acceptance, and effectiveness of Swasthya Pahal in wider settings. All analyses will be performed using SAS (version 9.1; SAS Institute), and the results will be reported as 95% CI values and $P<.05$.

Conclusions: The study proposes to enhance the self-management of NCDs in both rural and urban community settings through the implementation of the Swasthya Pahal program based on the SMAART informatics framework. The study aims to understand the implementation, acceptability, and usability of Swasthya Pahal among a diverse sample of people in urban and rural settings.

International Registered Report Identifier (IRRID): PRR1-10.2196/39950

(JMIR Res Protoc 2025;14:e39950) doi:10.2196/39950

KEYWORDS

interventions; Swasthya Pahal; acceptance; health behavior; NCDs risks; self-management; healthcare; noncommunicable disease

Introduction

Background

Noncommunicable diseases (NCDs), which include heart disease, stroke, cancer, diabetes, and chronic lung disease, are the leading causes of illness worldwide. This has been identified as one of the most significant challenges to sustainable development in the 21st century [1]. According to the World Health Organization, NCDs account for approximately 38 million (68%) of all deaths worldwide and approximately 5.87 million (60%) of all deaths in India [2]. The Sustainable Development Goal target 3.4 is to reduce premature mortality from NCDs by one-third by 2030 relative to 2015, as well as to promote mental health and well-being [3]. India faces a significant burden of NCDs, which poses a challenge in achieving Sustainable Development Goal 3 Good Health and Well-Being. In recent years, India has experienced demographic and epidemiological shifts, resulting in a shift from infectious diseases to NCDs. The World Health Organization reports that 1 in every 4 Indians is at risk of dying from an NCD before the age of 70 years [4]. If timely NCD prevention and control measures are not implemented, the total annual number of NCD deaths will rise to 55 million by 2030 [5].

In the current era, information and communication technologies (ICTs) serve as health systems, promoting, restoring, or maintaining health. They should be used for the prevention and control of both communicable and NCDs at multiple levels and in a variety of ways [4]. The use of ICT in a health-promoting lifestyle behavior program improves health behaviors that are crucial in the prevention of both communicable and noncommunicable diseases. eHealth is defined as the application of ICT in the world of health care. It includes mobile health, telemedicine, health information systems, electronic health records, and many more [6]. These technologies can be presented and accessed in a variety of ways, including web-based applications, mobile phone and alert systems, and phone and videoconferencing. They have been identified as effective measures for improving patient skills and knowledge, increasing the likelihood of healthy behavior [7]. It can provide both low-cost and high-quality services. Health information products can be designed to suit the needs of the community by incorporating high levels of interaction and accessibility. Technological solutions play an important role in health care systems by assisting individuals in self-checking their health status and providing low-cost, accessible, and affordable solutions to meet the demands of local communities across geographical locations, particularly those in resource-poor settings [8]. Studies have shown that the use of ICT through mobile health in India has benefitted both urban and rural healthy and unhealthy (“disease”) population groups. [9-11] Health kiosks will continue to play an important role in the digital health scene for the foreseeable future. One of the advantages of telehealth kiosks is that they bring medical and expert care to remote locations that medical practitioners rarely visit. In nations such as India, these locations could be distant rural areas with inadequate infrastructure [12]. A pilot study of the Swasthya Pahal (health for all) program, which is an advanced community-based program facilitated by an interactive, multilingual, standalone, and internet-enabled program, has highlighted the improvement of self-management of NCDs among police personnel [13]. The program was implemented through a digital, interactive touch screen platform Sustainable, Multisector, Accessible, Affordable, Reimbursable, and Tailored (SMAART) model. The potential outcome of the SMAART platform is that it is a personalized self-management action plan that enables easier self-management and that is backed up by continuous monitoring, interactive health information, and collaborative decision-making [8]. The pilot study had significant findings: the applicability of the study and its use beyond a purposive population group needed to be further studied. The program is based on the Population Health Informatics framework; to the best of our knowledge, this framework is now used to address the burden of NCDs in both urban and rural economic groups. This study aims to evaluate the usability of a portable health information kiosk that uses the SMAART framework to address the burden of NCDs by determining the usefulness, acceptance, and effectiveness of Swasthya Pahal in hospital and community settings of both rural and urban areas of Chennai, Tamil Nadu.

Objectives

The objectives of the research are as follows:

1. To use the digital health intervention Swasthya Pahal to assess the risk factor profile of NCDs in individuals from hospital and community settings in rural and urban areas of Chennai, Tamil Nadu.
2. To assess individuals’ Knowledge, Attitudes, and Practices (KAP) of their health status and self-management of chronic NCDs (diabetes, hypertension, high cholesterol, and obesity) through the Swasthya Pahal program among individuals from hospitals and community settings in rural and urban areas of Chennai, Tamil Nadu.
3. To investigate the usefulness and acceptance of the Swasthya Pahal program among individuals from the hospital and community settings in rural and urban areas of Chennai to enhance self-management of NCDs.

Methods

Study Design

The quantitative pre-post study will recruit 2800 study participants from the community and hospital settings in urban and rural areas of Chennai, Tamil Nadu. Individuals will have access to a touch screen device to register their health data in their respective languages. Subjective data on sociodemographic details, health behaviors, clinical status, and KAP will be gathered. Objective data will include measurements of height, weight, blood pressure, and blood glucose levels. Individuals will be randomly assigned to the intervention and control group. A total of 20% of the rural and urban samples will be assigned

to the control group (total N=560; n=280 from each urban and rural area) and intervention group (total N=560; n=280 from each urban and rural area). Those in the intervention group will have access to tailored messages through the use of multiple interactive digital formats using podcasts and SMS. Those in the control group will have access to standard of care and will be provided with a booklet in English and in the local dialect to self-manage the burden of NCDs. Individuals will receive interactive messages for 3 months on a daily or weekly basis. The message content and delivery will be tailored (based on sociodemographics, KAP, user preferences, and disease conditions) to meet the specific needs of the individuals. Monthly assessments will be done at month(s) 1, 2, and 3. At 6 months, retention analysis will be done for Knowledge. In addition, the usefulness, acceptance, and effectiveness of Swasthya Pahal will be assessed postintervention.

Study Setting and Study Population

The study population will be from hospital and community settings of selected rural and urban areas of Chennai, Tamil Nadu, namely Kannur, Pannur, Thirumanikuppam, Thodukadu, Kottaiyur, Nemili, Mannur, Kiloy, Ulundai, Narasamangalam, Karanai, Panimalar Medical College Hospital and the Research Institute and Rural Health Training Centre Chennai, and Maligaipattu village.

Sampling and Recruitment

Participants will be recruited using the nonprobability convenience sampling method from selected urban and rural sites of Chennai, Tamil Nadu. Data will be gathered from 2800 participants (1400 each from urban and rural sites).

Inclusion criteria were participants above the age of 18 years and those consenting to participate and exclusion criteria were individuals below the age of 18 years and those who would not give their consent.

Data Collection—Structured and Semistructured Questionnaire

Overview

A structured questionnaire will be used to determine the risk factor profile of NCDs in individuals from selected rural and urban areas of Chennai, Tamil Nadu. For objectives 1 and 2, data will be collected on the portable health information kiosk. Individuals will be enrolled in the Swasthya Pahal program with a unique code that will generate a SMAART health card. Information will be recorded electronically, that is, subjective data that captures sociodemographic profile, clinical status, information on health behavior, KAP of individuals, and objective data such as BMI, blood pressure, and blood glucose levels will be measured. After 3 months of intervention, a posttest will be conducted on KAP, and then a crossover of intervention mode is done. For objective 3, after the dual intervention, KAP will be conducted and the acceptance and usability of the program will be assessed by 2 tools: the Client Satisfaction Questionnaire and System Usability Scale (annexures 2 and 3 in Multimedia Appendix 1). The tool will be translated into the local language (Tamil). A small group of respondents will pilot test the study tool in the local language to ensure the clarity of the questions asked.

Variables Assessed

The following variables will be assessed in the study: variables A1, A2, A3, and A4 will be assessed with respect to objectives 1 and 2, and variables B1 and B2 will be assessed with respect to objective 3.

A1—Sociodemographic Details

Data will be gathered on the study participant's age, gender, region of residence, and education level.

A2—Health Behavior

Data on history and current smoking and alcohol consumption will be compiled. Data on the family history of consumption will also be collected.

A3—Clinical Status Details

This will include information on anthropometric measurements such as height (as measured by a Stadiometer), weight (as measured by a standard technique), and BMI. A sphygmomanometer will be used to take blood pressure readings. A glucometer will be used to measure blood glucose levels.

A4—Knowledge, Attitudes, and Practices

These data will collect information on an individual's understanding of their BMI, blood pressure, and blood sugar level. The information gathered will determine whether the individual is currently receiving treatment for any disease risks and what treatments have already been followed (eg, diet, medicine, and physical activity). The tool also captures the individual's level of understanding of obesity, hypertension, and diabetic risk factors. It also acquires information on individuals receiving treatment for any of the illness risks and information on individuals' understanding of their family's health history.

B1—Tool for Acceptance: Client Satisfaction Questionnaire

This questionnaire includes a total of 8 questions on a 4-point Likert scale that contains questions related to the accessibility of the computer-based software Swasthya Pahal.

B2—Tool for Usability: System Usability Scale

The System Usability Scale consists of 10 questions on which individuals rate the system on a 5-point Likert scale based on their opinion of the system's usefulness.

Data Collection, Data Entry, and Quality Assurance

To ensure efficient and high-quality data collection and processing, the following data management protocol will be followed: a well-defined study manual will be prepared, and a well-trained data collection team will be in charge of data collection, data entry, and data security procedures. Each question will be explained clearly by the data collector, and any doubt or confusion regarding the question will be addressed immediately. The data will be electronically recorded using the Swasthya Pahal (Health for All) software.

Data Security and Privacy

Regular backups will ensure data security by storing data files in one password-protected computer or laptop and deleted from other systems. The data files will have a unique password that only the concerned research team will be able to access. Data will be kept for 15 years after the study is completed in case it is needed to validate research findings, set priorities, or be re-analyzed by another researcher [14].

Data Analysis

The collected information will be entered in SAS (version 9.1; SAS Institute) and the results were reported as 95% CI values and $P<.05$. The data will be summarized by using frequency, percentage, mean, and SD values. Appropriate bivariate and multivariate analyses will be done. A *t* test to compare means between the continuous variables and a categorical dependent variable will be conducted. A chi-square analysis will be performed to determine whether the two independent variables are related.

Project Timeline and Milestones

A detailed research plan and schedule timeline of the tasks involved in the study are presented in Table 1.

Table 1. Scheduled timeline of the tasks in the Swasthya Pahal.

Task	Months									
	1	2	3	4	5-7	8-10	11-13	13-15	16-19	20-24
Review of the literature, initial design, and planning of the study	✓	✓								
Development of study protocol and ethical approval		✓								
Approval of the study		✓								
Development of the study tool		✓								
Review and revision of the study tool by the research team			✓							
Training of the data collection team			✓							
Pilot testing of Swasthya Pahal computer-based tool			✓							
Initial data analysis, results, discussion, and dissemination of the pilot study				✓						
Deployment of the Swasthya Pahal intervention and baseline data collection					✓					
Recruitment of the target sample and assignment into intervention and control groups					✓					
Post assessment at 1, 2, 3, and 6 months					✓	✓	✓			
Reviewing collected data by the research team								✓	✓	
Data analysis									✓	
Results and Discussion and Conclusion										✓
Dissemination										✓

Informed Consent

The research team will provide the informed consent form approved by the Institutional Review Board (IRB) to all eligible participants in the study (Multimedia Appendix 1). The team will explain the study details, the time commitment, and the benefits of the study results to the participants. Those who are willing to participate and provide consent will be enrolled in the study. If any participant is uneducated, ethical consent will be audio recorded. Furthermore, uneducated participants will be instructed on how to complete the questionnaire in the local Indian dialect, increasing the study's usefulness and generalizability. Data privacy and patient confidentiality will be assured. The study participants will have the right to withdraw from the study at any time.

Ethical Considerations

The study with protocol number PMCHRI-IHEC-058 gained approval from the Panimalar Medical College Hospital and Research Institute Institutional Human Ethics Committee (Central Drugs Standard Control Organization Registration number ECR/1399/Inst/TN/2020) in February 2022 with approval number PMCH&RI/IHEC/20221/021 dated February 18, 2022. The study will be conducted according to the Declaration of Helsinki, as it involves human participants [15].

Results

The program Swasthya Pahal aims to enhance the self-management of NCDs, including diabetes, hypertension, and obesity, in the rural and urban setting of Tamil Nadu, which will help in examining the individual's perception of NCDs and also help in behavioral changes among the general population. The data collected will determine the predictors of the outcome variables of usefulness, acceptance, and effectiveness of Swasthya Pahal and broaden the applicability of the Swasthya Pahal program among individuals from rural and urban settings.

Discussion

Overview

NCDs claim the lives of 40 million people worldwide each year, accounting for 70% of all fatalities. Cardiovascular illnesses (17.7 million deaths), malignancies (8.8 million deaths), respiratory diseases (3.9 million deaths), and diabetes (1.6 million deaths) account for 81% of these deaths [16,17]. NCDs have become a serious public health problem in developing nations like India. NCD imposes financial consequences for India's poorer households, as well as high out-of-pocket costs for the acute and long-term impacts of NCDs. This results in catastrophic health expenditure for households [18]. As a result, it is critical to screen individuals for NCDs and provide health education. Tailored ICT-supported NCD management programs such as Swasthya Pahal (Health for All) can make a difference by ascertaining an individual's risk factor profile, as well as their perspective on NCDs and their health status. The critical need of the hour is the applicability of tailored NCD management interventions that can enhance knowledge and prognosis of the disease to the patient while also influencing policy decisions among low- and middle-income countries [19]. This digital platform intervention across a wider population group cannot only enhance the self-management or prevention of NCDs in individuals but its usefulness and acceptance may assist researchers and policymakers in health education and communication across the country.

The limitation of the study is that it is cross-sectional, needs to evaluate the long-term impact of the Swasthya Pahal program, and covers a large population group in the self-management of NCDs.

Conclusions

Swasthya Pahal offers a personalized self-management plan that is supported by continuous monitoring, interactive health data, and collaborative decision-making. It focuses on an individual's risk factor profile and helps us understand how they perceive NCDs and their health status. The research will help us understand the acceptability and usefulness of Swasthya Pahal among a large sample from urban and rural settings. It can be used to raise awareness and address the burden of NCDs. The program can be used for developing cost-effective interventions that can be used to educate populations from remote or unreached areas.

Acknowledgments

The authors are the only ones who contributed to this paper, and they are appreciated.

Data Availability

The data sets generated during and/or analyzed during this study are available from the corresponding author on reasonable request.

Authors' Contributions

AJ, SKM, SRS, and DO contributed to conceptualization. AJ and HK assisted with data curation. AJ and AG performed the formal analysis. SKM assisted with methodology. SKM, HK, and SRS conducted project administration. AJ and DO assisted with resources. SKM assisted with software. AJ contributed to supervision. HK, SRS, and DO assisted with writing–original draft. AJ, SKM, and AG contributed to writing–review & editing.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Study tools.
[DOCX File , 27 KB - resprot_v14i1e39950_app1.docx]

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Abbreviations

ICT: Information and Communication Technology
KAP: Knowledge, Attitudes, and Practices
NCD: noncommunicable diseases
SMAART: Sustainable, Multisector, Accessible, Affordable, Reimbursable, and Tailored framework

Edited by A Mavragani; submitted 29.05.22; peer-reviewed by L Guo, N Mathew; comments to author 22.11.22; revised version received 12.12.22; accepted 29.12.22; published 06.02.25.

Please cite as:
Joshi A, Surapaneni KM, Grover A, Kaur H, Saggu SR, Oliveira D
Swasthya Pahal (Health for All) Using a Sustainable, Multisector, Accessible, Affordable, Reimbursable, and Tailored Informatics Framework in Rural and Urban Areas of Chennai, Tamil Nadu: Protocol for a Quantitative Study
JMIR Res Protoc 2025;14:e39950
URL: https://www.researchprotocols.org/2025/1/e39950
doi:10.2196/39950
PMID:

Protocol

Effectiveness of Anti-Gravity Treadmill Exercise After Total Knee Arthroplasty: Protocol for a Randomized Controlled Trial

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Abstract

Background: Postoperative rehabilitation following total knee arthroplasty (TKA) varies worldwide. In Finland, patients receive guidance on safe walking and home exercises from a physiotherapist both before and after TKA. These are performed independently after surgery. However, a sedentary lifestyle is rather common among patients who have undergone TKA, with pain often limiting postoperative walking, training, and activities of daily living.

Objective: This randomized controlled trial aimed to investigate the effectiveness of anti-gravity exercise, precisely the AlterG anti-gravity treadmill, on postoperative rehabilitation following TKA and to obtain new knowledge on this form of rehabilitation to better use it in the future.

Methods: This randomized controlled trial study divided the patients into two groups: the intervention group and the control group. The follow-up period was 12 months. Research data were collected through questionnaires and functional tests. All patients in both groups responded to the questionnaires and participated in functional tests before surgery as well as 4 and 12 months after surgery. Patients in the intervention group exercised on the AlterG treadmill 10 times after the surgery. All the patients in this study performed the exercises as instructed when they were in the hospital. The primary outcomes were perceived pain, walking ability, and quality of life.

Results: The data collection process began in 2018 and concluded in 2022, intending to obtain valuable information regarding the effect of AlterG training after TKA and determine whether it, along with traditional exercises, could be an effective form of rehabilitation that can be performed at home. We hypothesized that AlterG training would lead to faster rehabilitation, better walking quality, improved quality of life, improved physical activity, and improved overall functioning. The results of this study will be analyzed in 2025 and 2026.

Conclusions: This study provides information on how AlterG training can be used in rehabilitation after TKA, further enhancing the rehabilitation program for patients undergoing TKA in general.

Trial Registration: ClinicalTrials.gov NCT03904030; https://clinicaltrials.gov/study/NCT03904030

International Registered Report Identifier (IRRID): DERR1-10.2196/59935

(JMIR Res Protoc 2025;14:e59935) doi:10.2196/59935

KEYWORDS

total knee arthroplasty; AlterG; anti-gravity treadmill; postoperative rehabilitation; walking ability; quality of life; pain

Introduction

Overview

Pre- and postoperative rehabilitation for total knee arthroplasty (TKA) varies worldwide [1-3]. There are guidelines for postoperative physiotherapy after TKA [4], and physiotherapy guidance for self-directed home exercises is recommended [5]. In Finland, the current care guidelines provide guidance for pre- and postoperative rehabilitation [6], but the practices associated with the rehabilitation vary among different hospitals. Previous studies have shown that both inpatient and home-based rehabilitation are effective after TKA [7] and that resistance training in water is a feasible mode of rehabilitation with a wide range of positive effects on patients undergoing TKA [8]. Reportedly, a sedentary lifestyle is rather common among patients who have undergone TKA, with pain or discomfort while standing being the greatest barrier to increasing physical activity [9]. Pain limits postoperative walking training and activities of daily living [10].

Anti-gravity exercises could help address these challenges. They enable a more objective analysis of walking, showing the entire picture of a patient's walking problems. AlterG (AlterG, Inc., Fremont, CA), a patented compressed air technology (NASA differential air pressure technology), can be used to lighten the user's body weight and the load of gravity with 1% accuracy, thereby enabling a less painful walking exercise compared to normal land-based training [11]. While there is limited research on the effects of AlterG training, randomized controlled trials (RCTs) with small sample sizes have been reported, particularly among patients with neurological disorders, such as cerebral palsy [12] and stroke [13,14]. These studies demonstrated that AlterG training positively affected walking speed and dynamic balance and reduced the risk of falls [12-14]. Similar results were reported in studies investigating the effects of AlterG training in rehabilitation after lower limb fractures [15,16]. Precisely, it was found that AlterG training increased muscle strength in the hip area [15] and enabled better walking [16].

A pilot study on AlterG training after TKA revealed that it increased functional ability and is thus overall a safe, useful, and effective rehabilitation method after TKA [17]. Although previous researchers [17] concluded that while functional outcomes improved over time with the use of anti-gravity gait training, further studies with a larger sample size are required to define the role of this device as an alternative or adjunct to established rehabilitation protocols [17]. Furthermore, AlterG training in the acute phase of postoperative knee rehabilitation after knee surgeries, such as TKA and anterior cruciate ligament reconstruction, demonstrated a positive effect on balance in patients experiencing increased pain in weight-bearing postures [18]. AlterG training also decreased pain, enhanced joint function, improved quality of life (QoL), and maintained thigh muscle strength gains in patients with knee osteoarthritis [19]. However, as previously mentioned, not much research has been conducted on postoperative rehabilitation including AlterG training after TKA [17,18], thereby warranting further studies in the future to obtain more knowledge regarding its effects on walking and functional capacity.

Aims and Objectives

The exposures under investigation were the effects of anti-gravity treadmill training in postoperative rehabilitation following TKA and the added value it offered compared to traditional exercise. We hypothesized that AlterG training after hospitalization leads to faster rehabilitation, better walking quality, improved QoL, improved physical activity, and enhanced balance management compared to traditional rehabilitation methods with instructions, where patients perform the exercises independently at home. In addition, we hypothesized that the differences, in terms of the above factors, between the groups in the study—intervention group and control group—were larger in the early phase of the rehabilitation but became smaller over time. The study has been registered on ClinicalTrials.gov (NCT03904030).

This study aimed to determine the effectiveness of the AlterG anti-gravity treadmill in postoperative rehabilitation after TKA. Primary outcomes were perceived pain, walking ability, and QoL. To this end, AlterG rehabilitation and traditional postoperative rehabilitation with instructions were compared.

In detail, we aimed to measure the effects of AlterG training on:

- a patient's walking ability and walking distance after TKA,
- a patient's perceived QoL and functional ability after TKA,
- a patient's perceived pain, and
- lower limb and step symmetry during gait and if it normalizes the patient's stepping and walking.

Methods

Participant Selection and Sampling Strategy

Participants for this RCT study were recruited from two hospitals in the capital region of Finland: Orton Orthopaedic Hospital and Peijas Hospital, both of which are part of the HUS Helsinki University Hospital. Patients with grades 3 and 4 primary knee osteoarthritis and with a scheduled unilateral TKA were included in the study. Those with rheumatoid arthritis, who have undergone hip or knee arthroplasties within the last year, or with a BMI >40 kg/m^2 were excluded. All eligible patients who came for a knee arthroplasty surgery at Orton Orthopaedic Hospital between 2018 and 2021 and at Peijas Hospital between 2020 and 2021 were asked to participate in the study. The patients were recruited through a nurse's preoperative visit or a phone call made to the patients attending the surgery. The nurse then checked whether they met the inclusion and exclusion criteria; those who met the criteria were provided with written information regarding the study. The included patients were asked to provide signed consent forms (Multimedia Appendix 1), which they forwarded to the research assistant. When the patient had consented to participate in the trial, the randomization envelope was opened after the surgery. However, due to the nature of the intervention under study (rehabilitation intervention), it was not possible to blind the patients. The patients were randomly allocated either to the treatment group or the control group using a random number generator (StatTrek) by an expert who did not execute the study in practice. All the patients had free access to the available

health care services during the study. Overall, 62 patients (31 in each group) were recruited for the study.

Study Procedure

Patients in both groups underwent initial measurements 1-2 weeks before the surgery, which included questionnaires and functional tests performed by a physiotherapist. All the measurements were taken at Orton Orthopaedic Hospital. First, the patients were asked to complete the questionnaires, and functional tests were then performed. The questionnaires used were a visual analogue scale (measures perceived pain) [20], painDETECT [21], Tampa Scale of Kinesiophobia [22], RAND 36-item Health Survey 1.0 (RAND-36) [23], Oxford Knee Score [24,25], Western Ontario and McMaster Universities Osteoarthritis Index [26], Beck Depression Inventory [27], and State-Trait Anxiety Inventory [28] (Table 1). Functional tests performed were knee range of motion (ROM) [29], knee swelling [30], thigh circumference [31], single-leg stance test [32], Timed Up and Go test (TUG) [33,34], stair climbing test [35], and 6-minute walk test (6MWT) [36] (Table 1).

Patients were asked to complete the same questionnaires 6-8 weeks after surgery. The same questionnaires and functional tests were administered in the same order 4 and 12 months after the surgery at Orton Orthopaedic Hospital. This data can help obtain information regarding short-term (4 months) and long-term (12 months) changes. Then, 6 months after the surgery, the patients were sent a 6-month questionnaire regarding possible rehabilitation sessions, use of medication, and possible complications after TKA. The purpose of this questionnaire was to obtain information regarding their use of health care services and how their rehabilitation and recovery from the surgery have progressed.

After the surgery, the researcher informed each patient over the phone or face-to-face about their assigned group, either the intervention or control group. After that, the researcher booked training times on the AlterG for each member of the intervention group. Patients were sent a reminder through an SMS text message on the time reserved for them to ensure that the risk of forgetting was lower. If the time did not suit the patient, the physiotherapist was informed, and a new time was reserved accordingly. The patients in the intervention group exercised 10 times on the AlterG under the supervision of a registered physiotherapist. Both groups performed traditional postoperative exercises after TKA. The follow-up period was 12 months. Exercises began in the third week after surgery. In the third and fourth weeks after TKA, patients in the intervention group exercised twice a week on the AlterG and thrice a week in the fifth and sixth weeks considering individual variations. The AlterG training was recorded 3 out of 10 times—the first, fifth, and 10th training sessions. The recording began after the patient found a suitable walking speed and lightening. On average, the length of one recording was 2 minutes. The data obtained from the AlterG training was saved to a memory stick and then transferred to an electronic folder. The patient schedule of enrollment, interventions, and assessments are shown in Table 2. The study procedure is outlined in Figure 1.

The protocol has been developed using the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) checklist [37] (Multimedia Appendix 2).

Table 1. Questionnaires and functional tests.

Measurement	Explanation
Questionnaires	
Pain	
Severity of pain: VAS[a] [20]	The scale ranges from 0 to 100, where 0 indicates no pain at all and 100 indicates the worst possible pain.
Neuropathic pain: painDETECT [21]	The screening questionnaire identifies neuropathic components in patients with pain.
Fear of movement: TSK[b] [22]	The screening questionnaire detects fear of movement due to pain.
OKS[c] [24,25]	The 12-item questionnaire assesses knee pain and functionality.
WOMAC[d] [26]	The disease-specific questionnaire explores the effects of osteoarthritis treatment intervention.
Quality of life	
RAND-36[e] [23]	The questionnaire explores well-being and functional ability across eight dimensions: general health perceptions, physical functioning, emotional well-being, social functioning, energy, bodily pain, role functioning/physical, and role functioning/emotional.
Depression and anxiety	
BDI-21[f] [27]	The 21-item questionnaire measures depression.
STAI[g] [28]	The 40-item questionnaire measures trait and state anxiety.
Functional tests	
Knee ROM[h] in degrees (°) [29]	Knee ROM (flexion and extension) is measured using a goniometer.
Knee swelling (cm) [30]	Knee joint swelling is measured using a tape measure at the popliteal.
Thigh circumference (cm) [31]	The thigh circumference is measured using a tape measure 15 cm above the upper edge of the patella.
Single-leg stance (s) [32]	The balance test assesses static balance and upright posture control on a support surface narrower than a normal stance.
TUG[i] (s) [33,34]	The functional test measures an individual's mobility/ability to move.
Stair climbing test (s) [35]	The functional test measures the functionality of the lower extremities and balance control. Here, the test was systematically conducted on the same staircase, which had 11 steps. The depth of one step was 34 cm, and the height was 14.5 cm.
6MWT[j] (m) [36]	The functional test measures an individual's endurance and walking ability.

[a]VAS: visual analogue scale.

[b]TSK: Tampa Scale of Kinesiophobia.

[c]OKS: Oxford Knee Score.

[d]WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index.

[e]RAND-36: RAND 36-item Health Survey 1.0.

[f]BDI-21: Beck Depression Inventory.

[g]STAI: State-Trait Anxiety Inventory.

[h]ROM: range of motion.

[i]TUG: Timed Up and Go test.

[j]6MWT: 6-minute walk test.

Table 2. Patient schedule of enrollment, interventions, and assessments.

	Enrollment	Study period							
		Initial assessment	Allocation	Post-allocation					Closeout
	–2 to –3 weeks	–1 to –2 weeks	0 weeks	3-6 weeks	6-8 weeks	4 months	6 months	12 months	12 months
Enrollment									
Eligibility screen	✓								
Informed consent	✓								
Allocation			✓						
Interventions									
Intervention (AlterG)				✓[a,b]	✓[b]				
Control group (traditional exercises)				✓[b]	✓[b]				
Assessments									
Questionnaires (VAS[c], PainDETECT, TSK[d], RAND-36[e], OKS[f], WOMAC[g], BDI-21[h], and STAI[i])		✓			✓	✓		✓	✓
Functional tests (ROM[j], knee swelling, thigh circumference, single-leg stance, stair climbing test, and 6MWT[k])		✓				✓		✓	✓
6-month questionnaire							✓		

[a]AlterG training (10 times).

[b]Traditional home exercises that the patient was instructed to perform in the hospital after the total knee arthroplasty.

[c]VAS: visual analogue scale.

[d]TSK: Tampa Scale of Kinesiophobia.

[e]RAND-36: RAND 36-item Health Survey 1.0.

[f]OKS: Oxford Knee Score.

[g]WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index.

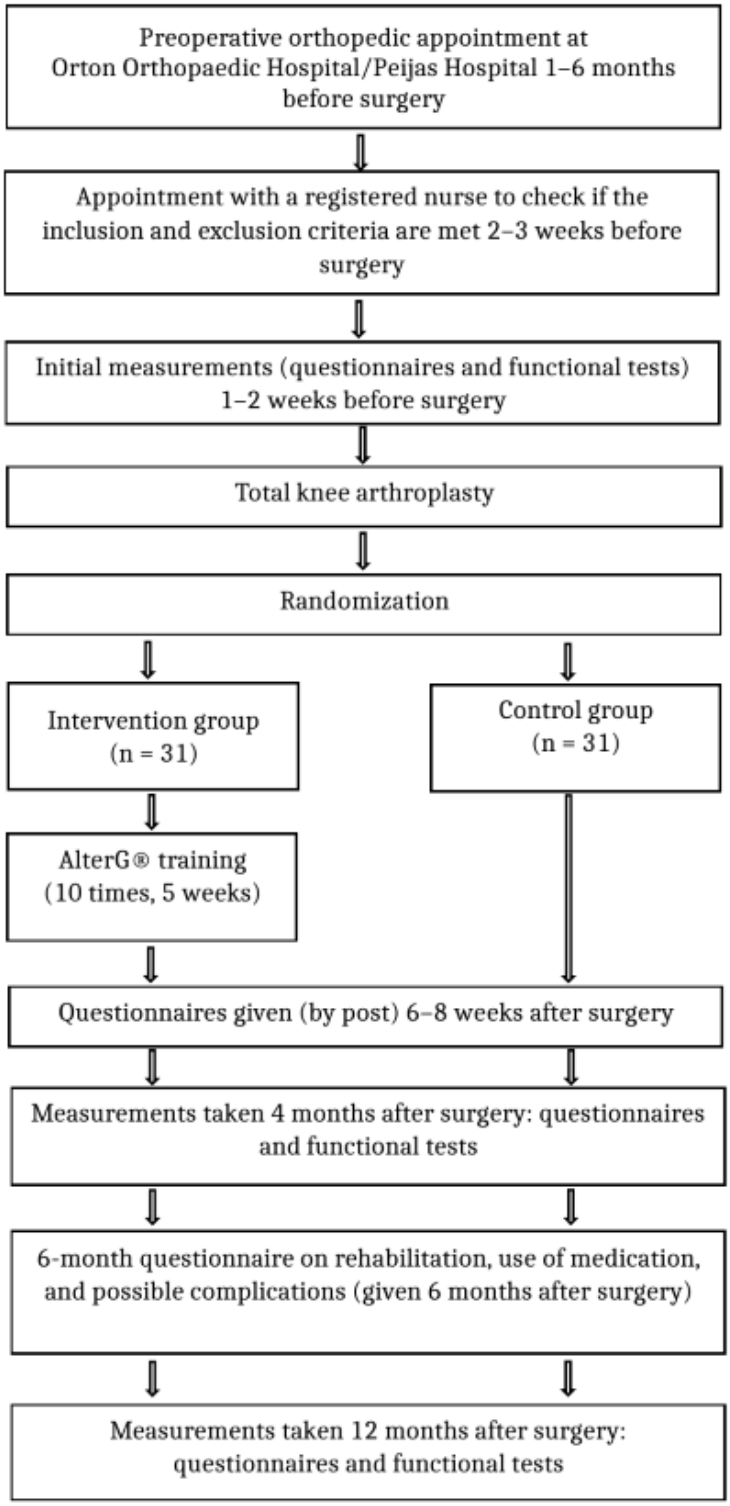
[h]BDI-21: Beck Depression Inventory.

[i]STAI: State-Trait Anxiety Inventory.

[j]ROM: range of motion.

[k]6MWT: 6-minute walk test.

Figure 1. Study procedure.



Postoperative Exercises

Furthermore, all the patients (intervention and control groups) in the study independently performed the postoperative exercises instructed by the hospital's physiotherapists. The exercises were aimed to improve knee ROM and quadriceps and hamstring muscle strength and to stimulate venous circulation. Patients also received guidance on walking with crutches. They were instructed to perform home exercises for approximately 2 months after surgery. However, the researchers do not have information on how actively the patients were engaged with home exercises. The home exercises are described in Table 3.

Table 3. Traditional home exercises.

Exercise	Description	Aim
Knee flexion (sitting/supine position)	Sitting on a chair or in the supine position, the patient flexes the knee as much as possible, sliding the sole of the foot backward on the ground. The patient keeps the knee flexed for a while and then returns the lower limb to the starting position, sliding the sole of the foot forward.	To increase knee mobility in the direction of flexion
Knee flexion (standing position)	In the standing position, the patient brings the operated foot on a stair and shifts the weight forward, stretching the knee in the direction of flexion.	To increase knee mobility in the direction of flexion
Quadriceps strengthening (sitting/supine position)	In the sitting or supine position on a bed, the patient extends the knee and presses it against the platform or a towel roll by activating the quadriceps muscles. When performing this in the supine position, at the end of the movement, the patient can lift the straight leg off the ground. Quadriceps strengthening can also be done by sitting on a chair and lifting the straight leg off the ground.	To activate and strengthen the quadriceps muscles and the end-extension of the knee
Ankle pump movements (flexion and extension)	In the supine position, the patient flexes and extends the ankles in turns.	To stimulate and enhance venous blood circulation
Dynamic calf stretching	In the standing position, the patient performs a dynamic calf stretch, taking a step backward with the operated leg and pressing the heel on the ground while extending the knee and then lifting the heel off the ground and letting the knee flex.	To stretch the calf muscles
Hamstring stretching	In the sitting position and with the operated leg straight on the bed, the patient bends the upper body forward and stretches the hamstring muscles.	To stretch the hamstring muscles
Toe raises	In the standing position, the patient takes support from the back of the chair with their hands and rises to their toes and then returns to the starting position.	To activate the calf muscles
Walking with crutches	The patient is instructed on how to walk with crutches after the surgery, using either three-point walking or alternating walking, or with only one crutch. The patient is also instructed to walk on stairs with a crutch/crutches.	To guide the patient on how to use crutches after the surgery

Outcome Assessment and Measurements

The primary outcomes were walking ability measured with the 6MWT, health-related QoL measured with RAND-36, and perceived pain measured with VAS. All outcomes were measured before the TKA and 4 and 12 months after the TKA. In addition to this, the patients were asked to complete the same questionnaires 6-8 weeks after the TKA. The initial measurements were performed 1-2 weeks before the TKA. Depending on the patient, it took a total of 1.5-2 hours to complete the questionnaires and execute the functional tests. The same measurements were performed 4 and 12 months after the surgery, and the time required for these was the same as in the initial measurements (1.5-2 hours). Regarding the functional tests, the test scores were not calculated within the testing situation; however, the physiotherapist noted the measurement results on the test form, which were then saved in an electronic format. The results obtained from the tests were compared throughout the study between the patient's own results and between the intervention and control groups; no comparisons were made with the general reference values of the tests. The knee ROM and swelling, thigh muscle circumference, TUG, stair climbing test, and 6MWT were performed only once. The tests were performed twice only in the static balance test, and the best test result was recorded (the maximum time was 60 seconds).

All the measures of the study are presented in Table 1. During the AlterG training, the weight-bearing symmetry, step length, stance time symmetry, and cadence during walking were measured (Textbox 1).

Textbox 1. AlterG measurements.

Weight-bearing symmetry

- Weight-bearing symmetry gives information about the symmetry of the stance phase. In pathological situations, the stance phase is shorter on the weaker side [38].

Step length symmetry

- Step length is the distance from the back of one heel to the back of the other heel [38].

Stance phase symmetry

- Stance phase is the period when the foot is on the ground [38].

Cadence (steps/min)

- Cadence is the number of steps taken per minute [38].

Data Collection and Statistical Analysis

We estimated that a difference of 30 m in the 6MWT between the two groups would represent a clinically relevant difference [39,40]. To identify such a difference with 2-sided testing (α=.05 and power of 85%), the study required 31 participants in each group, with the assumption of 20% loss to follow-up.

The analysis will use the intention-to-treat principle, which will include all randomized patients. Summary statistics will be described using mean and SD, median and IQR, or numbers and percentages. Statistical comparison between the groups will be performed using the *t* test, Mann-Whitney test, χ^2 test, or Fisher-Freeman-Halton test, as appropriate. A linear mixed model or generalized estimating equation model with appropriate distribution and link function for repeated measurements will be used for analysis. In case of a violation of the test assumptions, a bootstrap-type method or Monte Carlo method will be used. Normal distributions will be graphically evaluated using the Shapiro-Wilk W test. Stata 18 (StataCorp LP) will be used for the analysis. Access to data will be granted to the research team of this study.

Ethical Considerations

The study protocol was approved by the ethics committee of the Hospital District of Helsinki and Uusimaa in 2017 (HUS/3117/2017). Helsinki University Hospital, Peijas Hospital, was also included in the study in 2020, and updated ethical permission and research permission were received from HUS (HUS 234/2020). Good research ethics practices were maintained in the study in accordance with the Declaration of Helsinki. Before participating in the study, every patient was given an information letter that would help them decide whether they wanted to participate in the study; once the decision was made, they were asked to sign a written consent form. The patients had the right to discontinue the trial whenever they wanted without giving any reason. However, the data collected before the discontinuation can be used for research purposes (Multimedia Appendix 1).

There was no inclusion of vulnerable groups such as children, prisoners, or individuals with mental disability. No participant reimbursement was provided to prevent economic factors from impacting the recruitment process.

If there were any changes to the protocol, the ethics committee and other relevant parties were informed.

Ensuring Data Quality

Anonymity and confidentiality were ensured by using numerical codes for the participants. Only the research group members had access to the participants' names. Data protection and storage security were ensured by storing the participant information and questionnaires in a locked cabinet at Orton Orthopaedic Hospital. Data were securely stored with electronic passwords on the hospital's server.

Results

The data collection began in 2018 and concluded in 2022. This study aimed to obtain valuable information on the effect of AlterG training after TKA. AlterG, along with traditional exercises, could be an effective form of rehabilitation that can be performed at home. We hypothesized that AlterG training leads to faster rehabilitation, better walking quality, improved QoL, improved physical activity, and improved overall functioning. At baseline, there were 62 participants in the study, with 31 in each group. Of these, 35 (56%) were women, and 27 (44%) were men, with a mean age of 66 (SD 7) years. The results of this study will be analyzed in 2025 and 2026. Results from this study will be submitted for publication in peer-reviewed international scientific journals and presented at scientific meetings.

Discussion

Expected Findings

The expected findings were related to walking ability, health-related QoL, and perceived pain. The expectations were that pain would decrease, walking distance would be longer, and health-related QoL would improve. In addition, we expected that the differences between the groups would be larger in the short term and eventually level out in 12 months.

Comparisons With Prior Work

Studies on postoperative rehabilitation after TKA including AlterG training are scarce [17,18]. To our knowledge, Bugbee et al [17] were the only ones who investigated the effects of AlterG training in patients who underwent TKA in an RCT. Hence, the present study was conducted to further investigate and obtain more information on the effects of AlterG training in patients who underwent TKA.

Limitations and Strengths of the Protocol

One of the limitations of this study was the risk of dropouts when patients heard that they were not included in the intervention group. Second, not all patients were committed to the 12-month follow-up. Third, the implementation of the study coincided with the COVID-19 pandemic, impacting the progress of the study and leading to dropouts.

However, this study also has some strengths. First, this is an RCT study. Second, to the best of our knowledge, there has been only one pilot and feasibility study [17] that directly focused on this issue thus far. With this relatively novel study, it is possible to collect more valuable information on how anti-gravity exercise can be used in rehabilitation after TKA. Third, it investigated aspects of a patient's physical functioning, perceived QoL, and pain rather extensively, thereby providing an opportunity to control various sources of bias such as state of depression and neuropathic pain. Lastly, the study design was planned in a multi-professional manner.

Study Significance and Feasibility

The results of this study provided information on how AlterG can be used in rehabilitation after TKA. With this knowledge, hospitals may potentially develop and enhance the rehabilitation program for patients who undergo knee arthroplasty. It is also possible to use the research results more widely with other patient groups, such as those with lower limb problems and athletes.

Conclusion

The results of this study provided information on how AlterG training can be used in rehabilitation after TKA. This information may enable the enhancement and development of a rehabilitation program for patients undergoing TKA.

Acknowledgments

We would like to thank physiotherapist Iiris Vanhanen for helping to acquire the data needed for the study. We would also like to thank research assistant Arja Mäkelä and registered nurse Leene Torri, both of whom played a key role in recruiting the patients for this study.

This work was supported by the Research Institute Orton through grants from the Ministry of Social Affairs and Health in Finland (A2500/488). The principal investigator also received a personal grant from the Finnish Arthroplasty Association (SAPLY). The funders are not involved in the collection, analysis, and interpretation of data; the writing of the report; or the decision to submit the paper for publication as contracted. This is why a data monitoring committee was not needed.

Data Availability

The datasets generated or analyzed during this study are available from the corresponding author upon reasonable request.

Authors' Contributions

All authors made substantial contributions to the conception or design of the study; the acquisition, analysis, or interpretation of data for the study; the drafting or critical revision of the manuscript for important intellectual content; final approval of the version to be published; and agreement to be accountable for all aspects of the study in ensuring that questions related to the accuracy or integrity of any part of the study are appropriately investigated and resolved.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Consent form.
[PDF File (Adobe PDF File), 58 KB - resprot_v14i1e59935_app1.pdf]

Multimedia Appendix 2
CONSERVE (CONSORT and SPIRIT Extension for RCTs Revised in Extenuating Circumstances)–SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) checklist.
[PDF File (Adobe PDF File), 119 KB - resprot_v14i1e59935_app2.pdf]

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Abbreviations

QoL: quality of life
RAND-36: RAND 36-item Health Survey 1.0
RCT: randomized controlled trial
ROM: range of motion
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials
TKA: total knee arthroplasty
TUG: Timed Up and Go test
6MWT: 6-minute walk test

Edited by T Leung; submitted 26.04.24; peer-reviewed by M Janhunen; comments to author 11.07.24; revised version received 26.11.24; accepted 31.12.24; published 11.02.25.

Please cite as:
Jääskeläinen E, Manninen M, Hurri H, Rantasalo M, Zhou Y, Kautiainen H, Ristolainen L
Effectiveness of Anti-Gravity Treadmill Exercise After Total Knee Arthroplasty: Protocol for a Randomized Controlled Trial
JMIR Res Protoc 2025;14:e59935
URL: https://www.researchprotocols.org/2025/1/e59935
doi:10.2196/59935
PMID:39932768

Protocol

Blended Care Intervention for Cancer Aftercare in General Practice Centers: Protocol for a Randomized Controlled Trial

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Abstract

Background: Combining effective eHealth programs with face-to-face consultations in general practice may help general practitioners care for survivors of cancer.

Objective: This study protocol describes a 2-armed randomized controlled trial to evaluate the cost-effectiveness of a blended intervention integrating the Cancer Aftercare Guide in general practice centers (GPCs).

Methods: A parallel-group design will compare an intervention group with a waiting list control group. Participants will be nested within GPCs and randomization will occur at the GPC level. The participants in the intervention group will receive a blended care intervention. In contrast, the participants in the waiting list control group will receive care as usual for the duration of this study and will receive the online intervention afterward. All participants will be asked to complete an online questionnaire at baseline, 6 months, and 12 months after baseline, measuring self-reported adherence to lifestyle recommendations, psychosocial well-being, and quality of life. A process evaluation and cost evaluation are also included in this study. The effects will be evaluated based on differences in residual change scores between intervention and control group participants, using multilevel linear regression analyses. Moreover, effect analyses will be supplemented with Bayes factor analyses. Finally, an economic evaluation will be conducted from a societal perspective and will include medical costs, productivity costs, and costs of the blended care intervention.

Results: This study was funded in July 2020. Data collection started in August 2022 and is likely to be completed by April 2025. As of December 2024, a total of 127 participants have been included in this study, recruited across 26 GPCs in the Netherlands. Data analysis will commence once data collection is completed. Data analysis is estimated to start in the spring of 2025. The results will likely be published in 2026.

Conclusions: The results will provide insight into the effectiveness of blended care and may be relevant to cancer aftercare, general practice, and the field of eHealth implementation in general. Potential challenges lie in recruitment due to the strain on the health care system since the COVID-19 pandemic.

Trial Registration: ISRCTN ISRCTN12451453; https://www.isrctn.com/ISRCTN12451453

International Registered Report Identifier (IRRID): DERR1-10.2196/64662

(JMIR Res Protoc 2025;14:e64662) doi:10.2196/64662

KEYWORDS

cancer aftercare; general practice; blended care; eHealth; randomized controlled trial; cost effectiveness; general practitioners; online intervention

Introduction

In the coming decades, the growing number of survivors of cancer will challenge health care worldwide. Global data show the increased incidence and survival rates, indicating an increase in the number of survivors of cancer worldwide [1]. Data for the Netherlands (total population of 17 million) predict that in 2032, a total of 1.4 million people will be receiving treatment for cancer or will have been successfully treated for cancer [2]. This underlines the urgency of studying the needs of survivors and finding ways to meet these needs to safeguard the quality of life (QoL) after disease and treatment.

After treatment, survivors of cancer may face physical, psychological, and psychosocial challenges that affect their transition to normal life. In addition, survivors of cancer must adhere to lifestyle recommendations regarding physical activity (PA), diet, smoking cessation, and alcohol consumption to prevent recurrence or the development of comorbidities [3]. In reality, however, many survivors of cancer find it difficult to adhere to these guidelines [4]. They seek support to help them recover and cope with the effects of their disease [5]. However, due to a shortage of health care professionals and increasing demand for care in the general population due to aging, survivors of cancer may not always receive the support they need.

Over the past decades, several eHealth interventions have been introduced to support survivors of cancer in their healthy recovery. The online Cancer Aftercare Guide (CAG) is an example of such an intervention [6,7]. The CAG is a web-based eHealth intervention that targets lifestyle and common psychological and psychosocial problems experienced by survivors by promoting self-management of these problems using evidence-based techniques, such as cognitive behavioral therapy and problem-solving therapy. Effectiveness evaluation has shown that the CAG is effective in reducing fatigue, depression, and anxiety and in increasing PA and healthy eating [8-11]. This shows that the CAG can help survivors cope with common cancer-related problems and can help reduce the risk of future disease by promoting a healthy lifestyle.

The use of eHealth for applications such as disease management and patient data sharing is encouraged [12,13], but in reality, effective eHealth interventions struggle to reach their target population [7,14,15]. For survivors of cancer in particular, it has been found that while they use the internet to search for health information, their use of eHealth self-help programs is not common [16]. One reason for this may be that many eHealth interventions are not implemented in everyday practice [17]. To improve the use of eHealth, the Dutch eHealth Monitor suggests that health care providers play an important role in informing patients about eHealth self-help programs and that health care workflows should be designed to facilitate the use of eHealth through blended care [18]. Similarly, in the case of the CAG, Willems et al [11] and Kanera [6] state that the online intervention could be offered in a blended approach, where patient-therapist interaction is provided, to promote patient engagement with the intervention.

Apart from a biyearly follow-up aimed at detecting recurrence, no structural care is currently provided for survivors of cancer in the Netherlands. For issues related to cancer survivorship, patients are referred to their general practitioner (GP) [19], resulting in on-demand care requests. In addition, GPs are responsible for tertiary prevention, which targets healthy lifestyle behaviors in survivors of cancer. With the increasing number of survivors of cancer, this demand will pose a significant challenge to general practice workflows. Therefore, a structured approach is essential for GPs to meet the needs of their patients. This is illustrated by the Dutch College of General Practitioners (in Dutch: *Nederlands Huisartsen Genootschap*), which stated that general practice could structurally provide cancer aftercare [20]. Implementing the CAG in general practice in a blended care setting could provide a solution to the growing demand for cancer aftercare by promoting healthy recovery and improving self-management of problems, ultimately reducing the care needs of survivors of cancer.

This study protocol outlines a randomized controlled trial (RCT) to investigate the cost-effectiveness and associated process evaluation of a blended care approach offering the CAG in general practice. The blended care intervention has been co-designed with GPs, practice nurses (PNs), and survivors in a separate study (MJM Smits, unpublished data, 2025) and has been tested in a pilot study before starting this RCT.

Methods

Study Design

An RCT will be conducted to compare the effectiveness of the blended CAG intervention between the intervention group and the waiting list control group. A general practice center (GPC) is usually run by at least 1 GP, supported by one or more medical assistants. In addition, many Dutch GPs are supported by PNs who are dedicated to patients with chronic disease, older adult care, and mental health care. The PNs provide additional care for identified health problems, such as asthma, chronic obstructive pulmonary disease, and diabetes (for the somatic nurse) or mental health problems (for the mental health nurse). The intervention protocol is implemented by either the GP or the PN (under the supervision of the GP). A full list of participating GPCs can be requested from the researchers.

Recruitment of GPCs

GPCs will be recruited through a variety of channels, including calls published in online primary care newsletters distributed by Regional Collaborative Care Groups or special interest groups dedicated to oncology care or lifestyle counseling in primary care. In addition, direct mail will also be sent out by the research team. If no response is received within 4 weeks, the direct mailing will be followed by telephone calls to discuss potential participation. GPCs are eligible to participate if they are located in the Netherlands. If the GPC agrees to participate in this study, an appointment will be made for the researcher to visit the GPC to give instructions on this study protocol.

Recruitment of Participants

Overview

Survivors of cancer will be recruited by general practice personnel (GPP: either GP, PN, or assistants). From the GP's

electronic medical record (in Dutch: *Huisartsen Informatie Systeem*), the GPP will select patients who meet the following inclusion criteria: (1) patients who have completed primary treatment of cancer (eg, radiotherapy, chemotherapy, or surgery), with the last treatment having been between 6 weeks and 3 years ago, or who belong to a watchful waiting condition (eg, option for prostate cancer patients); (2) patients who are 18 years of age or older; (3) patients who are able to read and speak Dutch; (4) patients without a serious medical, psychiatric, or cognitive condition that would interfere with participation; (5) patients who have access to the internet and at least minimal experience of using it; and (6) patients who have access to a computer or a tablet.

If desired, the selection of participants can be assisted by the researcher (under the supervision of the GP).

Eligible patients will be invited to participate in this study using an invitation package distributed by the GPC. The information package consists of an information letter, an informed consent form (Multimedia Appendix 1), and a prepaid return envelope. Survivors of cancer who agree to participate will need to sign the consent form and return it to the research team with the return envelope. The researchers will notify the GPC when the consent form has been received and stored. Enrolled patients will receive a welcome email from the researchers, informing them of their randomization (intervention or control group) and providing a link to the first online self-report questionnaire (baseline measurement). Awareness of randomization can lead to selection bias, but studies on survivors of cancer have shown that this effect is minimal [8-11]. Informing patients about the group to which they are assigned is required in the Netherlands by the Medical Research Involving Subjects Act.

The CAG Intervention

The online CAG program provides personalized information in 8 modules covering healthy lifestyles and common psychosocial issues related to cancer survivorship (ie, PA, diet, smoking cessation, alcohol use, fatigue, anxiety and depression, return to work, and social relationships). The CAG will use data from the baseline assessment to create the Module Referral Advice (MRA; Multimedia Appendix 2). The MRA presents personal outcomes across the 8 subtopics featured in the CAG and advises the participant to visit the module that corresponds to their greatest need, as indicated by the MRA. The modules consist of textual information and advice, video clips (in which former cancer patients share their survivorship experiences), and tasks or exercises that the participants can complete independently.

Intervention Procedure

Participants in the intervention group will receive the CAG blended care intervention. This means that after completing the baseline measurement, they will be given access to the online CAG. Participants will use the online CAG program independently at home. In addition, they will be invited to 2 consultations with their GP or PN. Within the online CAG, the intervention group participants will receive personalized advice on 8 topics related to cancer survivorship based on their results at baseline. This is represented by the MRA. Participants are asked to share their MRA results with the GP or PN at their first consultation. During the first consultation, the GP or PN and the participant will discuss the MRA results. Through shared decision-making, the GP or PN will motivate the participant to choose at least 1 of the 8 subtopics to focus on for the next 4 to 6 weeks, after which the follow-up consultation will take place. During the follow-up consultation, the GP or PN will enquire about the participant's progress with the chosen topic or topics. Any questions or problems the participant may have in interpreting the (lifestyle) advice given by the program will be addressed in the personal consultation. After the follow-up consultation, the participant will retain access to the online CAG intervention for up to 6 months after the start of the baseline measurement.

After completing the baseline measurement, participants in the control group are directed to a message thanking them for completing the questionnaire, asking them to log out and return only for the next measurement. Per GP care, participants in the control group will receive care as usual, which is mostly initiated by patient request and is usually complaint-driven. At the end of this study, the researchers will actively inform and encourage control group participants to finally use the online CAG intervention. Study groups will have full access to other interventions during the trial, but only on their initiative. The use of cointervention will be assessed by questionnaires at all time points.

Measurements

All participants will be asked to complete an online questionnaire at baseline, 6 months, and 12 months after baseline. GPs and PNs will not be present during the self-report questionnaire (participants will complete this assessment digitally at home). Therefore, no influence of the GP or PN on the Patient Reported Outcome Measures is expected. The questionnaires will measure self-reported lifestyle behaviors, behavioral determinants, and experienced psychological problems (see the *Outcomes* section).

The second questionnaire, administered 6 months after baseline, will also include items measuring health-related costs and, for intervention group participants only, a process evaluation questionnaire. In addition, biomedical measurements will be taken from all participants at 6 months after baseline. Blood pressure, total cholesterol/high-density lipoprotein cholesterol, and blood glucose were originally planned for the biomedical measurement. However, due to current circumstances in Dutch primary care (see the *Discussion* section), total cholesterol/high-density lipoprotein cholesterol and blood glucose measurements will be discontinued in consultation with the funding agency.

Nonresponse will be prevented by using previously effective protocols, including automated reminders 1 week and again 3 weeks after the distribution of questionnaires to patients [7,21] and email reminders to GPCs to ensure blood pressure measurement at 6 months. The quality control procedures ensure that there will be little nonresponse [8-11]. To improve the engagement of GPCs, relationships will be maintained through regular emails or phone calls to the designated contact person. In addition, a Christmas card will be sent each year on behalf

of the research team. In addition, the GPCs will be offered support in patient selection and patient contact by a researcher on several occasions during this study.

Outcomes

Overview

The primary outcomes of this study are changes in lifestyle behaviors, measured by validated self-report questionnaires. PA will be assessed using the self-report Short Questionnaire to Assess Health [22,23]. Smoking behavior will be assessed using a validated (self-report) abstinence scale [24,25]. Alcohol consumption will be measured using a standardized alcohol consumption scale [26]. Dietary behavior will be assessed using a food frequency questionnaire on saturated fat intake and fruit and vegetable consumption [27-29].

Secondary outcomes are changes in experienced psychosocial problems such as anxiety and depression, fatigue, health-related QoL, and health-related costs, which will be assessed using validated self-report questionnaires. Anxiety and depression will be assessed using the Hospital Anxiety and Depression Scale [30,31]. Fatigue is assessed using the Checklist Individual Strength [32,33]. Health-related QoL is measured using the abbreviated European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire [34,35]. Health-related costs are considered from a societal perspective and are measured as health care consumption in the last 3 months using the Institute for Medical Technology Assessment Medical Consumption Questionnaire, productivity losses in the last 4 weeks for both paid and unpaid labor using the Institute for Medical Technology Assessment Productivity Cost Questionnaire, and quality-adjusted life years (QALY) using the EQ-5D-5L [25,36-42]. All questionnaires used are validated, we do not conduct additional validation research as part of this research project.

Secondary outcomes are also blood pressure measurements, taken from all participants at 6 months postbaseline. Blood pressure will be assessed by clinical measurements performed by GPP.

In addition to outcome measures, relevant medical data (type of cancer, time since diagnosis, type of treatment, and recurrence) and social demographics (age, sex, level of education, income, living situation, comorbidities, and BMI), as well as intention toward PA, healthy diet, reduced alcohol consumption, and smoking cessation will be assessed at baseline. Items assessing recurrence, use of cointerventions, BMI, and lifestyle behavioral intentions will be repeated at the 6-month measurement and 12-month assessments.

In addition, the process evaluation will be measured by (1) dose delivered: the number of intended modules accessed; (2) dose received: the extent to which participants actively engage with the material in the module; (3) satisfaction with the program; (4) practice-patient interaction: perceptions of the level of collaboration, satisfaction, and active engagement with the blended care program; and (5) context: aspects of the environment that influenced program implementation, impact, or outcomes. In addition to self-report measurements, log data from the online CAG (use of the website and individual CAG modules) will be automatically collected throughout the intervention.

Process evaluation will also take place with GPs and PNs. During the interview session at the end of the trial, they will be asked to report on (1) their satisfaction with the blended care program; (2) the type of patients involved; (3) the number of consultations carried out by the GP or PN; (4) the practice-patient interaction: perceptions of the level of cooperation, satisfaction, and active engagement with the program; and (5) the context: aspects of the environment that influenced the implementation/impact or outcomes of the program.

Sample Size

The effect evaluation of the online CAG intervention showed small to medium effect sizes (ES=0.20-0.40) on lifestyle behaviors at 6 months. In the current design, we expect an ES of 0.40 at 6 months follow-up [8]. Based on previous research on computer-tailored lifestyle interventions, we estimate an ES of 0.30 at 12 months [8,43-48]. Based on CAG data and other research in the primary care setting [49], we estimate an intracluster correlation of 0.03 to account for the multilevel design. Sample size calculation (ES=0.30; power=0.80; intracluster correlation=0.03, design effect 1.27) indicates that 282 participants are required for the effect study (141 in each condition). From 2 previous RCTs of online lifestyle interventions in patients or survivors of cancer, we know that dropout is 20%-25% [8,48]. Accounting for a 25% dropout, 376 survivors of cancer need to start in the RCT (188 per condition).

Furthermore, based on cancer prevalence figures, cancer survival rates, and the number of GPCs in the Netherlands, we expect that a standard GPC (consisting of 1-4 GPs and additional PNs) will have at least 20-40 survivors of cancer who meet the inclusion criteria. Therefore, to achieve a sufficient sample size, we aim to recruit approximately 40 GPCs, each of which will recruit 10 participants.

Randomization

A cluster-randomized design is used, which means that randomization to either the intervention or control condition takes place at the GPC level, and that all participants in a GPC are assigned to the same condition. Neither GPCs nor participants are blinded to their assigned condition during the trial. However, during recruitment, both GPCs and the researcher are unaware of the randomization outcome to ensure that participation is not influenced by assigned conditions. The randomization outcome will be defined by a computer-generated randomization list using simple randomization (1:1), which was generated before the start of recruitment and stored with a third person.

Statistical Methods

Overview

The first 2 steps of the analysis will test for statistical differences at baseline in lifestyle behaviors, QoL, demographics, and psychosocial and medical symptoms between the 2 study groups. Blinding of the analyst will be applied for primary outcomes.

Patterns and mechanisms of missing data will be explored. Thereby, special attention will be paid to dropouts. Randomization of the GPCs should account for an even distribution between the experimental and control conditions of socioeconomic factors or other confounding factors that may skew our results. However, in case conditions are unbalanced, these factors will be adjusted for in the analysis. If necessary, other statistical adjustment procedures will be applied to minimize the impact of any bias.

Multilevel linear regression analyses will be conducted to test for differences in residual change scores between the intervention and control groups on the primary and secondary outcomes at the 6-month follow-up and the 6- and 12-month follow-up combined. Intention-to-treat (ITT) analyses with multiple imputations will be applied. Participants will be nested within GPCs to account for potential interdependence between participants. Multilevel linear regression analyses with a random intercept for GPC level will be performed to account for possible interdependence in the effect analyses. The effects on the population will be assessed via CIs.

The primary outcome measures will be the residual change scores in lifestyle behaviors, but also differences in the secondary outcomes (anxiety and depression, fatigue, [health-related] QoL, and health-related costs). Blood pressure at 6 months will be compared between the intervention and control groups. In addition, moderation analyses will be conducted to examine different potential moderators such as age, gender, type of treatment, and level of education [8-11]. Subanalyses may be performed to explore individual differences that may be attributed to the degree of participation in the intervention. Besides factors on the level of participants, factors on the level of GPCs will be considered for further analysis. Finally, process evaluation data will be analyzed and summarized descriptively.

In addition, Bayes factor analyses will complement the primary analysis of the effects of the blended CAG intervention on the primary and secondary outcomes. A Bayes factor analysis expresses the relative strength of the evidence supporting competing hypotheses. This study examines support for the hypothesis that the blended CAG intervention has greater effects than care as usual as opposed to support for the hypothesis that the conditions do not differ or that the blended CAG intervention has a smaller effect than care as usual. In addition, the strength of support for the hypothesis that the blended CAG intervention has no smaller effects than care as usual will be compared to the support for the hypothesis that the blended CAG intervention has smaller effects than the effects found in the online-only CAG intervention, as studied in previous research [8-11]. In principle, default prior distributions will be used. It will be verified that these prior distributions are sufficiently diffuse, do not overwhelm the data, and do not destabilize the analysis.

Economic Evaluation

To calculate QALYs, utility scores will be obtained from the EQ-5D-5L scores and multiplied by the duration of follow-up (12 months). The economic evaluation will be conducted from a societal perspective and will therefore include medical costs (as measured by the Institute for Medical Technology Assessment Medical Consumption Questionnaire at T1), productivity costs (as measured by the Institute for Medical Technology Assessment Productivity Cost Questionnaire at T1), and costs of the blended care intervention. Intervention program costs include GP and PN training time, time for 2 consultations in the GPC, costs for program updates, and user licenses divided by a conservative number of potential annual users. Costs for the development of the intervention as well as research-specific costs were excluded.

Incremental cost-effectiveness ratios and incremental cost-utility ratios will be calculated by comparing the costs and effects (probability of maintaining a healthy lifestyle and QALYs) of the usual care group with those of the intervention group. Statistical differences in nonnormally distributed costs and QALYs will be tested using bootstrapped 1-tailed *t* tests. A cost-effectiveness acceptability curve will be constructed with the bootstrapped incremental cost-effectiveness ratio to visualize the probability that the blended care intervention is cost-effective at specific willingness-to-pay thresholds. The ceiling ratio for the cost-utility of the interventions will be set at €20,000 (US $20,900.80) per QALY. This is an accepted Dutch cutoff point for the willingness to pay for each QALY gained by preventive interventions and is commonly used to evaluate this type of intervention in the Netherlands [46,50-52].

Data Management

Data will be collected and handled according to the Data Management Plan that has been drafted for this project on the Data Management Plan online portal [53] and approved by ZonMw (ie, the grant provider). The progress of this study will be described in an annual report to the Medical Research Ethics Committee of Zuyderland Hospital and Zuyd University of Applied Sciences (in Dutch: *medisch-ethische toetsingscommissie van Zuyderland en Zuyd Hogeschool* [METC Z]) and the grant provider. Data will be password-protected and stored on hard disks on systems equipped with power-failure backup devices and automatic backup systems. All data will be kept confidential and anonymous. Each participant will be given a unique respondent number, not linked to a name or personal details, under which the data will be stored. Only researchers working on this project will have access to the data.

Potential Benefits and Risks

There are no risks or adverse effects associated with the trial. The participants in the intervention group can decide for themselves if, when, and how often they use the intervention. In addition, all the participants (intervention and control) can withdraw from this study at any time. It is expected that the use of the intervention will contribute to a healthier lifestyle, improve self-management, and have a positive impact on participants' QoL. During this study, the control group will only participate in the online self-report questionnaires and blood pressure measurements at the GPC. They will not be denied medical care and will be able to seek additional professional support if they wish to do so. Insurance was not compulsory for this trial, as assessed by the medical ethics committee.

Ethical Considerations

This study was approved by the METC Z before patient enrollment (NL806166.096.21, version 4.0; April 25, 2023). Informed consent (Multimedia Appendix 1) will be obtained from all the participants or legal guardians for this study. All patients will be required to provide written informed consent to participate. Participation can be discontinued at the request of the participants. Participants will receive a €10,- (10,31 USD) book voucher after completing the study. Modifications to this study protocol will be communicated to the METC Z through amendments. The METC Z has revised the informed consent materials to be given to participants and adapted them to accord with the Medical Research Involving Subjects Act. The protocol was amended to version 6.0 as of April 2023. This study conforms to the Declaration of Helsinki and is registered with the ISRCTN (International Standard Randomised Controlled Trial Number; ISRCTN12451453; registration date: December 15, 2021; last edited: September 12, 2023). All data will be kept confidential and anonymous.

Results

This study was funded in July 2020. Data collection started in August 2022 and is likely to be completed by April 2025. As of December 2024, this study is still ongoing. Data analysis is estimated to start in the spring of 2025. A total of 127 participants have been recruited across 26 GPCs in the Netherlands. The first results are expected to be published in 2026.

Discussion

Overview

This study protocol describes an RCT to evaluate the effects on self-reported lifestyle behavior, psychosocial well-being, (health-related) QoL, medical consumption, and productivity costs of the blended CAG intervention integrated into general practice.

Principal Findings

Overview

Previous research has investigated the effectiveness of the CAG in an online-only format [8-11]. This research found effects on PA, diet, fatigue, depression, and QoL, suggesting that the CAG is an appropriate eHealth intervention to support cancer survivorship. If similar results are found in this study, this would confirm that the online-only intervention has been appropriately adapted to the blended care context, maintaining its effectiveness. It would also suggest that the CAG could be integrated into the GPC workflow to facilitate the integration of cancer aftercare into general practice, as was proposed by the Dutch College of General Practitioners [20].

Comparison to Prior Work

Delivering the CAG in a blended care format improves the personalization of the care provided. This may strengthen the intervention and allow it to be better tailored to the individual recipient. Moreover, the integration of eHealth in general practice to facilitate cancer aftercare may address barriers to the uptake of cancer aftercare by general practice, as previously identified by Duineveld et al [54]. These barriers consisted of time constraints and a lack of expertise in cancer survivorship. Both of these can be complemented by effective eHealth tools such as the CAG.

Strengths and Limitations

Overview

This paper describes the study protocol for an RCT of the effectiveness of a blended care intervention for cancer aftercare in general practice. Conducting an RCT strengthens our interpretation of the results by controlling for confounding through randomization. In addition, the current research is very similar to the previous research evaluating the effectiveness of the online-only CAG intervention, which allows the results to be compared and the added value of blended care to be identified. The blended care format is being added to increase the reach of our intervention, specifically targeting a population that would not access an online-only intervention on their own. The blended care protocol has been developed in cocreation with survivors, GPs, and PNs to ensure the best fit with the general practice context and the needs of survivors (MJM Smits, unpublished data, 2025). However, some challenges cannot be foreseen. Conducting the RCT in a period following the global COVID-19 pandemic may place limitations on our study protocol. For example, it may be difficult to achieve our target sample size due to recruitment problems with both GPCs and survivors of cancer. In the aftermath of COVID-19, the health care sector is facing a workforce shortage, partly due to the retirement of a large proportion of the working population [55,56]. In primary care, this is leading to the closure of GPCs as owners are not being replaced by a new generation. Meanwhile, the COVID-19 pandemic has resulted in a high rate of delayed care, further increasing the demand for GPCs and leaving little room for trial participation and research activities such as patient recruitment. This resulted in a difference in the number of GPCs recruited compared to our target. We aimed to recruit 40 GPCs, but in reality, only 26 GPCs were recruited.

Future Directions

Future research could further investigate the implementation of eHealth for survivors of cancer in general practice or, depending on the results of this study, in different practice contexts. Emphasis should be placed on reaching survivors who are at risk of developing comorbidities or recurrence, or who have a high burden of disease that translates into medical costs or loss of productivity.

Dissemination of Research Findings

Research findings will be discussed with the consortium partners and published in academic journals. This study is the next step in disseminating the CAG in a practical context. However, to translate our findings to the real world, further research should be conducted to investigate how the intervention is sustained outside of the research protocol. Depending on our findings, the RCT will be followed by an implementation study in which survivors, GPs, and other stakeholders will be invited to share

their views on the integration of blended CAG into regular cancer care.

Implications and Relevance

The number of survivors of cancer is expected to increase in the coming decades [2]. These survivors consult their GP with issues related to cancer survivorship, resulting in a high demand for general practice [19]. To support survivors of cancer in maintaining a healthy lifestyle and managing psychosocial needs, the online CAG program was developed [57]. The program was shown to be effective in promoting healthy lifestyle behaviors and reducing fatigue, depression, and anxiety [8-11]. Structurally embedding the CAG in general practice could support GPs and PNs in caring for their patients and help reach more survivors who need support after treatment. The expected ESs are small but arguably clinically relevant given the affordability, minimal associated risks, and widespread implementability of the blended CAG intervention [58,59]. The results of this study may have implications for cancer aftercare and general practice, and may also be relevant to the wider field of eHealth implementation.

Conclusion

The research described in this study protocol will investigate the effectiveness (and cost-effectiveness) of a blended care intervention for survivors of cancer in general practice. The blended care intervention combines the use of a proven effective eHealth program (CAG) with face-to-face consultations with a GP or PN. Integrating eHealth for cancer aftercare into general practice may help GPs and PNs in caring for the growing number of survivors of cancer and may effectively improve their QoL, leading to reduced care needs in the future. The results of this study may be relevant to the field of cancer aftercare and general practice and will add to the literature on eHealth implementation.

Acknowledgments

The authors thank in advance all the patients, general practitioners, and practice nurses involved in this study. We also thank Xynthia Kavelaars, PhD, a statistician at the Open University for providing statistical advice, and the project's advisory committee for their ongoing support throughout the project: Jelle Stoffers, Silvia Evers, Brigitte Gijsen, Nederlandse Federatie Kankerpatiënten-organisaties, Centraal Ziekenfonds, Peter van Dijk, Donna Lenders, and Robert Willems. This study is supported by ZonMw: The Netherlands Organization for Health Research and Development (dossier 50-55515-98-015). The funding body played no role in the design of this study and collection, analysis, and interpretation of data and in writing this paper. The grammar, spelling, and style of the textual content of this paper have been checked with the assistance of DeepL Write (DeepL SE, 2024) [60].

Data Availability

The datasets will be available from the corresponding author upon reasonable request.

Authors' Contributions

LL is the principal investigator, CAWB and IM are coapplicators, and MJMS is the PhD candidate on this research project. LL, CAWB, and IM contributed to the conceptualization, funding acquisition, and supervision. MJMS was responsible for the project administration and writing of the original draft of this paper. All authors contributed equally to the investigation, methodology, validation, and writing (review and editing) of this paper.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Informed consent form.
[DOCX File , 16 KB - resprot_v14i1e64662_app1.docx]

Multimedia Appendix 2
Example of the Module Referral Advice (MRA).
[PDF File (Adobe PDF File), 322 KB - resprot_v14i1e64662_app2.pdf]

Multimedia Appendix 3
SPIRIT checklist. SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials.
[PDF File (Adobe PDF File), 138 KB - resprot_v14i1e64662_app3.pdf]

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Abbreviations

CAG: Cancer Aftercare Guide
ES: effect size
GP: general practitioner
GPC: general practice center
GPP: general practice personnel
ISRCTN: International Standard Randomised Controlled Trial Number
ITT: intention-to-treat
METC Z: Medical Research Ethics Committee of Zuyderland hospital and Zuyd University of Applied Sciences (medisch-ethische toetsingscommissie van Zuyderland en Zuyd Hogeschool)
MRA: Module Referral Advice

PA: physical activity
PN: practice nurse
QALY: quality-adjusted life year
QoL: quality of life
RCT: randomized controlled trial

Edited by T Leung; submitted 24.07.24; peer-reviewed by K Edmunds, J Roca; comments to author 27.11.24; revised version received 04.12.24; accepted 05.12.24; published 12.02.25.

Please cite as:
Smits MJM, Bolman CAW, Mesters I, Lechner L
Blended Care Intervention for Cancer Aftercare in General Practice Centers: Protocol for a Randomized Controlled Trial
JMIR Res Protoc 2025;14:e64662
URL: https://www.researchprotocols.org/2025/1/e64662
doi:10.2196/64662
PMID:

Protocol

Improving the Health and Well-Being of Individuals by Addressing Social, Economic, and Health Inequities (Healthy Eating Active Living): Protocol for a Cohort Study

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Abstract

Background: Health inequity is interlinked with the good health and well-being of an individual. Health inequity can be due to various socioeconomic factors like income levels or social status. Digital health interventions have the potential to reduce the existing health inequities.

Objective: This study aims to identify determinants of social, economic, and health inequity in diverse settings to enhance healthy eating and active living. It further aims to design and develop a digital health intervention HEAL (Healthy Eating Active Living) that incorporates a human-centered design framework in order to improve healthy eating and active living among rural and urban population groups in Chennai, Tamil Nadu, India.

Methods: A prospective, 3-year cohort study will be conducted. This study aims to recruit 6350 individuals across rural and urban settings of Chennai. A total of 11 sites have been selected for participation in the study. Data on sociodemographic characteristics; economic inequity; HEAL profile; depression, anxiety, and stress; well-being; sources of health information; perceived access to health care; health literacy; navigation of health literacy; and satisfaction with the health system will be gathered. This study would help to explore the determinants of social, economic, and health inequity across multiple sites. SAS (version 9.3; SAS Institute Inc) will be used for data analysis, and results will be reported as 95% CI and *P* values. This study's findings will guide the design and development of a tailored, human-centered digital health intervention to enhance the health and well-being of Chennai's population groups.

Results: As of December 2024, the literature review for the development of the intervention has been completed. The recruitment for the baseline data collection will begin shortly, followed by the development of HEAL intervention.

Conclusions: The proposed study will help in examining the role of the proposed HEAL intervention to enhance the health and well-being of the population groups of Chennai.

International Registered Report Identifier (IRRID): PRR1-10.2196/41169

(JMIR Res Protoc 2025;14:e41169) doi:10.2196/41169

KEYWORDS

health inequity; health; well-being; digital interventions; social health; lifestyle

Introduction

Background and Rationale

The World Health Organization (WHO) identifies health inequities as "systematic differences in the health status of different population groups" [1]. Further, the WHO refers to health as "a state of complete physical, mental, and social well-being and not merely the absence of disease or infirmity" [2]. Consequently, research on health inequity is a central agenda component of the 2030 Sustainable Development Goals and various government and development dialogues [3,4]. Despite this, the WHO reports that health inequalities exist at varying degrees around the world, both within and between countries [5]. These inequalities further exacerbate health disparities between high-income and low-income, urban and rural, employed and unemployed populations, as well as between low-, middle-, and high-income countries [6] due to socioeconomic factors such as social status or income levels [7].

According to the Centers for Disease Control and Prevention, health equity can be attained when every individual can "attain his or her full health potential" and no one is "disadvantaged from achieving this potential because of social position or other socially determined circumstances" [8]. This also emphasizes the significance of measuring health inequity, promoting opportunities and monitoring the progress in health and intersectoral strategies. Additionally, measuring the interrelationship between health and its social determinants is vital to promoting effective interventions for health equity [9].

Inequalities are unfair, affect everyone, and are avoidable; however, the underlying factors causing inequality are imperfectly understood, and evidence on the effectiveness of interventions to reduce inequalities is limited [10]. Prior research has further highlighted the issue of good health for socioeconomically vulnerable groups and the need for targeted public health interventions in India [11]. A study indicated that health inequity in India is favored toward high-income populations and that despite services being available to people, there was a lack of awareness around it, especially in the rural region [12]. Considering the diversity in India and the prevalent social inequalities, the literature also emphasizes on the importance of research on health inequalities for monitoring health policies and programs [11].

Equity was also identified as one of the key principles of India's 2017 National Health Policy [13]. However, with a limited evidence base of health equity in India, there is a need to generate empirical data for the variables that create, sustain, and reinforce inequity. This would further help the policy makers to prioritize and strategize the limited resources available for the health system of the country [14].

However, the paucity of data on health inequalities in India and the subsequent research gap on critical issues related to health inequity in the country also underscore the probable impact of policies and strategies deployed to enhance the well-being of population groups. Moreover, the COVID-19 pandemic has exacerbated the health inequity worldwide [15]. In addition, eating habits are possibly determined by the socioeconomic status of the individuals [16]. Thus, this study aims to enrich the current understanding of health inequity with empirical research. The findings will also help with the design and development of digital health intervention HEAL (Healthy Eating Active Living) to improve the good health and well-being of individuals by addressing social, economic, and health inequities. Tamil Nadu, India, was the chosen region of study as it seems to be a state that has progressed in health care in recent years, and hence, this study aims to see the receptivity to digital intervention of the study population in these settings [12].

Study Objectives

This study aims (1) to identify determinants of social, economic, and health inequity to enhance healthy eating and active living among rural and urban population groups of Chennai, Tamil Nadu; (2) to design and develop a digital health intervention HEAL using the SMAART (Sustainable, Multi-Sector, Accessible, Affordable, Reimbursable, Tailored) model, targeted to enhance healthy eating and active living among rural and urban population groups of Chennai, Tamil Nadu; and (3) to evaluate impact of the proposed intervention to address burden of social, economic, and health inequity to enhance healthy eating and active living among rural and urban population groups of Chennai, Tamil Nadu.

Methods

Study Overview

The proposed research involves a multidisciplinary team with expertise in population health, epidemiology, sociobehavioral sciences, anthropology, and biochemical sciences.

Study Design and Population

The HEAL cohort study is a prospective, 3-year cohort study with the aim to recruit 6350 individuals across rural and urban settings of Chennai, Tamil Nadu. The study sample will be recruited from Kannur; Pannur; Thirumenikuppam; Thodukadu; Kottaiyur; Nemili; Mannur; Kiloy; Ulundai; Narasamangalam; Karanai; Panimalar Medical College Hospital and Research Institute; Rural Training Health Centre Chennai; and Maligaipaddu village of Chennai, Tamil Nadu. Baseline evaluation will be performed at the time of recruitment of study participants. The study participants will be recruited through convenience sampling. This will serve as cross-sectional data to estimate the prevalence of determinants of social, economic, and health inequity.

Study Intervention

The HEAL intervention will be designed based on the SMAART model to enhance healthy eating and active living for the individuals participating in the study. This intervention will ensure the coordination of social, economic, and health-related parameters to enhance the health and well-being status of the population. The SMAART model works on the principles of data, information, and knowledge; human-centered approach; information processing theory; and humanistic, behavioral, and learning theories [17]. The intervention stage will have two

parallel groups (case and control) for comparison. Individuals in the intervention group will be provided access to the informatics-based intervention for enhancing their healthy eating and active living. The participants from the intervention stage will be included in the study based on participants from the baseline stage consenting to participate in the intervention. The participants will be assigned to the intervention or control group through randomization. They would be provided information on good dietary habits and the importance of regular physical exercise for maintaining good health and well-being. Individuals in the control group will be provided an educational booklet as standard care. The intervention will be a tailored multilingual digital health intervention. Both the groups will undergo a series of baseline and follow-up assessments for estimation of change in eating patterns, physical activity, and well-being to assess the impact of intervention. The study location includes both the urban and rural areas of selected sites, and the study duration is 3 years. The study population includes all adults aged 18 years and older. The inclusion criteria are (1) individuals aged 18 years and older, (2) individuals from both urban and rural areas, and (3) individuals who consent to participate in the study.

Efforts will be made to include individuals of varied age groups, gender, location, and socioeconomic status. The exclusion criteria consist of (1) individuals younger than 18 years of age, (2) individuals who would not give their consent, and (3) individuals who have impaired cognition.

Ethical Considerations

This study (protocol PMCHRI-IHEC-067) gained approval from the Panimalar Medical College Hospital and Research Institute Institutional Human Ethics Committee (Central Drugs Standard Control Organization Registration ECR/1399/Inst/TN/2020) in March 2022, with approval PMCH&RI/IHEC/2021/078 dated March 15, 2022. The study will be conducted according to the Declaration of Helsinki, as it involves human participants [18].

The institutional review board–approved informed consent form will be administered by the research team to the eligible individuals for the study. The research team will describe the study, time required, and benefits of the study results to the participants, and those willing to participate and give their consent will be enrolled in the study. Written informed consent will be obtained in both English and local Indian dialects at the time of data collection if the participants are able to read and understand the questionnaire. In the case of participants without formal education, an audio recording of the consent will be done. Study participants will be allowed to withdraw from the study at any time [19]. No compensation will be provided.

Data security will be ensured through regular backups in password-protected computers in the locked office of the principal investigator. Data will be stored for 5 years from the point of study completion, after which it will be destroyed. All the physical data files will be stored in a locked file cabinet in the office. The information will be accessible to members of the research team only.

Data Collection, Data Entry, and Quality Assurance

Data collection and data entry will be performed by a team of trained field data collectors and data management. Data will be gathered in the field on paper and then entered on the computer. The data will be entered into the computer using Excel (Microsoft Corp). For quality assurance, a clearly defined data collection and management protocol will be in place. This will include a well-defined study manual with all the relevant instructions. For quality assurance, we will have a trained team of data collectors, weekly meetings with the research team, weekly data checks, maintenance of study participant contact, and maintenance of study participant data instrument logs.

Variable Assessment

Sociodemographic Characteristics

Information will be collected on the participant's age, gender, educational status, migration status, disability status, occupation, household size, family size, income, and number of earning members in the household.

Economic Inequity

The wealth index is a division of households into 5 wealth quintiles to show the relationship between wealth, population, and health indicators [20].

HEAL Profile

Data will be collected on the respondent's health and lifestyle profile. We will use the WHO STEPwise approach to noncommunicable diseases risk factor surveillance questionnaire. It is a simple, standardized method for collecting, analyzing, and disseminating data on key noncommunicable disease risk factors in countries. The survey instrument covers key behavioral risk factors: tobacco use, alcohol use, physical inactivity, and unhealthy diet, as well as key biological risk factors: overweight and obesity, raised blood pressure, raised blood glucose, etc [21].

Depression, Anxiety, and Stress

Data will be gathered from the respondents about their mental and well-being. We will use the Depression, Anxiety, and Stress Scale (DASS). The DASS is a set of three self-report scales designed to measure the negative emotional states of depression, anxiety, and stress. Each of the three DASS scales contains 14 items, divided into subscales of 2-5 items with similar content [22].

Well-Being

The Short Warwick Edinburgh Mental Well-Being Scale is a shortened version of the Warwick-Edinburgh Mental Well-Being Scale. It measures both mental and emotional well-being (how "good" somebody feels) and psychological functioning (how well somebody thinks they are functioning). This scale is suitable for ages 13-74 years and works well as a "before" and "after" tool to measure the change in well-being during an intervention or specific program [23].

Sources of Health Information, Social Media, Technology Access, and Familiarity

Information will be gathered about cell phone ownership in households, type of cell phone, access to the internet, and knowledge of SMS text messaging [24,25].

Perceived Access to Health Care

Information will be collected from the respondents regarding access to health care. We will use the Perceived Access to Health Care questionnaire. The questionnaire includes six dimensions: (1) availability, (2) accessibility, (3) affordability, (4) accommodation, (5) acceptability, and (6) awareness. In addition, the psychometric evaluation was conducted on the instrument's initial version with 31 items on a 5-point Likert scale (strongly agree to strongly disagree) [26].

Health Literacy

Rapid Estimate of Adult Literacy in Medicine will be used to assess the health literacy of the study participants. It is a quick screening tool to assist physicians in identifying patients with limited reading skills and in estimating patient reading levels. "At risk patients" are defined as those with a score of six or less [27].

Satisfaction With Health System

The Patient Satisfaction Questionnaire yields separate scores for each of seven different subscales: general satisfaction (2 items), technical quality (4 items), interpersonal manner (2 items), communication (2 items), financial aspects (2 items), time spent with the doctor (2 items), and accessibility and convenience (4 items). This questionnaire will be used both at baseline and postintervention [28,29].

Outcomes

The study outcomes include the identification of determinants of social, economic, and health inequity. The research would further help in identifying the key areas that need to be addressed through intervention to improve the health and well-being status of the general population. Additionally, the study would also help in developing tailored interventions targeted to reduce social, economic, and health inequities.

Data Analysis

Descriptive analysis will be conducted to report the mean and SD of the continuous variables and frequency analysis of the categorical variables. A 1-tailed *t* test will be performed to compare means between the continuous variables and a categorical dependent variable while a chi-square analysis will be performed for the categorical variables. Multivariate regression analysis will be performed to determine the determinants of social, economic, and health inequity. All analysis will be performed using SAS (version 9.1; SAS Institute Inc), and reporting of the results will be done at 95% CI and $P<.05$.

Projected Timelines and Milestones

A detailed research plan and scheduled timeline of the tasks involved in the study are presented in Table 1.

Table 1. Scheduled timeline of the tasks in the HEAL[a] study.

Variables	Month 1	Months 2-5	Months 6-7	Months 8-10	Months 11-18	Months 14-30	Months 31-33	Months 34-36
Stakeholder meeting	✓							
Baseline data collection		✓						
Design and development of human-centered intervention			✓					
Heuristic evaluation			✓					
Usability of the proposed system				✓				
Refine the proposed SMAART[b] informatics self-management intervention				✓				
Final deployment of the proposed SMAART informatics self-management intervention tool				✓				
Study recruitment (baseline data)					✓			
Follow-up data collection					✓	✓		
Statistical analysis					✓	✓	✓	
Report writing and paper preparation							✓	✓

[a]HEAL: Healthy Eating Active Living.

[b]SMAART: Sustainable, Multi-Sector, Accessible, Affordable, Reimbursable, Tailored.

The study is in accordance with the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guideline for case-control studies (Multimedia Appendix 1) [30].

Results

As of December 2024, the literature review for the development of the intervention has been completed. Recruitment for the baseline data collection is scheduled to begin in the upcoming months, followed by the development of HEAL intervention.

The findings of the study will be disseminated through peer-reviewed publications and national and international conference presentations.

Discussion

Expected Findings

In order to reduce the health inequity in India, it is imperative to have the requisite knowledge base. This study would help to fill the research and knowledge gap by identifying key areas that need to be addressed to improve the health status of the population. The baseline data will enable us to find the socioeconomic inequity faced by the participants, their health literacy, and their awareness regarding their health status and health care. These findings would also help to design and develop tailored population health interventions to enhance the healthy eating and active living of the population groups.

Health inequities have existed throughout time, as resonated by the concept of inverse care law (1971), which highlighted how good medical care is inversely related to people's needs in low- and middle-income countries [31]. Similarly, Cookson et al [32] recently proposed the law of disproportionate care (2021) where they argue that in high-income countries, socially disadvantaged groups receive more care but of worse quality to meet their health care needs. The available studies also reinstate the need to address health inequities by collecting and analyzing the relevant health equity data [33]. This study would therefore help in filling the requisite knowledge gaps by identifying the key determinants of health inequity. It would also help in contributing to the advancement of evidence-based strategic decisions on health inequity. The findings from this research project would also help in designing, developing, and implementing data-driven, evidence-based, and human-centered interventions to enhance the healthy eating and active living of the population groups.

Limitations

This study's limitations include that it is confined to one geographic region, and implementing it in diverse geographic and population settings would help to better understand and compare the impact of the HEAL intervention.

Conclusions

The HEAL intervention offers a model to enhance healthy eating and active living for the individuals participating in the study through the SMAART framework. The findings from the study will contribute to the understanding of the role of digital health interventions to enhance healthy eating and active living of the population groups, which will help in understanding and addressing determinants of health equity in the population.

Acknowledgments

The authors are the only contributors to this manuscript and are acknowledged.

Data Availability

The datasets generated during or analyzed during this study will be available from the corresponding author upon reasonable request.

Authors' Contributions

All authors have contributed to the design of the study, development of the questionnaire, and preparation of the manuscript, and have approved the manuscript for publication.

Conflicts of Interest

None declared.

Multimedia Appendix 1
STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) checklist.
[DOCX File , 19 KB - resprot_v14i1e41169_app1.docx]

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Abbreviations

DASS: Depression Anxiety, and Stress Scale
HEAL: Healthy Eating Active Living
SMAART: Sustainable, Multi-Sector, Accessible, Affordable, Reimbursable, Tailored
STROBE: Strengthening the Reporting of Observational Studies in Epidemiology
WHO: World Health Organization

Edited by A Mavragani; submitted 18.07.22; peer-reviewed by J Alvarez Pitti, F Gomez, C Leung; comments to author 18.01.23; revised version received 01.03.23; accepted 01.06.23; published 13.02.25.

Please cite as:
Joshi A, Mohan SK, Pandya AK, Grover A, Kaur H, Gupta M, Aurora H, Bhatt A
Improving the Health and Well-Being of Individuals by Addressing Social, Economic, and Health Inequities (Healthy Eating Active Living): Protocol for a Cohort Study
JMIR Res Protoc 2025;14:e41169
URL: https://www.researchprotocols.org/2025/1/e41169
doi:10.2196/41169
PMID:

Protocol

Future Patient—Telerehabilitation of Patients With Atrial Fibrillation: Protocol for a Multicenter, Mixed Methods, Randomized Controlled Trial

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Abstract

Background: Atrial fibrillation (AF) is a chronic cardiovascular condition with a lifetime risk of 1 in 3 and a prevalence of 3% among adults. AF's prevalence is predicted to more than double during the next 20 years due to better detection, increasing comorbidities, and an aging population. Due to increased AF prevalence, telerehabilitation has been developed to enhance patient engagement, health care accessibility, and compliance through digital technologies. A telerehabilitation program called "Future Patient—telerehabilitation of patients with AF (FP-AF)" has been developed to enhance rehabilitation for AF. The FP-AF program comprises two modules: (1) an education and monitoring module using telerehabilitation technologies (4 months) and (2) a follow-up module, where patients can measure steps and access a data and knowledge-sharing portal, HeartPortal, using their digital devices. Those patients in the FP-AF program measure their heart rhythm, pulse, blood pressure, weight, steps, and sleep. Patients also complete web-based questionnaires regarding their well-being and coping with AF. All recorded data are transmitted to the HeartPortal, accessible to patients, relatives, and health care professionals.

Objective: This paper aims to describe the research design, outcome measures, and data collection techniques in a clinical trial of the FP-AF program for patients with AF.

Methods: This is a multicenter, mixed methods, randomized controlled trial. Patients are recruited from AF clinics serving the North Jutland region of Denmark. The telerehabilitation group will participate in the FP-AF program, while the control group will follow the conventional care regime based on physical visits to the AF clinic. The primary outcome measure is AF-specific health-related quality of life, to be assessed using the Atrial Fibrillation Effect on Quality-of-Life Questionnaire. Secondary outcomes are knowledge of AF; measurement of vital parameters; level of anxiety and depression; degree of motivation; burden

of AF; use of the HeartPortal; qualitative exploration of patients', relatives', and health care professionals' experiences of participating in the FP-AF program; cost-effectiveness evaluation of the program; and analysis of multiparametric monitoring data. Outcomes are assessed through data from digital technologies, interviews, and questionnaires.

Results: Patient enrollment began in January 2023 and will be completed by December 2024, with a total of 208 patients enrolled. Qualitative interviews conducted in spring 2024 will be analyzed and published in peer-reviewed journals in 2025. Data from questionnaires and digital technologies will be analyzed upon study completion and presented at international conferences and published in peer-reviewed journals by the fall of 2025.

Conclusions: Results from the FP-AF study will determine whether the FP-AF program can increase quality of life for patients with AF and increase their knowledge of symptoms and living with AF in everyday life compared to conventional AF care. The cost-effectiveness evaluation will determine whether telerehabilitation can be a viable alternative for rehabilitation of patients with AF.

Trial Registration: ClinicalTrials.gov NCT06101485; https://clinicaltrials.gov/study/NCT06101485

International Registered Report Identifier (IRRID): DERR1-10.2196/64259

(JMIR Res Protoc 2025;14:e64259) doi:10.2196/64259

KEYWORDS

atrial fibrillation; telerehabilitation; quality of life; research design; patient education; co-creation; randomized controlled trial; chronic; cardiovascular disease; adult; aging; prevalence; comorbidity; Future Patient; patient engagement; primary outcome; cost-effectiveness; monitoring; health care professional; digital health; remote therapy; telehealth

Introduction

Atrial fibrillation (AF) is a chronic cardiovascular condition occurring in 3% of the adult population, the prevalence of which is predicted to more than double over the next 20 years [1]. The increase in AF prevalence may be attributed to better opportunistic screening for silent AF, aging of the population, and an increase in conditions predisposing to AF, such as obesity, hypertension, diabetes, obstructive sleep apnea, and physical inactivity [2]. If untreated, AF is associated with a 5-fold increase in the risk of stroke; 20%-30% of all strokes are due to this type of arrhythmia [1,3].

AF imposes a substantial economic burden on the health care system, with 10%-40% of patients with AF being acutely hospitalized each year [1]. AF patients may experience a variety of symptoms, such as palpitations, fatigue, dyspnea, chest pain, sleeping difficulties, fear, and anxiety, although there is great variation in the individual symptom levels. While up to 40% of patients with AF are asymptomatic, others report severe or disabling symptoms [1]. Sleeping difficulties such as sleep apnea are also observed and may be associated with increased cardiovascular risk, further underscoring the importance of AF management [4,5]. Patients with AF trying to live with their disease can benefit from some form of effective, prolonged, and specialized cardiac rehabilitation (CR).

CR is an outpatient chronic disease management intervention that includes structured exercise. CR is based on a risk-factor assessment combined with health management interventions. Patients are educated and encouraged to quit smoking, attend vocational and nutritional counseling sessions, and seek psychosocial support. A review of CR aimed at patients with AF found gaps in the CR research, notably the need for more rigor in the reporting of intervention details, outcomes, and gender-based characteristics of CR and its effectiveness for patients with AF [6]. Many patients with AF do not feel that they have received sufficient knowledge regarding how to live with their disease [7], while other studies have shown that patients with AF often have poor knowledge about arrhythmia, its treatment, and self-management strategies [6]. In 2019, Denmark published the first national guidelines for CR for patients with AF [8], but actual rehabilitation programs have not yet been implemented. A new, innovative alternative to CR is cardiac telerehabilitation (CTR), in which certain elements of the CR program take place in the patient's home with the help of wearables and other technologies, such as a blood pressure monitor, and using remote communication between the patient and the health care professionals (HPs) [9]. Continuous monitoring, combined with the use of oral anticoagulation for stroke prevention and maintenance of normal sinus rhythm, has demonstrated benefits such as reduced hospitalization, limiting disease progression, and improving survival [10]. Reviews focusing on digital patient education for patients with AF found improvements in patient knowledge of AF [11]. For example, Desteghe et al [4] found that tailored web-based education was an effective strategy for improving AF knowledge and that patients were positive about using web-based patient education. These findings are in line with a review by Fredericks and Yau [12], who found that individualized patient education in heart surgery patients increases quality of life (QoL), improves performance of health behavior, and ameliorates psychological distress [12].

Psychological distress, such as anxiety and depressive symptoms, is prominent among patients with AF, with prevalence rates ranging from 28% to 38% [13]. Some studies have shown that AF may be a causal factor in the onset of depression, while a few studies find that depression may also cause AF [14-18]. Both anxiety and depression have been associated with recurrent AF [19], while anxiety is also described as a side effect of living with AF [15,20]. Overall, psychological distress has been associated with poorer QoL [19,21] and increased severity of AF symptoms [13,19], whereas QoL has been associated with AF severity [19]. This association highlights the importance of examining the impact of both AF

severity and psychological distress on QoL. It should be noted that psychological distress may also impair the patient's motivation for engaging in rehabilitation, thus reducing participation in rehabilitation and self-care [22,23], whereas successful alleviation of AF symptoms is often associated with reduced emotional distress [24].

The educational CTR program "Future Patient—telerehabilitation of patients with AF" (FP-AF) was developed in Denmark through a cocreation process with patients with AF, their relatives, and researchers. The program was evaluated in a pilot study [25], which showed that patients with AF and their relatives found the FP-AF useful because it created an increased sense of security, increased knowledge about mastering symptoms, and a community of practice linking patients with AF and their relatives with HPs. These findings suggest that there is a potential for increasing the QoL of patients with AF by providing educational telerehabilitation programs that can permit sufficient individualization for patients (and relatives). Following the pilot study, the intention is for the FP-AF program to be evaluated in a multicenter, mixed-methods, randomized controlled trial (RCT). The development of the program is in line with the strategies of user involvement developed by the Danish Heart Association and with national strategies promoting digital health in Denmark, as well as current recommendations for AF rehabilitation [8].

The purpose of the FP-AF program (ClinicalTrials.gov NCT06101485) is to increase the QoL of patients with AF by providing both patients and their relatives additional knowledge about AF and practical guidance on how to live with AF in everyday life. The program aims to individualize the rehabilitation process by helping patients and their relatives develop their own self-management strategies using their own clinical data and enhanced knowledge about AF. This paper describes the research design, outcome measures, and data collection techniques used in the FP-AF research project.

Methods

Research Design

The FP-AF program will be evaluated in a multicenter, mixed methods, RCT study. The telerehabilitation group will participate in the FP-AF program, while the control group will follow the conventional care regime based on physical visits to the AF clinic. Enrollment of patients began in January 2023, and the RCT is expected to end in June 2025.

Ethical Considerations

The Future Patient project has been approved by The Scientific Ethics Committee for the North Denmark Region (N-20220056). The study is listed in ClinicalTrials.gov (NCT06101485). The study is being carried out in accordance with the Helsinki Declaration, and all participants have signed an informed consent form prior to enrollment in the study. Participants have been informed that they have the right to withdraw their consent at any point in time during the study, and the reason for their withdrawal will also be documented if the participant so wishes. The participants have not received any compensation for their participation in the study. Upon the randomization, all patients have been assigned an individual identification number so their data remain anonymous. The project team will then collect the equipment upon request.

Procedure and Eligibility Criteria

All patients diagnosed with AF at the Departments of Cardiology at Central Region Hospitals in Viborg, Skive, and Silkeborg will be assessed for eligibility in the study. The inclusion criteria are as follows: patients must be diagnosed with AF; they must be adults aged 18 years or older; they must live in Skive, Viborg, or Silkeborg municipalities; they must live at home and be capable of caring for themselves; and they must possess basic computer skills or have a relative or friend with basic computer skills.

Exclusion criteria are as follows: pregnancy; refusal or inability to cooperate; patient does not speak, read, or understand Danish; and patient has a life expectancy of less than a year.

A CONSORT (Consolidated Standards of Reporting Trials) diagram will be used to document all data pertaining to the recruitment process, as well as patient withdrawal or dropout.

Power Calculation

The primary outcome of this study is AF-specific health-related QoL (HRQoL) as measured by the Atrial Fibrillation Effect on Quality-of-Life Questionnaire (AFEQT) through the use of telerehabilitation compared to conventional rehabilitation. A clinically significant mean difference of 11 points between the intervention and control groups and an SD of 23 points were used in the study power calculation, based on prior literature [26]. A sample size of 184 patients would have 90% power to demonstrate a difference between the groups. This project estimates a dropout rate of about 10%. Thus, the total number of patients required in the study is 208, with 104 patients in the intervention group and 104 in the control group.

Randomization

Randomization of the patients will be conducted according to a randomized block design using random sized blocks of 4, 6, and 8 patients. The blocks will be stratified by center and appropriate age group and sex. The randomization will be digital and blinded for the project nurses who will be recruiting patients for the study.

Theoretical Framework

The FP-AF program is based upon self-determination theory (SDT), which describes motivation as an essential part of any successful rehabilitation [27]. SDT describes human motivation as the fulfillment of 3 basic needs: autonomy, competency, and relatedness. To ensure continuous motivation, it is necessary that this motivation is intrinsic to the patient, which requires that the patient feels that all 3 of these primary needs are being supported simultaneously [27]. As such, intrinsic motivation is achieved when a patient (1) experiences autonomy, that is, identifies with the goals of rehabilitation and values these as personally important; (2) experiences competency, that is, the patient believes that he or she has the necessary knowledge and skills to achieve the goal and receives guidance and feedback; and (3) experiences relatedness, that is, the HP's and the

patient's social network create a milieu in which the patient feels respected, understood, and supported.

Future Patient Telerehabilitation Program

The FP-AF education program for patients with AF and relatives consists of two modules: (1) an education and monitoring module using telerehabilitation technologies (4 months) and (2) a follow-up module, where the patients use their own personal devices to measure steps and to access the HeartPortalen (3 months).

After enrollment, those patients randomized to the intervention group meet individually with the project nurse. At this meeting, the patient (and relatives, if necessary) are instructed in the use of the technologies (see details below), and an individual plan is formulated for the AF patient's telerehabilitation program. The project nurses at the AF clinics (Regional Hospitals in Viborg and Silkeborg) review all the patients' measured values twice a week and have continuous contact with the patients during their enrollment in the project. For each patient, the physicians at the hospital set limit values for blood pressure, pulse, and weight. If patients register values that are out of range, they are instructed to contact the project nurse or the cardiology ward. Furthermore, the patients and relatives are invited to participate in an educational module at the local health care center, where offerings include topics such as living with AF, symptoms of AF, management of own disease using digital technologies, and how you as a relative can support your spouse or partner.

The HeartPortal

The HeartPortal (version 1.0), a web-based portal used by patients, relatives, and HPs at the hospitals and health care centers, functions as a digital toolbox and learning module. Patients and relatives in the telerehabilitation group will have access to the HeartPortal, where they can read texts and watch animations about AF, have access to visualization of the patients' measured data (steps, weight, pulse, blood pressure, and sleep), and communicate in video and chat with HPs at the hospitals and health care centers. The patients can access the data from the electrocardiogram (ECG) on a separate platform. Screen captures of the HeartPortal are shown in Figure 1, and the context of the Future Patient study is shown in Figure 2.

The HeartPortal consists of 4 elements (Textbox 1).

The technologies being used in the CTR group are listed in Textbox 2.

Figure 1. Screen captures from the HeartPortal. (A) The patients front page. (B) Measurement from the sleep sensor. (C) The information platform. (D) Measurement from the pedometer.

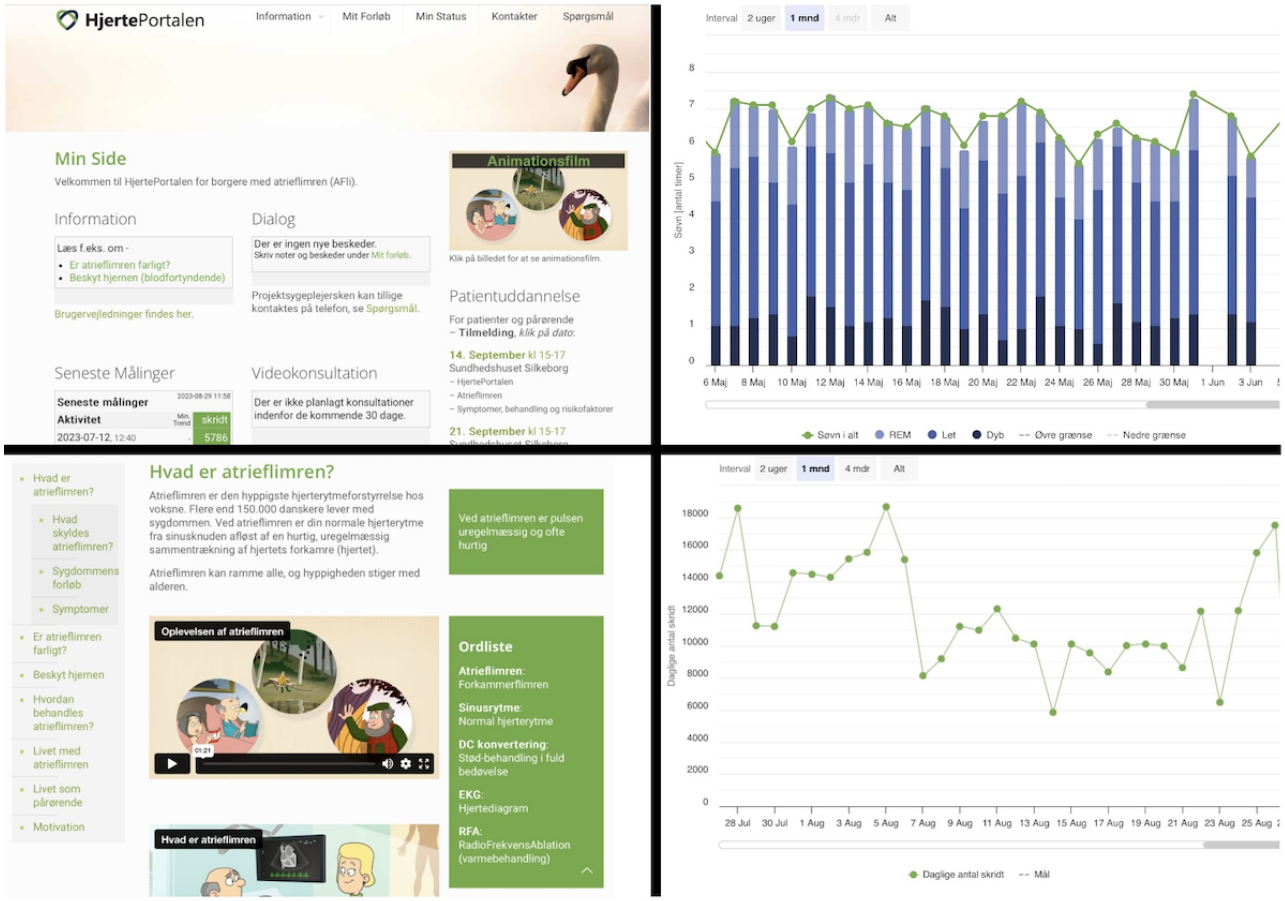
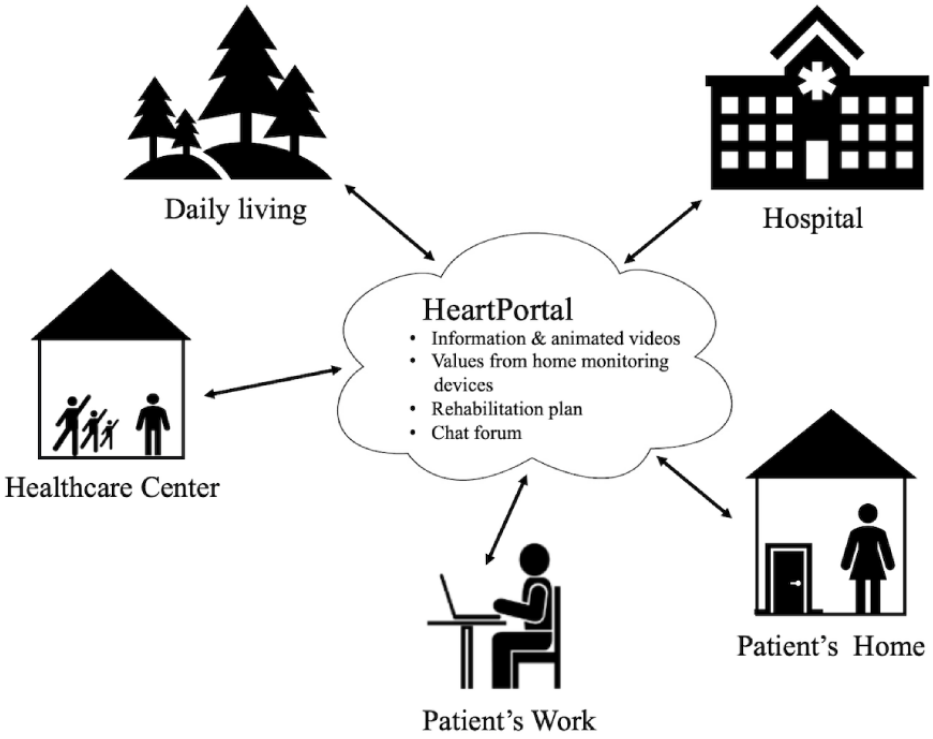


Figure 2. The context of the Future Patient program.



Textbox 1. Four elements of HeartPortal.

- A platform containing atrial fibrillation and rehabilitation related information pages (text, images or illustrations, animation, link to other validated sources, etc).
- Visualization of measured values (steps, weight, pulse, blood pressure, and sleep) in graphs that offer an easy overview and trends in data.
- A communication platform (video and chat) that enables patients to communicate directly with health care professionals. Video consultations will be conducted at 1 month and 4 months after enrollment in the study and additionally as needed on an individual basis.
- A rehabilitation plan. For each patient, an individualized rehabilitation plan is defined in a dialogue between the patient, the doctor, and a project nurse. The rehabilitation plan is formulated using individual parameters such as weight, physical status, pulse, and blood pressure. The patients write down their personal rehabilitation goals on the HeartPortal. The patients start the rehabilitation plan at the time of enrollment in the study. A project nurse monitors the patient's data twice a week and contacts the patients if the rehabilitation goals have not been met, data have not been transmitted to the HeartPortal, or in case data are not within the normal range set for the patient.

Textbox 2. Technologies used in the cardiac telerehabilitation group.

- Blood pressure monitor (iHealth Neo [BP5S]) [28]. Measurement of systolic and diastolic pressure and pulse. Connects to an app on the tablet to record the measurement and the tablet's internet connection to transfer the measured values. Blood pressure is measured twice a week.
- Weight scale (iHealth Lina) [29]. Allows the patient to follow his or her weight and observe weight loss or gain. Connects to an app on the tablet to record the weight, and the tablet's internet connection transfers the measured values to the HeartPortal. Weight is measured twice a week.
- Activity tracker (Fitbit Inspire 3|Health & Fitness Tracker) [30]. Measures physical activity, counted as steps and calories burned as well as pulse throughout the day. The activity tracker can also measure sleep if worn while sleeping. An app on the tablet is used for viewing and reviewing the tracked data and for data transfer. Activity, measured as steps, is measured every day and transmitted to the HeartPortal.
- Electrocardiography (ECG) monitor (KardiaMobile) [31]. Consists of a small device with touchpads, one for each hand. The monitor uses ultrasound to communicate with an app on the tablet. The app transfers the data to a General Data Protection Regulation-compliant system for clinicians, KardiaPro. ECG is carried out twice a week. The Kardia device includes an artificial intelligence–powered algorithm with an accuracy rate of 97% [31]. When patients measure their ECG, the device detects their heart rhythm. Patients have also been taught to interpret the results, such as the difference between sinus rhythm and AF.
- Sleep sensor (Emfit QS) [32]. Monitors pulse and respiration during sleep, sleep duration, stages, and sleep quality. Sleep is measured in hours every night, and the sensor data are transmitted to the HeartPortal.
- Video solution (VDX, Medcom) [33], a national video platform in Denmark within health care.

Data and Network Security

The telerehabilitation program has a strong focus on data and network security and resiliency. Security and resiliency in eHealth is a general issue that requires special measures in an environment where data are generated both from a health system (pulled data) and from the users or patients (pushed data). The format of metadata for reliable integration (source traceability), encryption, and infrastructure reliability (VPNs, VLAN, centralized vs federated storage) will be addressed by including perspectives from the different endpoints in the system (home, workplace, health center, etc), the technology used (wired, wireless, and dual technology), and the classification of information. Standardization activities, such as those from ITU-T, Continua, ENISA, etc, will be monitored and applied where possible.

Usual Care Intervention

Patients in the control care group have received AF education as usual, with the standard 45-60 minutes of orientation in AF, symptoms, treatment, and management of their own disease delivered in person at the hospital and by consultancy if needed by their general practitioner.

Baseline Characteristics

Sociodemographic data, such as civil status, level of education, work status, and IT competences, will be collected from both groups at baseline using data from the patient's electronic medical record and questionnaires.

Clinical baseline data, such as clinical status, primary and secondary diagnoses, and prescribed medicine, will also be collected for both groups using the electronic patient record.

Outcome Measures

Table 1 presents an overview of the primary and secondary outcome measures, along with the scheduled data collection dates. Except for progression in clinical data, including adverse events and dropout, all outcome measures will be collected using packages of questionnaires relevant to the specific point in time. The patients answer questionnaires in a web-based version, or on paper if they prefer.

Table 1. Primary and secondary outcome measures and data collection dates.

Outcomes	Time of measurement				End of tele- rehabilitation (at 4 months)	Follow-up at 7 months
	Baseline	Every day	Twice a week	As needed		
Primary						
Changes in AF[a]-specific quality of life	(I[b],C[c])				(I,C)	(I,C)
Secondary						
Changes in AF knowledge	(I,C)				(I,C)	(I,C)
Measurement of vital parameters						
Weight	(I,C)		(I)	(I)		
Blood pressure	(I,C)		(I)	(I)		
Pulse	(I,C)	(I)		(I)		
Steps	(I)	(I)			(I)	(I)
Sleep	(I)	(I)				
Electrocardiogram	(I,C)		(I)	(I)		
Changes in anxiety and depression	(I,C)				(I,C)	(I,C)
Changes in motivation	(I,C)				(I,C)	(I,C)
Burden of AF	(I,C)				(I,C)	(I,C)
Use of HeartPortal					(I)	
Patients' and relatives' perspective and experiences					(I)	
Health care professionals' perspective and experiences					(I)	
Cost-effectiveness evaluation					(I,C)	(I,C)
Trends and patterns in multiparametric clinical data					(I)	

[a]AF: atrial fibrillation.

[b]I: intervention group.

[c]C: control group.

Primary Outcome

Changes in AF-Specific Health-Related Quality of Life

AF-specific HRQoL is measured using the AFEQT [34]. The AFEQT is a 20-item self-administered questionnaire designed to assess the impact of AF on the patients' HRQoL across symptoms, daily activities, treatment concerns, and treatment satisfaction. Scores range from 0 to 100, with higher scores indicating better HRQoL.

Secondary Outcomes

Changes in AF Knowledge

The Jessa Atrial Fibrillation Knowledge Questionnaire (JAKQ) is a 16-item scale used to assess the knowledge of patients' AF about the arrhythmia illness [4]. For every item, false responses or "I don't know" responses are scored as 0, and the correct responses are scored as 1. The total score of the scale is calculated by adding up all item scores.

Measurement of Vital Parameters

Clinical data on weight, blood pressure, pulse, steps, sleep, and ECG in the intervention group will be collected as specified in Table 1.

Changes in Anxiety and Depression

Symptoms of anxiety and depression are measured using the Hospital Anxiety and Depression Scale (HADS) [35]. The HADS is a 14-item self-reported questionnaire often used for screening of psychological distress in patients with cardiac conditions. Each item is scored on a 4-point Likert scale ranging from 0 to 3. The 2 subscales, anxiety and depression, each comprise 7 items, and scores on these subscales range from 0 to 21, with higher scores indicating higher levels of anxiety or depressive symptoms.

Changes in Motivation

Motivation is measured by the Health-Care Self-Determination Theory Questionnaire Packet (HC-SDTQ). The HC-SDTQ

includes 3 separate questionnaires: the Treatment Self-Regulation Questionnaire, which focuses on autonomy as stipulated by SDT [36]; the Perceived Competence Scale, which assesses patients' sense of competence about engaging in, or maintaining, a healthier behavior [37]; and the Health Care Climate Questionnaire, which assesses the patient's perception of autonomy support from their health care provider [38].

Burden of AF

The burden of AF is measured using the Arrhythmia-Specific Questionnaire in Tachycardia and Arrhythmia (ASTA) [39]. The ASTA measures symptoms and HRQoL in patients with different forms of arrhythmias, including AF. The ASTA is divided into 3 parts: Part I assesses demographic data, such as the most recent episode of arrhythmia, current medication, and the presence of arrhythmia at the time of follow-up; Part II measures the arrhythmia-specific symptom burden; and Part III measures HRQoL. Parts II and III are scored using a 4-point Likert-type scale (0="No" to 3="Yes, a lot"). The total score range is from 0 to 100, with a higher score indicating a higher symptom burden or a negative effect on HRQoL.

Use of HeartPortal

Time log files for login and logout of patients and relatives will be analyzed in order to identify which parts of the HeartPortal are being used and for how long. The patients will be asked for their consent prior to extracting their log files from the database for analysis.

Perspectives and Experiences From Participating in the FP-AF Program

Participant-observation [40,41] will be used in situations such as educating and counseling the patients and relatives in using the technologies at home and to observe how patients and relatives use the digital technologies and the HeartPortal.

Perspectives and experiences of patients, relatives, and HPs participating in the FP-AF program will be explored using semistructured qualitative interviews, inspired by Brinkmann and Kvale [42]. Interviews will be performed until data saturation is reached, with a minimum of 10 interviews conducted for each group: patients, relatives, and HPs. The interviews will be recorded, transcribed, and analyzed in themes inspired by Brinkmann and Kvale [42] and based on their phenomenological approach. The interviews will be coded by 2 researchers using NVivo (version 14.0) software [43].

Cost-Effectiveness Evaluation

Throughout the duration of the study, we will also collect information on unplanned admissions for any reason with at least 1 overnight stay, unplanned readmissions for any reason and length of stay, visits to outpatient clinics, rehabilitation activities, visits to the general practitioner, equipment used, driving distance, personnel use, and numbers of phone or video calls. The analysis will be based on the guidelines for economic evaluation elaborated by Drummond et al [44].

Data Storage

Demographic data are being stored within the Future Patient database, and the questionnaire data are stored in the REDCap (Research Electronic Data Capture; Vanderbilt University) software for quantitative analysis.

Adverse Events, Dropout, and Technical Issues

All adverse events, dropouts, and deaths, as well as any technical issues related to the equipment, will be registered. No preterm study stop criteria are planned.

Data Analysis

Statistical Analysis

Baseline characteristics will be presented as frequencies and percentages or as medians and IQRs, as appropriate, and the data will be stratified by randomization groups and by sex. Changes over time on the primary outcome will be analyzed in accordance with the intention-to-treat principle, using a mixed-effects model for repeated measures design with robust variance in order to relax the assumption of normally distributed residuals. In addition, margin plots will be produced in order to investigate the interaction of time and randomization group. A sensitivity analysis will be conducted in order to investigate the effects of missing data as a result of dropout by comparing baseline characteristics between complete cases and dropouts, followed by adjusted analyses of the primary outcome using appropriate baseline characteristics as adjustment parameters. Secondary outcomes will be analyzed in a manner similar to the primary outcome. We will also examine overlaps between and variations within groups of different sexes. In examining sex differences, we will adjust for possible confounding factors (eg, age).

Trends and Patterns in Multiparametric Clinical Data

Data will be analyzed in order to identify correlations in multiparametric data collected during the 4 months. Initial analysis of the multiparametric data will be carried out by assessing the architectural structures and complexities of the data design through basic statistical and distributive analysis. Differences in the multiparametric data between baseline and postintervention measurements will be tested with paired *t* tests. Correlations of multiparametric data will be compared with patient-reported symptoms of AF. Paired *t* tests will be performed for the multiparametric data between periods both with and without patient-reported symptoms of AF in patients experiencing symptoms. Also, *t* tests will be performed for multiparametric data between patients with and without symptoms of AF. Simplistic features will be developed based on the statistical analyses and correlations between data.

Qualitative Analysis

A research assistant will transcribe all interviews into text files. Data will be coded in NVivo (version 14.0; QSR International), drawing inspiration from the SDT theoretical framework and using methods developed by Brinkmann and Kvale [42]. Two different researchers will be responsible for conducting the interviews and analyzing the data. The data will be presented in terms of key themes and major findings.

Economic Evaluations

A cost-effectiveness analysis of the FP-AF telerehabilitation program compared to conventional care will be made at 7

months after inclusion for both groups. The analysis will be based on the guidelines for economic evaluation elaborated by Drummond et al [44].

Results

The findings of the RCT will be analyzed during the spring of 2025 and subsequently published in peer-reviewed journals in the fields of telerehabilitation, clinical cardiology, and health economics. In addition, these results will be presented at relevant international scientific conferences. A total of 208 patients will be enrolled, 104 in the telerehabilitation group and 104 in the control group.

The evaluation of the FP-AF program comprises both clinical data recorded by the patients and data gathered through interviews and questionnaires. The evaluation involves quantitative analysis of primary and secondary outcomes (questionnaires) as well as qualitative exploration of the perspectives and experiences of patients with AF, their relatives, and HPs. Finally, a health economic evaluation will be conducted. Taken together, the data and the associated analyses will provide a comprehensive perspective on the effectiveness of the FP-AF program as seen from clinical, patient, relatives, psychological, organizational, and economic perspectives.

Discussion

Telerehabilitation Program

The aim of the study is to test an individualized CTR program for patients with AF. The primary outcome measure is to assess potential changes in QoL among those patients with AF using telerehabilitation. The secondary outcome measures are changes in AF knowledge, changes in anxiety and depression, changes in motivation, the burden of AF, patients' and relatives' perspectives and experiences, patients' and relatives' use of the HeartPortal, perspectives and experiences of HPs, the development of clinical data, and a cost-effectiveness analysis.

CR for patients with AF is a fairly new initiative, and national guidelines for AF CR have only recently been published [8]. In this study, we take this initiative further by examining the potential of a CTR program for patients with AF, as telerehabilitation provides a promising and innovative alternative to conventional rehabilitation. The potential advantage of telerehabilitation is that it can provide easier access to rehabilitation assistance and activities and may therefore be a means of overcoming some of the barriers to participation in CR that have been identified in other cardiac patient groups [45]. Use of telerehabilitation may be especially relevant for patients with AF, as this group is very diverse in terms of the subjective impact of their disease; hence, some patients may not feel the need to attend physical appointments at the clinic, but they may be willing or even positive about participating through digital communication and technology. The digital option offered by telerehabilitation may thus improve their QoL.

The FP-AF program will be tested in a multicenter study in order to increase the validity of the study. The FP-AF program is based upon SDT theory and the exploration of how patients, their relatives, and HPs use the HeartPortal. We will therefore analyze the linkages between motivation and use of the digital platform. In a previous study of patients with heart failure, we have documented that telerehabilitation motivates patients with heart failure just as effectively as conventional rehabilitation and that it does not lead to higher levels of psychological distress [46].

To obtain a more in-depth understanding of how patients, relatives, and HPs perceive CTR, we also plan to conduct qualitative interviews with all groups in order to learn more about how they experience the program as part of their everyday life and work, including their evaluation of the specific modules of the program. Using interviews together with questionnaire data will allow for a more holistic understanding of the usability, effect, and acceptance of the proposed program.

Limitations

The expected limitations for the interpretations of the results are as follows. The study relies heavily on commercial tracking devices that have been chosen for their ability to automatically transmit data to the HeartPortal. Any changes in device regulations during the study could make it necessary to replace these devices, potentially leading to inconsistency in the data. In addition, the proposed intervention is complex, consisting of a chain of events and interventions and based on multiple commercially available technologies that may become outdated. This complexity, including the rapidly changing nature of technology, may pose a challenge to future replication studies.

Conclusions

Analyzing data from primary and secondary outcomes will help determine whether the FP-AF program has the potential to increase QoL for patients living with AF and give them more knowledge of how to master the disease. The cost-effectiveness analysis will provide an assessment of the health economic sustainability of the FP-AF program and shed light on whether telerehabilitation can be a viable alternative for rehabilitation of patients with AF.

Acknowledgments

The project was financed with DKK 4.3M by a grant from The Danish Heart Association and DKK 300,000 from Snedkermester Sophus Jacobsen og Hustru Astrid Jacobsens Fond through The Danish Heart Association, with DKK 1,277,097 from Aage and Johanne Louis Hansens Fond, DKK 1,223,904 from MedCom, DKK 300,000 from Viborg Municipality, DKK 864,000 from Region Midtjylland's Forskningsinnovationspulje, and DKK 40,000 from Rosa og Asta Jensens Fond. We wish to thank the project nurses Helle Mark, Cardiology Ward, Regionhospital of Viborg, and Hanne Kastbjerg, Cardiology Ward, Regionhospital

of Silkeborg. We also wish to thank health care consultants Maria Kamstrup Oeland, Skive Healthcare Center, and Susanne Engbirk Grud and Helen Skov Kjaersgaard, Silkeborg Healthcare Center.

Conflicts of Interest

None declared.

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Abbreviations

AF: atrial fibrillation
AFEQT: Atrial Fibrillation Effect on Quality-of-life Questionnaire
ASTA: Arrhythmia-Specific Questionnaire in Tachycardia and Arrhythmia
CONSORT: Consolidated Standards of Reporting Trials
CR: cardiac rehabilitation
CTR: cardiac telerehabilitation
ECG: electrocardiogram
FP-AF: Future Patient—Telerehabilitation of patients with atrial fibrillation
HADS: Hospital Anxiety and Depression Scale
HC-SDTQ: Health-Care Self-Determination Theory Questionnaire
HP: health care professional
HRQoL: health-related quality of life
JAKQ: Jessa Atrial Fibrillation Knowledge Questionnaire
QoL: quality of life
RCT: randomized controlled trial
REDCap: Research Electronic Data Capture
SDT: self-determination theory

Edited by A Schwartz; submitted 12.07.24; peer-reviewed by L Desteghe, T Vagg; comments to author 13.09.24; revised version received 10.10.24; accepted 10.11.24; published 18.02.25.

Please cite as:
Dinesen B, Albertsen AE, Joensen EDR, Spindler H, Jensen KM, Kidholm K, Frost L, Dittman L, Gunasegaram M, Johnsen SP, Jochumsen MR, Svenstrup D
Future Patient—Telerehabilitation of Patients With Atrial Fibrillation: Protocol for a Multicenter, Mixed Methods, Randomized Controlled Trial
JMIR Res Protoc 2025;14:e64259
URL: https://www.researchprotocols.org/2025/1/e64259
doi:10.2196/64259
PMID:

Protocol

Cognitive Training for Emotion-Related Impulsivity and Rumination: Protocol for a Pilot Randomized Waitlist-Controlled Trial

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Abstract

Background: Inhibitory deficits are common in psychopathology. Emotion-related impulsivity (ERI) and rumination are general risk factors for psychiatric distress that are similarly associated with dysfunctional inhibition—particularly in affective contexts. A number of cognitive remediation procedures have been developed to improve inhibitory control; however, most remediation programs focus on "cold" cognition independent of affective processing. This pilot trial will gather preliminary evidence for a new cognitive training intervention targeting "hot" affective control (ie, inhibitory functions during elevated emotional arousal) in a transdiagnostic sample of adults who report heightened emotion dysregulation.

Objective: This manuscript describes a protocol for a pilot randomized waitlist-controlled trial to assess changes in ERI and rumination after neurobehavioral affective control training (N-ACT), an 8-week cognitive training intervention designed to improve emotional response inhibition and emotional working memory. Our primary aim is to evaluate the efficacy, feasibility, and acceptability of N-ACT in reducing rumination and ERI, which we respectively conceptualize as complementary cognitive and behavioral consequences of emotion dysregulation. Secondarily, we will examine whether N-ACT leads to improvements in inhibitory control and, more distally, psychopathology symptoms.

Methods: The final sample will comprise 80 adults who report high ERI or rumination. Participants will be randomized to (1) begin the N-ACT program without delay or (2) join a waitlist condition and then complete N-ACT. Exclusion criteria include active alcohol or substance use disorders, psychosis, and suicide risk. At the baseline and postintervention time points, participants will complete measures of emotion dysregulation and psychiatric symptoms, as well as a neuropsychological assessment of inhibitory control. Individuals assigned to the control group will undergo an identical assessment before joining the waitlist, followed by parallel assessments before and after N-ACT.

Results: This trial is funded by support from the University of California Board of Regents and the Peder Sather Foundation (funding period: October 2022-September 2025). Recruitment is scheduled to begin in spring 2025. We will begin data analysis once data collection is complete, which is planned to occur in fall 2025.

Conclusions: This pilot randomized waitlist-controlled trial is designed to assess the initial efficacy, feasibility, and acceptability of N-ACT, a novel cognitive remediation approach developed to address 2 key contributors to psychopathology: ERI and rumination. The N-ACT program uses computerized adaptive behavioral tasks to strengthen the affective control processes theoretically and empirically linked to ERI and rumination. We hope this work will help inform future studies with sufficient

statistical power to ascertain whether enhancing affective control through cognitive training (N-ACT) produces downstream reductions in psychiatric symptoms via improved emotion regulation.

Trial Registration: ClinicalTrials.gov NCT06226467; https://www.clinicaltrials.gov/study/NCT06226467; Open Science Framework Registry rak5z; https://osf.io/rak5z

International Registered Report Identifier (IRRID): PRR1-10.2196/54221

(JMIR Res Protoc 2025;14:e54221) doi:10.2196/54221

KEYWORDS

cognitive control; cognitive training; emotion regulation; emotional response inhibition; emotional working memory; executive function; impulsivity; rumination; transdiagnostic; urgency

Introduction

Background

Emotion dysregulation is an established risk factor for nearly all psychiatric syndromes, with particularly strong effects for anxiety and depression—the 2 most common psychological disorders [1,2].These links between emotion dysregulation and psychiatric dysfunction are well documented across ecological and laboratory studies, as well as in large-scale prospective work [3-5]. This research will evaluate a novel intervention, neurobehavioral affective control training (N-ACT), which is designed to target two trait-like facets of emotion dysregulation: (1) *rumination*, the tendency toward self-focused, past-oriented, repetitive negative thinking about the causes and consequences of negative affect [6,7]; and (2) *emotion-related impulsivity* (ERI; [8]), the tendency toward reduced behavioral control during states of high affective arousal [9], most commonly captured using measures of Urgency. These 2 aspects of emotional dysregulation reflect cognitive and behavioral responses, respectively, to negative affect. Robust associations have been documented of rumination and ERI with anxiety and depressive disorders as well as numerous other psychiatric conditions [6,7,10-18].

Inhibitory Control Deficits in Psychopathology

Rumination and ERI are both tied to problems with cognitive (inhibitory) control. Cognitive control is a multifaceted construct that includes (1) the ability to update and manipulate the contents of working memory; and (2) the inhibition of task-inappropriate behavior (ie, response inhibition), alongside closely related executive functions (eg, cognitive inhibition, set shifting or task switching). This project targets both working memory and response inhibition, which represent promising candidate mechanisms linking emotion regulation deficits to varied manifestations of psychopathology.

Cognitive difficulties associated with major depressive disorder (MDD) and other internalizing syndromes often have severe consequences for the individuals affected, likely through adverse influences on symptoms and role functioning. Systematic reviews of this literature suggest that cognitive control deficits in MDD are not simply epiphenomenal effects caused by symptoms—as some have recently suggested [19]—but rather often persist after remission, thereby exerting continued influence on everyday functioning and the likelihood of symptom recurrence [20,21]. Indeed, impaired cognitive control predicts relapse in patients with first-episode depression [22] up to 5 years after the index episode through its association with rumination [23,24]. One of the longest prospective studies of cognition in MDD revealed cognitive control impairment a full decade after symptom remission [25]. In sum, a substantial literature implicates poor cognitive control in prolonged vulnerability to depression recurrence and relapse.

Evidence for chronic neuropsychological deficits in MDD and other psychiatric disorders has generated interest in improving mental health through strengthening cognitive control and other executive functions. However, traditional psychotherapeutic interventions have limited effects on cognitive control; for example, meta-analyses indicate little to modest changes in cognitive control capacities after psychological [26] or pharmacological treatment for depression [27]. The recognition of the need for new approaches to enhancing executive functions has led to a growing focus on development of cognitive remediation or training programs that directly target inhibitory control [28-30].

However, many studies—of major depression or otherwise—rely on measures of “cold” cognitive control, in that the assessment procedures lack emotionally salient stimuli or probes. *Affective control* refers to the ability to exert inhibitory control in situations or tasks involving emotionally arousing content, often referred to as “hot” executive functions. Emotional contexts may be more likely to activate or aggravate symptoms compared to contexts without such affective components [31]. Rumination and ERI—as well as psychopathology more broadly—may be more closely linked to affective control deficits than to cold cognitive control deficits. For example, among people with remitted MDD compared to healthy controls, Ronold et al [32] observed working memory deficits (during high cognitive load) especially for negative compared to positive emotional content; moreover, in 2 independent samples, such impairment was tied to heightened rumination [33], which in turn predicted elevated risk for depressive relapse [32]. ERI is similarly associated with impaired inhibitory control, particularly during higher arousal states [34]. Moreover, poor affective control is associated with symptoms of eating disorders [35], nonsuicidal self-injury [36-40], and suicidal behaviors [31,41,42]. Thus, affective control is an empirically justified and theoretically informed target to remediate and prevent the recurrence of psychiatric symptoms.

A growing corpus of research has converged on 2 components of affective control, both of which are targeted by N-ACT: (1) *emotional working memory*, which involves the temporary

storage and manipulation of emotional information in short-term memory; and (2) *emotional response inhibition*, or the ability to regulate motor impulses driven by automatic emotional reactions. Dysfunction in working memory or response inhibition—*specifically in the context of negative emotion*—is independently tied to rumination, ERI, and internalizing symptoms, as well as self-injurious thoughts and behaviors [39,41,43-46]. Several studies have shown that emotional response inhibition, as indexed by an emotional stop-signal task (ESST), shows significant correlations with measures of ERI and psychiatric severity [37,39,43]. Negative emotional response inhibition impairment is a strong predictor of symptoms, including increased risk of future suicide attempts [41].

Cognitive Remediation in Psychiatry

The goal of cognitive remediation is to improve dysfunctional neurocognitive processes. This improvement relies on the repeated practice of specialized cognitive training exercises using computer algorithms that adjust task difficulty according to user performance. A burgeoning literature suggests that cognitive remediation may be a promising transdiagnostic intervention approach [28,47-55]. Working memory training has been found to reduce the recurrence of mood episodes among patients with remitted MDD, with stronger protective effects—apparent up to 2 years after the intervention—for those who reported reduced rumination after training [52,56]. Although accumulating evidence supports the efficacy of cognitive remediation in psychiatric disorders, meta-analytic effect sizes tend to be small to medium [28], and a substantial proportion of individuals do not respond to existing training programs for symptom reduction [57].

Numerous issues likely contribute to the relatively modest treatment effects associated with standard cognitive remediation programs. N-ACT is novel in 3 ways. First, we focus on emotion regulation rather than psychiatric symptoms as our primary outcome. Second, extant literature shows considerable variability in the delivery methods of cognitive remediation. Following consensus recommendations from an expert working group [47], we will implement scaffolding techniques to facilitate the generalization and functional impacts of N-ACT. More specifically, we will follow recommendations to provide support to facilitate translation of skills into everyday activities, so as to enhance the ecological validity and effectiveness of cognitive training programs [47-55]. Participants will accordingly complete N-ACT intervention sessions guided by a "coach," who will deliver semistructured and (partially) personalized psychoeducational content. N-ACT coaching sessions will include the identification of compensatory problem-solving strategies for emotion regulation, skills practice, motivational enhancement, discussion of the ecological relevance of the cognitive skills being trained, and procedures to promote the transfer of training effects to real-world situations. Therefore, we will be testing the effects of repeated affective control exercises, coupled with therapeutic coaching. Our hope is that this combination of techniques will support generalization to improved functional outcomes.

Third, although the stimuli and parameters in many cognitive control training tasks (eg, those using geometric shapes and letters) lack inherent salience value, our trial builds from a smaller body of work on cognitive remediation using the affective variants of inhibitory control tasks as well as traditional tasks (with neutral stimuli) that may naturally induce emotional arousal [50]. As an example of the latter, the Paced Auditory Serial Addition Test [58], which uses numerical stimuli and has been extensively implemented as an adaptive training task [29,30,59], characteristically evokes frustration [58]. To our knowledge, the only direct comparison of cold versus hot cognitive remediation was performed in a pilot trial of emotional working memory training, which yielded promising results in symptoms and cognition (but not rumination) among patients with depressive symptoms [60]. This early work is consistent with recent meta-analytic findings suggesting that hot inhibitory control training may be more effective than nonaffective cognitive remediation procedures for psychopathology [61]. Accordingly, N-ACT incorporates affective stimuli (eg, naturalistic images with standardized emotional content) into traditional training tasks designed to improve cognition such that users learn to use these mental operations in socioemotional contexts that more closely match in vivo experiences. The inclusion of affective stimuli is particularly important, given a substantial body of work suggesting that difficulties sustaining inhibitory control during states of elevated arousal are particularly relevant to emotion regulation and psychiatric symptoms.

This Study

Overview

This pilot randomized waitlist-controlled trial will enroll adult participants with high rumination or ERI scores. The primary aim of this study is to examine the acceptability, feasibility, and efficacy of N-ACT as a novel therapeutic approach to reduce rumination and ERI by improving 2 facets of affective control: emotional working memory and emotional response inhibition. Secondarily, we will test the effects of N-ACT on behavioral indices of ability transfer as well as on other subjective measures of emotion dysregulation (beyond trait rumination and ERI) and psychopathology symptom severity (refer to Multimedia Appendix 1 for details). Finally, we will conduct exploratory analyses to examine the potential mechanisms that might influence predicted changes in emotion dysregulation, informing future work to systematically test these effects in a sufficiently powered sample. In addition to performing intent-to-treat analyses, we will conduct sensitivity analyses to evaluate the extent to which program adherence predicts the hypothesized effects.

Hypotheses

We propose the following hypotheses:

- H1: Participants will rate N-ACT as an acceptable intervention to reduce emotion dysregulation.
- H2: Participants will demonstrate adherence to the N-ACT program at levels comparable to those observed in established cognitive remediation protocols [33,52,62-64].
- H3 (primary): Compared to baseline, participants assigned to complete N-ACT (without a waitlist) will report greater decreases in rumination and ERI at the postintervention

assessment than those assigned to the control condition at the postwaitlist assessment.

- H4 (secondary): Compared to baseline, participants assigned to complete N-ACT (without a waitlist) will demonstrate greater improvements in targeted affective control processes (ie, enhanced emotional working memory and emotional response inhibition) at the postintervention assessment than those assigned to the control condition at the postwaitlist assessment.
- H5 (secondary): Compared to baseline, participants assigned to complete N-ACT (without a waitlist) will demonstrate near (ie, enhanced hot affective flexibility) and far (ie, enhanced cold working memory and cold response inhibition) transfer of trained neurocognitive abilities at the postintervention assessment than those assigned to the control condition at the postwaitlist assessment.
- H6 (secondary): Compared to baseline, participants assigned to complete N-ACT (without a waitlist) will report greater decreases in self-rated psychopathology symptom severity (ie, reduced internalizing and externalizing symptoms) at the postintervention assessment than those assigned to the control condition at the postwaitlist assessment.

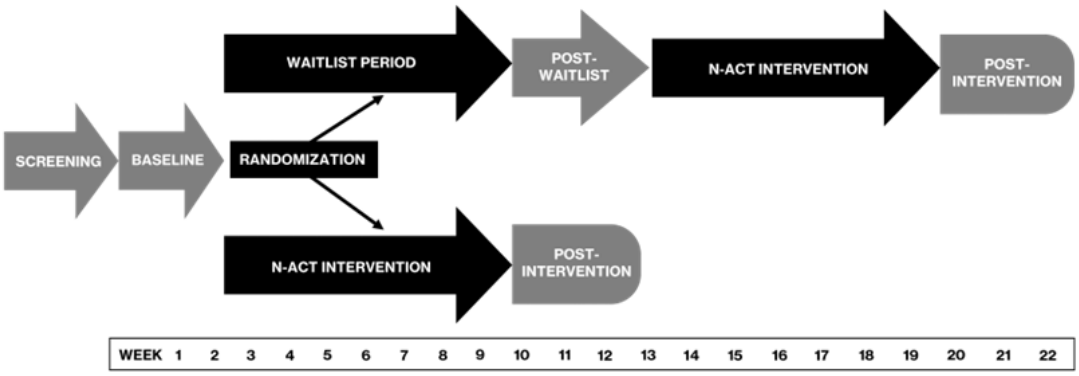
Methods

Overview

This research comprises a delayed intervention randomized waitlist-controlled trial with a mixed, 2-group (2 between-subject levels: active vs control), repeated measures (2 within-subject levels: T1=baseline or preintervention time point; T2=postwaitlist or postintervention time point) design, for which we will recruit English-speaking adults (aged 18-65 y) from the San Francisco Bay area of the United States. The inclusion criteria include high self-reported rumination or ERI. Eligible individuals will be invited to the university for an initial baseline session. At this session, they will complete informed consent procedures and an assessment battery consisting of computerized neuropsychological tasks with concurrent psychophysiological monitoring. After the baseline session, participants will complete a battery of questionnaires, followed by 1 week of baseline ecological momentary assessment (EMA) of real-world daily fluctuations in mood, rumination, and ERI.

After the baseline assessment (laboratory session, questionnaires, and EMA), we will randomly assign participants to receive active treatment (ie, N-ACT without delay) or the waitlist control condition, unblinded, using an asymptotic maximal procedure to achieve a maximally tolerated imbalance of 2, while maintaining a 1:1 allocation ratio between the 2 trial arms [63]. Participants in the active N-ACT group will begin the intervention, which consists of 8 weekly coached training sessions, within 1 week after baseline EMA. We will recontact waitlist control participants after a period equivalent to the intervention duration (ie, 2 months) to complete a second (postwaitlist) assessment session and EMA before starting the N-ACT program for the following 8 weeks. After the intervention, participants will be asked to complete a second week of EMA, and then a postintervention assessment session with comparable measures to baseline. We will recontact waitlist control participants approximately 10 weeks after their (prewaitlist) baseline assessment session to complete a second (postwaitlist) assessment and 1 week of EMA, parallel with the pre-intervention assessment procedures of the N-ACT group,. The waitlist group will then be offered 8 weeks of N-ACT, followed by a second week of postintervention EMA, and then a final assessment session. In sum, we will follow participants assigned to receive the intervention without delay for 12 weeks (3 mo) and those assigned to the waitlist control group for 22 weeks (5.5 mo). This delayed intervention randomized waitlist-controlled trial design enables us to offer all interested participants the opportunity to participate in the program and maximizes our ability to rapidly accrue a sufficiently sized sample for analyses. Figure 1 demonstrates the flow of potential participants through the study procedures.

Figure 1. Flow of participants through the trial with a delayed intervention randomized waitlist-controlled design. N-ACT: neurobehavioral affective control training. Assessments are indicated in gray.



Hypotheses and analyses were preregistered at OSF. We plan to detail any changes to this protocol in future publications and disseminate our findings to the scientific community in accordance with the CONSORT-EHEALTH (Consolidated Standards of Reporting Trials of Electronic and Mobile Health Applications and Online Telehealth) checklist (V 1.6.1) [64].

Ethical Considerations

The University of California Berkeley Committee for Protection of Human Subjects granted approval for this research (2023-01-15949) before data collection. All participants will complete written informed consent before commencing study procedures.

Participants will be assigned an ID number, which will be used in place of their name or other identifying information on all research materials. Data will be kept in secure, password-protected files. Although we plan to make data publicly available for reanalysis, we will carefully deidentify data before doing so. In publishing or presenting the results, we will not provide any information that could identify an individual participant.

Participants will receive course credit or monetary compensation for completing assessment procedures but will not be paid for time spent on screening or the intervention itself. Students will be able to earn credit toward required research hours in their psychology classes. We plan to increase the hourly payment rate slightly over the course of the trial to promote retention, from US $20/h for the baseline assessment to US $30/h for the postwaitlist and postintervention assessments. We will compensate participants up to US $60 (or 3 h of course credit) for completing the baseline assessment (2.5-h in-person session plus 30 min of questionnaires), a US $10 “bonus” for performance on an unrelated computer task during the baseline session, US $10 for each week of EMA if they complete at least 75% of the prompts, and US $60 for the postintervention assessment (1.5-h in-person session plus 30 min of questionnaires). Those randomized to the waitlist control condition will be eligible to receive up to an additional US $60 for completing the postwaitlist assessment (identical to the postintervention assessment).

In sum, participants assigned to complete N-ACT without the waitlist can earn up to US $150 (or 3 h of course credit plus up to US $90), while those in the waitlist control condition could earn up to US $70 in addition to those amounts. Payments will be prorated if participants complete only part of an assessment.

We will remunerate participants within 1 week of each completed assessment via digital credit cards, which will be replenished as necessary.

Study Procedures

Recruitment and Screening

We will invite up to 500 adults to complete preliminary screening procedures and an estimated 100 participants to complete the initial baseline assessment session. After accounting for 20% expected attrition, we expect 40 participants in each condition to complete all study procedures.

Study advertisements will be posted locally in public spaces and distributed by web (eg, via email listserves, Craigslist, and social media sites). We will also administer a prescreening survey to students enrolled in psychology classes at the University of California Berkeley, and we will invite students who meet the preliminary inclusion criteria based on those responses to take part in the study. Potential participants (recruited either from the community or from the student participant pool) will be directed to our website, where they can view additional details about the trial. We intend to recruit only secondarily from the student participant pool to supplement community-based recruitment, which will constitute most of the targeted sample. All questionnaires, including screening items, will be administered through REDCap (Research Electronic Data Capture; Vanderbilt University) software [65], which will also be used for the secure storage of collected data.

After providing informed consent, interested individuals will complete the brief web-based screening via REDCap to assess preliminary eligibility. The inclusion and exclusion criteria are presented in Textbox 1.

Textbox 1. Inclusion and exclusion criteria.

Inclusion criteria

- Current California residency
- Age 18 to 65 y
- Elevated scores on self-report measures of rumination (Mn >2 on the Brooding subscale of the Ruminative Responses Scale [13]) or emotion-related impulsivity (Mn >3 on the Feelings Trigger Action factor of the Three-Factor Impulsivity Index [9])

Exclusion criteria

- Insufficient English literacy to understand study procedures (as assessed by self-report) or careless responding as indicated by the following:
- Failing ≥50% of the attention check items embedded in the screening questionnaires
- Overly rapid responding (ie, mean response time of <2 s for multiple-choice items)
- Qualitative review of long strings of identical entries
- Positive history of brain tumors, neurological disorders, or head injuries accompanied by the following:
- Loss of consciousness of >5 min
- >2 separate instances of clinically significant head trauma
- Recent alcohol or other substance use disorder (in the past 6 mo) or current psychosis (in the past 2 wk) according to the Psychiatric Diagnostic Screening Questionnaire [66]
- Past-month active suicidal ideation paired with either of the following:
  - An identified method, specific plan, or intent
  - Lifetime history of suicide attempts as assessed by the screen version of the Columbia Suicide Severity Rating Scale [67]

The exclusion criteria do not cover the presence of anxiety, depression, or other psychiatric symptoms, given our intention to target emotion dysregulation broadly and to assess the generalizability of effects across psychiatric diagnoses and severity, including participants with few or no symptoms and those without treatment history. However, the screening will include items from the self-rated screen version of the Columbia Suicide Severity Rating Scale (C-SSRS; for suicidal thoughts) as well as the alcohol, substance, and psychosis subscales from the Psychiatric Diagnostic Screening Questionnaire (PDSQ) [66]. Individuals who do not respond to the requisite screening items or do not meet eligibility requirements, including those whose responses to the psychiatric screening questions surpass established clinical thresholds, will be automatically informed that they will not be able to join the trial and will receive a list of mental health resources along with an invitation to contact our team should they desire additional referral assistance. We will provide further support for engaging with psychiatric care providers to respondents who endorse past-month active suicidal ideation with an identified method, specific plan, or intent on the C-SSRS.

Assessment

Overview

Each in-person assessment session will involve core measures expected to take 90 minutes, including a battery of computer-based behavioral tasks measuring cold and hot executive functions as well as the Positive and Negative Affect Schedule (PANAS) [68] to evaluate subjective mood before and after the neuropsychological examination. Within 24 hours of each session, participants will be asked to complete self-rated questionnaires to evaluate psychiatric symptoms and other variables of interest, which will require an additional 30 to 40 minutes. Table 1 presents key measures included at each assessment and intervention time point (refer to Multimedia Appendix 1 for a comprehensive list and additional details).

Table 1. Administration schedule of core measuresa.

Domains and measures	Format	Screening	Baseline assessment	Postwaitlist assessment	N-ACT[a] assessment	Post–N-ACT assessment
Emotion dysregulation						
Ruminative Responses Scale–Brooding	Self-report	✓		✓		✓
Three-Factor Impulsivity Index–Feelings Trigger Action	Self-report	✓		✓		✓
Three-Factor Impulsivity Index–Pervasive Influence of Feelings	Self-report		✓	✓		✓
Psychiatric symptom severity						
Columbia Suicide Severity Rating Scale	Self-report	✓				
Demographic questionnaire or mental health history survey	Self-report	✓				
Psychiatric Diagnostic Screening Questionnaire–Alcohol Use Disorder or Substance Use Disorder or Psychosis	Self-report	✓				
Externalizing Spectrum Inventory–Revised	Self-report		✓	✓		✓
Inventory of Depression and Anxiety Symptoms, Expanded Version	Self-report		✓	✓		✓
Neuropsychological assessment battery						
Digit Span Backward	Behavioral		✓	✓		✓
Stop-signal task	Behavioral		✓	✓		✓
Trail-making test	Behavioral		✓	✓		✓
Wechsler Adult Intelligence Scale, Fourth Edition–Vocabulary	Interview		✓	✓		✓
Emotional stop-signal task	Behavioral		✓	✓		✓
Memory and affective flexibility task	Behavioral		✓	✓		✓
Affective control training (N-ACT)						
Adaptive emotional n-back task	Behavioral				✓	
Emotional stop-signal task–adaptive	Behavioral				✓	

[a]A comprehensive list of secondary measures and additional outcomes is available in Multimedia Appendix 1.

Neuropsychological Battery

At each assessment session, participants will perform 5 computerized neuropsychological tasks (in a pseudorandom order) to index the hypothesized effects of N-ACT on emotional working memory and emotional response inhibition as well as the transfer of targeted inhibitory control processes from T1 (baseline time point) to T2 (postwaitlist or postintervention time point). The assessment battery accordingly includes 3 widely used gold standard cold executive functioning tasks that measure key components of cognitive control: (1) Digit Span Backward [69], a working memory test that requires participants to select (using the computer cursor) a series of numbers in the opposite order from which the digits were presented (in numerical strings of increasing length); (2) the stop-signal task (SST) [70], a measure of prepotent response inhibition in which participants must quickly indicate (via keypress) the direction of rapidly presented arrow stimuli, except on trials that include an unpredictable buzzer tone, which require termination of the initiated motor response; and (3) the trail-making test [71], an assay of set-shifting or task-switching ability that involves using

the computer cursor to draw a path connecting an array of alphanumeric stimuli in an alternating sequential pattern (eg, "A" to "1" to "B" to "2," and so on) as quickly as possible. The neuropsychological battery additionally includes the administration of the Vocabulary subtest from the Wechsler Adult Intelligence Scale, Fourth Edition [72], to assess crystallized intelligence, which we will examine in exploratory analyses of the specificity of intervention effects.

Participants will also complete 2 tasks to confirm the efficacy of N-ACT in augmenting 2 core facets of affective control, emotional response inhibition and emotional working memory: (1) the ESST [37,39,43], which follows procedures parallel to those of the traditional SST but differs in that participants must rapidly categorize affective pictures according to perceived valence (ie, "positive or pleasant" vs "negative or unpleasant") instead of indicating the direction of arrow stimuli, while still inhibiting prepotent motor responses on a subset of trials with an unpredictable auditory stop signal (buzzer or tone); and (2) the memory and affective flexibility task (MAFT) [73], a novel modified n-back procedure that provides indices of emotional working memory as well as affective flexibility (as captured by emotional set shifting or task switching trials) by asking participants to recall whether they have previously seen (1-3 trials earlier) serially presented images with affective content (ie, "n-level," which varies by block), with occasional interspersed "switch" trials prompting them to respond instead to perceived image valence (identical to ESST go or no-signal trials).

Psychophysiology

During the administration of the computerized cognitive assessment tasks, we will gather 2 metrics of arousal—pupil dilation, which reflects phasic norepinephrine signaling; and skin conductance, an index of autonomic sympathetic nervous system activity—to evaluate the physiological correlates of cold and hot executive functioning. We will consider incorporating physiological reactivity variables gathered during the latter set of tasks as secondary indicators in exploratory mechanistic analyses of the hypothesized treatment effects (Multimedia Appendix 1).

Pupil measurements will be recorded noninvasively with a Tobii T-120 infrared eye tracker [74] using E-Prime Extensions for Tobii [75]. We will not gather pupillometry data from participants who report a history of epilepsy or seizures triggered by arcade or video games, computer or television screens, or flickering fluorescent bulbs. Skin conductance levels will be monitored by electrodes placed (by the participant) on the inner sole of the foot. Trained research staff will calibrate physiological recording hardware (eg, by ensuring proper electrode placement and adjusting a chin rest to limit movement-related artifacts) for maximum comfort and signal.

EMA Surveys

We will use EMA to capture the temporal dynamics of real-world affect and regulation using a probes delivered via REDCap. Each EMA survey will ask participants to complete (1) PANAS items to rate current levels of anxiety, irritability, and sadness on a 7-point Likert scale; (2) the Momentary Ruminative Self-Focus Inventory–Abbreviated [76], a 3-item questionnaire evaluating state-level fluctuations in rumination, each rated on a 7-point Likert scale; and (3) the Momentary Impulsivity Scale [77], a 4-item questionnaire measuring momentary impulsivity on a 5-point Likert-type scale. Our chief EMA emotion dysregulation indices, which we predict will decline from the preintervention assessment to the postintervention assessment, include the (1a) average levels of, and (1b) variability (ie, mean square of successive difference) in, daily negative affect (derived from mean scores on the mood probes); (2) average daily levels of rumination via the Momentary Ruminative Self-Focus Inventory–Abbreviated; and (3) average daily levels of ERI, as measured by Momentary Impulsivity Scale scores during periods of elevated momentary negative affect (ie, scores above the person-level mean).

We will provide an in-person tutorial at baseline to help familiarize participants with the structure and content of EMA surveys, and to facilitate the completion of practice items. Participants will use their personal mobile phones or other internet-capable devices to submit EMA responses. Specifically, participants will receive automatic "push" notifications to complete EMA surveys 5 times per day. We will randomize notifications by binning participants' available waking hours into 5 equal windows and then randomly selecting a survey time within each bin, with an interval of at least 90 minutes between notifications. Surveys will be available for completion for 80 minutes, and reminder prompts will be sent within 40 minutes of missed survey notifications.

Questionnaires

After each in-person assessment session, we will ask participants to complete questionnaires administered via REDCap (Table 1) as promptly as possible. Each set of questionnaires includes primary and secondary outcome measures related to emotion dysregulation as well as measures of psychiatric symptom severity, perceived functional impairment in cognitive abilities and activities of daily living. The baseline assessment will also include potential moderators of treatment effects for exploratory analyses. We will ask participants who request premature withdrawal from the trial to complete an identical assessment of the major outcomes of interest (ie, self-rated emotion dysregulation, psychiatric symptom severity, cognitive deficits, quality of life, and treatment acceptability) at the time of discontinuation.

N-ACT Intervention

Overview

The N-ACT program comprises 8 in-person training sessions over 2 months. The intervention is limited to weekly 1 h sessions to maximize adherence and minimize attrition. Each N-ACT session is guided by a trained "coach" (supervised by a licensed clinician) who will explain intervention procedures and rationale, offer relevant psychoeducation, and use motivational interviewing principles to encourage and support participants. At each training session, participants will practice 2 computer-based adaptive tasks targeting affective control. Approximately half of each N-ACT session will be spent performing these exercises, and the other half will be dedicated to coaching and assessment. Coaches will discuss standard

cognitive behavioral psychoeducational content regarding emotion regulation (drawn from established therapy protocols).

Psychoeducational Content

To begin each weekly N-ACT session, a coach will review information from the previous session and discuss the implementation of learned techniques over the prior week. Coaches will then present information from 1 psychoeducational module, adapted from empirically supported interventions, on the topics presented in Textbox 2. Modules 2 to 7 will also include theoretical justification for cognitive training to enhance emotion regulation.

Textbox 2. Topics covered in coaching sessions.

Coaching session sequence

1. Introduction and orientation, which includes an overview of session procedures and program structure, rationale, and personal goal setting
2. Cognitive behavioral approaches to emotion, which introduces fundamental concepts derived from cognitive behavioral therapy to elucidate links among affect, cognition, and behavior, plus an emotion regulation strategy (“STOP”) drawn from dialectical behavior therapy (DBT)
3. Environmental influences on feelings, in which participants identify risk and resilience factors that impede or facilitate emotional self-regulation, paired with distress tolerance skill adapted from DBT (“Self-soothing”)
4. Functional analysis of behavior, which involves functional analysis of problematic patterns of thought or behavior related to personal goals for emotion regulation
5. Mindfulness, involving a guided meditation practice
6. Psychological flexibility, which introduces key elements of acceptance and commitment therapy
7. Interpersonal skills, covering 2 closely related techniques (also borrowed from DBT) to promote adaptive emotional self-regulation and communication within relationships (“DEARMAN”)
8. Review, summary, and wrap-up, involving an examination of progress toward overarching treatment goals, review of key concepts, and solicitation of participant feedback on program components via interview and self-report

After engaging with psychoeducational content in each module, participants will complete the N-ACT tasks, and coaches will end each session with an informal debriefing to help consolidate learning and identify implementation intentions (ie, interim objectives toward participants’ identified treatment goal) for the coming week. Coaches will additionally administer the PANAS before and after the training tasks. We will audio record N-ACT training sessions (with participant consent) for regular review by independent raters to evaluate coach adherence and fidelity to the intervention guidelines using session-specific standardized forms created for this study.

N-ACT Task Battery

Overview

Participants will be asked to perform the same 2 computerized training tasks each week, in counterbalanced order: (1) an adaptive emotional n-back (AEnB) task targeting emotional working memory and (2) the ESST-adaptive (ESST-A), which targets emotional response inhibition. These are adaptive versions of the affective control behavioral measures completed during assessment sessions, modified to dynamically adjust the level of difficulty according to participant performance, which we expect to improve with additional training over time. Both training tasks include gamified graphical elements (eg, user-selected avatars) to facilitate user engagement (refer to Multimedia Appendix 1 for task instructions and other details).

The AEnB Task

The AEnB training task is an adaptive variant of procedures originally described by Levens and Gotlib [78,79], in which participants are instructed to indicate (as quickly and accurately as possible via keypress) whether a *target* affective picture stimulus is a “match” or a “mismatch” to a *cue* image shown *n* trials earlier, where *n* equals the number of interim trials between the presentation of the original cue and the to-be-evaluated target stimulus (ie, the “n-level”). The AEnB task additionally draws from an adaptive version of the dual-dimension emotional (n-back) working memory training task developed by Pan et al [53], such that cue-target pairs are only considered to match if the images are identical *and* spatially congruent, as each stimulus appears in 1 of 9 positions on an invisible 3×3 grid.

All AEnB task stimuli are pseudorandomly presented and counterbalanced to ensure equivalent numbers of matched and mismatched cue-target image pairs from 3 valence categories (neutral, negative, or positive) within each of 6 blocks, resulting in 36+n trials per block, or 216+n total trials. Image stimuli are shown for 1000 milliseconds on each trial, followed by a 2500-millisecond response window and a feedback screen shown for 1000 milliseconds. Trials are separated by a jittered intertrial interval of approximately 250 milliseconds (150-350 ms) assigned pseudorandomly on each trial.

The AEnB task involves 2 orthogonal adaptive components. The first is a tracking algorithm that adjusts the number of trials per condition (ie, emotional valence of cue-target pairs) to prioritize the encoding of spatial information (over affective content) into working memory for emotionally arousing images. Specifically, independent of the current n-level, higher accuracy for emotional (negative or positive) versus nonemotional (neutral) cue-target pairs will result in 2 fewer “match” trial pairs on the subsequent block. Crucially, the emotional images on these 2 trial pairs will remain identical but will be mismatched in spatial location. The algorithm will continue to swap matched emotional pairs with identical mismatched images until the participant achieves greater accuracy for neutral cue-target pairs (that are spatially congruent throughout the

task), at which point the number of emotional trial pairs per condition returns to baseline, on a per-block basis, with 1 negative and 1 positive identical but spatially mismatched pair replaced by fully matched emotional cue-target pairs.

The second adaptive feature of the AEnB task is the n-level itself, which is adjusted after the first block either upward (n=3) or downward (n=2) at the start of each subsequent block (range: n=1-7), contingent on participants' accuracy and response times (with larger values indicating greater working memory load). Specifically, the n-level decreases if a participant is unable to achieve at least approximately 80% accuracy (ie, at least 30 correctly identified pairs out of 36+n trials) within a given block; conversely, once a participant surpasses this accuracy threshold, the n-level increases at the start of the next block but only if the mean reaction time during trials with neutral target stimuli is faster than that during trials with emotional stimuli (regardless of whether cue-target pairs are matched or mismatched, provided that responses are accurate). This training approach is intended to encourage the development of relatively more rapid—but equally accurate—evaluative responses to less arousing or salient images. In sum, the AEnB task involves multiple adaptive components designed to facilitate diminished stimulus reactivity or enhanced engagement of affective control when processing emotionally evocative stimuli (eg, via enhanced attentional focus on key perceptual features rather than affective information, per se) for immediate recall in working memory.

The ESST-A Task

The ESST-A is a training variant of the original ESST [37,39,43], with comparable design elements; however, the ESST-A is distinct in that emotional (negative or positive) image stimuli are presented exclusively on no-go or stop trials (n=60 per valence), and, conversely, neutral images are only shown on go or no-signal trials (n=90 per block over 4 blocks) without an inhibitory cue. Participants must accordingly terminate emotional reactions to the most arousing and evocative stimuli on the ESST-A. This unique design feature of the ESST-A is meant to facilitate implicit associative learning, wherein salient affective content serves as a reliable "cue" that predicts upcoming stop signals, while stimuli with neutral information are consistently delivered without accompanying inhibitory demand. Therefore, repeated training with the ESST-A is expected to promote more automatic, reflexive engagement of inhibitory control at earlier stages of emotional information processing.

Similar to the nonadaptive version, the ESST-A comprises 4 blocks of 120 trials each, with stimuli presented pseudorandomly and counterbalanced across blocks to ensure equivalent numbers of trials per condition. Each ESST-A trial spans 2000 milliseconds, which includes a fixed pretrial pause period of 500 milliseconds, followed by a central fixation cross displayed for approximately 250 milliseconds, depending on a jittered latency value assigned on a trial-by-trial basis (150-350 ms), comparable to the AEnB task. The target image stimulus replaces the fixation cross in the center of the screen, where it is displayed for 1250 milliseconds. The initial (50 ms) stop signal is presented 250 milliseconds after stimulus onset, separately for positive and negative stimuli.

The primary adaptive component of the ESST-A is identical to the assessment version of the ESST (and similar to other SSTs). Specifically, the ESST-A includes 2 independent staircase algorithms that adjust valence-specific stop-signal delay (SSD) values (ie, distinct tracking values for negative and positive images) in 50-millisecond increments depending on participant performance, such that successful inhibition results in a longer SSD on the next no-go or stop trial with the same type of image, thereby increasing inhibitory demand. By contrast, commission errors (ie, false alarms) shorten each SSD by 50 milliseconds on subsequent no-go or stop trials with images from the same emotional valence category. These 2 stepwise algorithms are programmed to maintain commission error rates at approximately 50% of the no-go or stop trials, separately for negative and positive images, which enables calculation of valence-specific indices of emotional response inhibition (ie, stop-signal reaction time).

Data Quality Assurance

The screening survey and assessment questionnaires will randomly incorporate simple "attention checks" (eg, "2 + 2 = ?" and "for our data quality checking, please answer '1' to this question") to identify patterns of careless responding, which we will supplement by manual review to confirm the validity of self-report data. As previously noted, we will exclude participants who demonstrate patterns of careless responding during the screening questionnaire. Before conducting statistical analyses, research staff will perform comprehensive data cleaning and processing procedures as needed (eg, ascertaining violations of distributional assumptions for parametric tests and comparison with published norms).

Training and Reliability

Our team has comprehensive preparation procedures for all staff members involved in data collection. Before study recruitment, N-ACT coaches will receive extensive training in each session-specific intervention module to promote protocol adherence. Coach training and group supervision will comprise regular team-based meetings led by clinically licensed investigators, with didactic instruction, role-play, the development of interrater reliability to evaluate coach fidelity, and a review of practice tapes by senior researchers. We will conduct session adherence evaluations (as a group) monthly and provide retraining as necessary to address drift.

Risk Management

Overview

Trial procedures are designed to balance respect for participants' autonomy with the need for safety. Study consent forms will provide contact information for crisis hotlines and other mental health resources. We will offer referral assistance to interested individuals. All team members with direct participant contact will receive training regarding psychiatric emergencies, suicide risk assessment, and crisis management. A detailed manual will provide assessment probes, decision rules, referral resources, and contact information for use during emergency situations. Training will emphasize procedures for providing feedback in a clinically sensitive manner, and senior investigators will use role-play to demonstrate fundamental principles related to

assessment, obtaining supervision, providing referrals, and preparing documentation according to legal and ethical guidelines. This training will cover circumstances in which staff are permitted to breach confidentiality to contact emergency services.

Research assistants and coaches will be trained to carefully monitor cues indicating participant distress or discomfort, and we will offer breaks or opportunities to reschedule as warranted for fatigue or distress. Participants who endorse significant distress or endorse active suicidal ideation will be given the opportunity to speak with clinically licensed senior investigators, who will evaluate and determine the need for further follow-up. Research staff will work with these participants to develop a plan to obtain support, which may include strategies for discussing symptoms with their current provider, removing access to lethal means, and the provision of feedback or referrals. Our team has developed relationships with local sites to facilitate referral for individuals with insurance or those without; after referral, we will follow up with these participants as warranted to ensure that they received sufficient support.

Adverse Events

We will describe the limits of confidentiality as part of informed consent procedures to minimize the likelihood of study-related adverse events. During the consent process, we will also emphasize that our team is unable to provide emergency services or review research data in real time, and it is therefore important for participants to have access to other sources of care. Consent documents will encourage participants to contact the senior investigators with any concerns.

Throughout the trial, N-ACT coaches will also informally solicit information about potential issues at each training session. We will formally assess adverse events at the postintervention session. We will follow up with participants who show apparent clinical deterioration and will attempt to determine whether emergent symptoms or concerns might be somehow connected to study procedures. Adverse events will be reported to the university's Committee for the Protection of Human Subjects within 1 week.

Measures

Screening

The screening survey will include a demographic questionnaire to assess inclusion criteria in addition to the self-report measures outlined in the following subsections.

Mental Health History Survey

The mental health history survey includes items to identify individuals whose linguistic abilities or cognitive, neurological, or psychiatric condition might interfere with completing study procedures or fully engaging in the intervention.

C-SSRS, Screen Version

The screening includes the self-report screen version of the C-SSRS [67], a well-validated and widely used instrument designed to assess suicidal thoughts and behaviors. Endorsement of the C-SSRS ideation item (Have you actually had any thoughts of killing yourself?) will trigger 3 follow-up items, to cover past-month presence of an identified method, intent, and a specific plan. Responding affirmatively to any of these 3 items will result in automatic study exclusion. Regardless of their responses, all participants will be asked an item to evaluate lifetime history of suicidal behavior; those who endorse this item in addition to past-month active suicidal ideation will also be automatically excluded from study participation.

PDSQ Prompts

The screening survey includes the Psychosis, Alcohol Use Disorder, and Substance Use Disorder scales of the PDSQ (6 *yes* or *no* items per scale) [66]. Questions regarding psychosis refer to the previous 2 weeks, and substance-related questions cover the previous 6 months. Prospective participants who respond affirmatively to at least 1 of these prompts (on any of the 3 PDSQ scales) will be automatically excluded, based on established clinical cutoffs for this measure [62].

Ruminative Responses Scale–Brooding

The Ruminative Responses Scale–Brooding (RRS-B) [13] will be used to assess study inclusion criteria. The RRS-B comprises 5 items to evaluate the dispositional propensity to engage in past-oriented patterns of repetitive negative thinking. Respondents rate prompts on a scale ranging from 1 (*almost never*) to 4 (*almost always*) based on characteristic reactions to dysphoric mood described by each item.

Three-Factor Impulsivity Index

Eligibility will be further determined using the Feelings Trigger Action (FTA) scale of the Three-Factor Impulsivity Index (TFII) [9], a 54-item multidimensional measure of trait-like impulsiveness that asks respondents to rate their agreement with each prompt on a scale of 1 (*I disagree a LOT*) to 5 (*I agree a LOT*). FTA includes 26 items describing tendencies to engage in impulsive speech and action in response to emotional states. The TFII includes 2 additional scales derived from factor analysis: Pervasive Influence of Feelings, which comprises 9 items reflecting powerful cognitive and motivational responses to emotion; and Lack of Follow Through, which captures distractibility and lack of perseverance. Pervasive Influence of Feelings is included as a secondary measure of emotion dysregulation (assessed in conjunction with FTA, at baseline).

Emotion Dysregulation

Our primary measures of emotion dysregulation will comprise self-reported rumination (RRS-B) and ERI (FTA). The secondary indices of emotion dysregulation further include EMA indices of daily negative affect, rumination, and ERI, in addition to scores on questionnaires capturing conceptually related constructs (Multimedia Appendix 1).

Psychiatric Symptom Severity

Participants will complete the following questionnaires at baseline, postwaitlist, and postintervention time points to evaluate the hypothesized clinical effects of N-ACT (refer to Multimedia Appendix 1 for the secondary symptom outcome measures).

Externalizing Spectrum Inventory–Revised

The Externalizing Spectrum Inventory–Revised (ESI-R) [80] is a 100-item questionnaire that covers 23 facets of externalizing

psychopathology, including aggression, alcohol and other substance use problems, and fraudulent behavior. Respondents rate each ESI-R item as *true*, *mostly true*, *mostly false*, or *false*. Items referring to impulsivity (ie, redundant with the TFII) will not be included in the scale totals.

Inventory of Depression and Anxiety Symptoms, Expanded Version

The 99-item Inventory of Depression and Anxiety Symptoms, Expanded Version [81], is a validated questionnaire that assesses various emotional syndromes across the internalizing spectrum of psychopathology (eg, anxiety, depression, obsessions and compulsions). This instrument produces scores on 3 major factors (distress, fear, and mania), which are each composed of multiple subfactors (18 in total).

Statistical Analysis Plan

Our final target sample size (n=80) was derived from power analysis (1-β>0.85), based on hypothesized medium between-groups effect sizes (Cohen d=0.35) for the main outcomes of interest (α=.05). Before conducting the analyses, data will be checked for errors, statistical assumptions, and potential confounding variables to examine as covariates. Missing data imputation will also be performed as appropriate; we will present the results with and without imputed values for comparison. Our primary analyses will follow the International Conference on Harmonization E9 statistical principles for clinical trials. In accordance with these principles, we will use intention-to-treat analyses to estimate the main effects of N-ACT, using the final assessment scores of all randomized participants. To augment these findings, we will conduct sensitivity analyses restricted to data from participants who complete preintervention and postintervention assessments and at least 6 of the 8 weekly N-ACT sessions.

Descriptive statistics will be calculated to address the preliminary hypotheses regarding N-ACT's acceptability and adherence. Mean scores on the Interest or Enjoyment and Value or Usefulness subscales of the adapted Intrinsic Motivation Inventory [82] will serve as our main indices of the N-ACT program's acceptability (H1); specifically, we predict that participants who complete the intervention will provide average ratings of at least 5 (out of 7) across both scales. We further hypothesize that N-ACT participant adherence and retention will be comparable to those observed in other cognitive remediation interventions (H2); specifically, we anticipate median person-level adherence levels between 70% and 75%, which we expect to decrease at the group level by approximately 5% each week [63,64], with most participants (ie, >66%) completing all 8 N-ACT training sessions [33,52]. Consistent with other cognitive remediation protocol procedures [63], we will calculate percentage adherence for each participant as a function of the number of *completed* N-ACT training task trials divided by the *total* number of trials, that is, individual differences in the "dosage" of training.

We will consider potential confounds before testing key hypothesized effects. Of particular import, we will examine whether participants differ significantly in treatment gains based on assignment to a specific training coach and control for this unintended influence as necessary. Specifically, we will use multivariate analysis of covariance (MANCOVA) to explore the effect of coach assignment (independent variable) on postintervention emotion dysregulation (ie, scores on the TFII-FTA and RRS-B; dependent variables), controlling for scores at initial screening.

The core aim of this pilot trial is to determine whether N-ACT significantly reduces ERI and rumination, as measured by the TFII-FTA and RRS-B, respectively (H3). To achieve this aim and the related objective to explore potential mechanisms, we will conduct parallel 2 (group: immediate N-ACT vs waitlist control condition; between-subjects factor)×2 (time: T1 vs T2; within-subjects factor) mixed MANCOVAs to evaluate whether N-ACT completion is associated with greater pre-postintervention improvement in these 2 primary outcomes compared to the waitlist control condition. Among all participants, T1 will represent data collected at the baseline assessment; for participants assigned to the immediate N-ACT group, T2 refers to the postintervention assessment, whereas for those assigned to the control condition, T2 refers to the postwaitlist assessment. Thus, these models will not include postintervention data for participants initially allocated to the waitlist, permitting direct comparisons of the slope of change over time associated with completing N-ACT or the waitlist period. The key index of treatment effect in all MANCOVA models will be the group×time interaction. We will also perform a parallel set of multivariate cluster-robust general linear models with time (T1: baseline time point vs T2: postintervention time point) as the sole regressor on key outcomes of interest, which will include all participants who complete N-ACT (regardless of initial group or condition assignment) to maximize statistical power.

In addition to testing the hypothesized effects on emotion dysregulation, mixed MANCOVA and multivariate cluster-robust general linear models will be used to evaluate performance changes over time on (1) 2 hot executive functioning tasks (ESST and MAFT), which will be used to assess the hypothesized effects on the targeted aspects of affective control (H4); and (2) one hot (MAFT) and 2 cold (Digit Span Backward and SST) executive functioning tasks, which will be used to ascertain transfer to the nontargeted cognitive processes (H5). We will specifically derive key dependent variables from the ESST (valence-specific indices of stop-signal reaction time) and the MAFT (valence-specific indices of accuracy) to assess intervention-related changes in emotional response inhibition and emotional working memory, respectively. We will similarly calculate summary metrics of hot affective flexibility from the MAFT (valence-specific indices of accuracy and reaction time on less frequent "switch" trials prompting emotional reactions instead of working memory recall [73]) as well as cold working memory, updating from the Digit Span Backward (mean span) and cold response inhibition from the traditional SST (stop-signal reaction time) to evaluate near and far transfer of hypothesized N-ACT training effects, respectively.

Finally, we will perform a complementary set of secondary analyses (ie, mixed MANCOVA and multivariate cluster-robust generalized linear models) to explore the hypothesized

downstream effects of N-ACT on changes in psychiatric symptom severity (H6). We will use dimension-reduction techniques (eg, confirmatory factor analysis) to extract the summary indices of internalizing and externalizing symptoms from the Inventory of Depression and Anxiety Symptoms, Expanded Version and ESI-R, respectively. Statistical models will use these latent factors as dependent variables, potentially providing preliminary evidence for the efficacy of affective control training as a transdiagnostic intervention to address psychopathology (via diminished emotion dysregulation; refer to Multimedia Appendix 1 for more information). Support for this hypothesis will motivate future work to more directly and precisely examine the effectiveness of the N-ACT program in sufficiently powered samples of patients with psychiatric conditions.

Results

This trial is funded by support from the University of California Board of Regents and the Peder Sather Foundation (funding period: October 2022-September 2025). Recruitment is scheduled to begin in spring 2025. We will begin data analysis once data collection is complete, which is planned to occur in fall 2025. We anticipate publishing the findings in 2026.

Discussion

Summary

This randomized waitlist-controlled trial extends cognitive remediation research by testing a novel intervention program focused on facets of hot cognition typically unaddressed in this body of work. The trial will also be novel in testing a transdiagnostic sample comprising individuals with emotion regulation difficulties. Drawing on a substantial theoretical and empirical literature, we aim to modulate 2 aspects of affective control (ie, emotional working memory and emotional response inhibition) putatively underlying the problems with emotional self-regulation strongly implicated in common forms of psychopathology. Given the low cost, minimal coach training requirements, and relatively simple delivery of the N-ACT program, success in this project has major implications for reducing the public health burden associated with prevalent psychiatric conditions—as well as subclinical distress or dysfunction—involving tendencies toward rumination or ERI.

If our findings align with our hypotheses, this pilot trial will provide early data to support the further refinement and larger-scale deployment of N-ACT in a fully powered randomized clinical trial of patients with psychiatric conditions. Our findings will help identify the levels of interest and adherence and may suggest components that need to be refined for greater acceptability. Beyond the results concerning change in cognitive processes, we hope to learn more about how cognitive changes generalize to psychopathological outcomes. The profile of effects may help us understand which participants would be most likely to benefit from inclusion in future trials.

Limitations

The potential impact of this work should be considered in the context of several limitations. Regarding the study sample, we will make every effort to maximize participant diversity and, accordingly, the generalizability of our findings; however, the modest target sample size (n=80) for this pilot trial will constrain our ability to ensure adequate representation of all psychiatric symptom types and severity levels. Relatedly, patients with acute symptoms of alcohol or substance use disorders and psychosis will be excluded. Additional studies will thus be necessary to elucidate the putative mechanisms identified in this work. Although our protocol incorporates a variety of well-validated multimodal measures to assess key constructs, 1 of the 2 primary behavioral outcomes will be derived from the MAFT, which is a novel task developed for this study. This limitation is somewhat lessened in that the MAFT includes design elements drawn from existing tasks that are widely used to index working memory and shifting and switching (eg, other emotional n-back procedures [73]). Finally, we see 2 core needs for enhancing the N-ACT intervention if the initial findings are promising. The current N-ACT intervention is limited in its scope of training around transfer to real-world tasks. Others have more extensively integrated ecological elements into cognitive remediation programs, including simulated work situations [83] and compensatory transfer sessions to supplement computerized training procedures [84]. Future work might help clients practice their skills in the context of mood inductions as a method to facilitate skills transfer. It will also be important to consider gamification [85,86] and other techniques to enhance the appeal of training programs.

Conclusions

In conclusion, this study represents an important step in translating knowledge from basic affective science to produce interventions (with empirically informed treatment targets) that can be widely disseminated and easily implemented. This area of research is promising, given the need for alternative approaches to improve mental health because a substantial portion of patients do not seek nor respond to traditional treatment modalities. In addition, current rapid technological advancements, such as the proliferation of accessible and affordable mobile devices capable of delivering cognitive training, support the feasibility of digital therapeutics. Therefore, N-ACT has the potential to reduce barriers to mental health treatment, particularly among people from underserved groups or cultures with persistent stigma against talk-based psychotherapy as well as those who may be more amenable to computerized interventions for various reasons (eg, youth and patients with social phobia). Crucially, we expect N-ACT to have transdiagnostic applications, given that the program's central aim is to address emotion regulation problems, which include shared features across a broad range of psychopathologies. We hope that establishing efficient and cost-effective means of modulating these common risk factors might eventually facilitate prevention among individuals considered vulnerable before diagnosable psychiatric disorders emerge.

Acknowledgments

The authors are grateful to have received funding for this project from the Peder Sather Foundation. The authors further acknowledge the support of their investigative teams' volunteer research assistants, clinicians, and coaches who collectively make this collaboration possible.

Data Availability

The datasets generated and analyzed during this study will be available in this project's Open Science Framework repository [87].

Authors' Contributions

KJDA, MVE, EHR, AH, and SLJ were responsible for conceptualization. KJDA, EHR, AH, and SLJ were responsible for funding acquisition. KJDA, MVE, EHR, LM, AH, and SLJ were responsible for methodology. KJDA, NR, and SLJ were responsible for project administration. SLJ was responsible for resources. KJDA, MVE, and SLJ were responsible for supervision. KJDA and SLJ wrote the original draft of this manuscript. All authors reviewed the final manuscript.

Conflicts of Interest

KJDA is the director of Brain Health Consulting, which provides consultation on neurocognitive approaches to mental health assessment and intervention. The neurobehavioral affective control training program is not currently being offered through Brain Health Consulting.

Multimedia Appendix 1
Additional details on measures, tasks, and secondary analyses.
[DOCX File , 41 KB - resprot_v14i1e54221_app1.docx]

Multimedia Appendix 2
CONSORT-eHEALTH checklist (V 1.6.1).
[PDF File (Adobe PDF File), 414 KB - resprot_v14i1e54221_app2.pdf]

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Abbreviations

AEnB: adaptive emotional n-back
C-SSRS: Columbia Suicide Severity Rating Scale
CONSORT-EHEALTH: Consolidated Standards of Reporting Trials of Electronic and Mobile Health Applications and Online Telehealth
EMA: ecological momentary assessment
ERI: emotion-related impulsivity
ESI-R: Externalizing Spectrum Inventory–Revised
ESST: emotional stop-signal task
ESST-A: emotional stop-signal task–adaptive
MAFT: memory and affective flexibility task
MANCOVA: multivariate analysis of covariance
MDD: major depressive disorder
N-ACT: neurobehavioral affective control training
PANAS: Positive and Negative Affect Schedule
PDSQ: Psychiatric Diagnostic Screening Questionnaire
REDCap: Research Electronic Data Capture
RRS-B: Ruminative Responses Scale–Brooding
SSD: stop-signal delay
SST: stop-signal task
TFII: Three-Factor Impulsivity Index

Edited by A Mavragani; submitted 03.11.23; peer-reviewed by IV George, E Ahern, M Friehs; comments to author 21.03.24; revised version received 07.07.24; accepted 13.11.24; published 19.02.25.

Please cite as:
Allen KJD, Elliott MV, Ronold EH, Mason L, Rajgopal N, Hammar Å, Johnson SL
Cognitive Training for Emotion-Related Impulsivity and Rumination: Protocol for a Pilot Randomized Waitlist-Controlled Trial
JMIR Res Protoc 2025;14:e54221
URL: https://www.researchprotocols.org/2025/1/e54221
doi:10.2196/54221
PMID:

Protocol

Evaluation of Comparative Efficacy of Polyherbal Steam Inhalation Versus Polyherbal Nasal Fumigation (Dhoopana) in Children With Rhinitis (Pratishyaya): Protocol for an Open-Label Randomized Controlled Trial

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Abstract

Background: Rhinitis is a condition characterized by inflammation of the nasal mucosa. It causes obstruction and congestion in the nasal cavity. Clinically, it resembles *pratishyaya* (rhinitis) in Ayurveda, which is caused by accumulation and downward movement of the *tridoshas* (3 elements, named *vata*, *pitta*, and *kapha*) in the nasal cavity. Rhinitis is one of the most common diseases among children. There is no role for antibiotics in rhinitis, and nasal decongestants have also not been found to be effective in its management. In Ayurveda, *dhoopana* (nasal fumigation) is mentioned in the *pratishyaya* treatment protocol. However, we have found no previous study regarding its efficacy. The efficacy of *tulsi*, *vasa*, *nirgundi*, and *nilgiri* is already proven when they are used for steam inhalation in respiratory tract infections. Therefore, in this study, a *dhoopana* of a polyherbal formulation containing *tulsi*, *vasa*, *nirgundi*, and *nilgiri* will be compared with the inhalation of steam containing *arka* (a liquid obtained by distillation) of *tulsi*, *vasa*, *nirgundi*, and *nilgiri* leaves in children with *pratishyaya.*

Objective: We aim to evaluate the efficacy of polyherbal steam inhalation as a standard control against *dhoopana* in children aged 7 to 14 years with *pratishyaya*.

Methods: A total of 70 participants fulfilling the inclusion criteria were selected and distributed into 2 groups of 35 each. The intervention group received *dhoopana* and the control group received polyherbal steam inhalation, both twice daily for 7 days. The primary outcome measure was the change in Total Nasal Symptom Score and a modified cold spatula test. At the same time, the association between *prakriti* (body constitution) and the prevalence of *pratishyaya* in children was analyzed as a secondary outcome. Assessments were performed on days 3, 5, and 7, with a follow-up time of 28 days. Appropriate descriptive and inferential statistics will be used for data analysis.

Results: As of November 2024, we have completed our enrollment of 70 patients, with 35 patients in each group. Data analysis will be completed by February 2025, and we expect results to be published in March 2025.

Conclusions: We anticipate that polyherbal nasal fumigation will be found to be equally as effective as polyherbal steam inhalation in the management of acute rhinitis in the pediatric population. This study may provide a standardized, herbal, safe, and cost-effective treatment for rhinitis in children in the form of *dhoopana*.

International Registered Report Identifier (IRRID): DERR1-10.2196/58197

(JMIR Res Protoc 2025;14:e58197) doi:10.2196/58197

KEYWORDS

pratishyaya; Ayurveda; allergic rhinitis; rhinitis; dhoopana; nasal fumigation; steam inhalation; polyherbal; vasa; nirgundi; nilgiri; tulsi; sneezing; nasal cavity; nasal decongestants; evaluation; efficacy; child; adolescent; randomized controlled trial

Introduction

Overview

Rhinitis is defined as inflammation of the nasal mucosa due to any infection, allergy, or injury. Symptoms of rhinitis are sneezing, discharge from the nose, obstruction in the nasal cavity, irritation in the nasal cavity, body ache, a feverish sensation, and headache [1]. As per Ayurveda, a clinical picture of rhinitis is seen in the disease *pratishyaya*. It is one of the *nasagata roga* (nasal disorders) in which *kaphadi tridoshas* (the 3 elements of the body) are continuously eliminated through the nose. These vitiated *doshas* accumulate in the head, and their further movement toward the nose causes *pratishyaya* [2]. According to Acharya Charaka, the definition of *pratishyaya* is "*pratikshnam shyayatiitipratishyaya*," which means the "continuous outward movement of *vata*, *pitta*, and *kapha* doshas from the nostrils." The prevalence of nonallergic rhinitis is about 40% [3]. The prevalence of allergic rhinitis in India was reported as "11.3% in children aged 6-7 years and 24.4% in children aged 13-14 years" [4]. Acharya Videha explained the clinical presentation of *pratishyaya* as excessive secretions from the nasal cavity and eyes, fever, and generalized weakness with severe headache [2]. *Pratishyaya* is classified into 5 types: *vataja*, *pittaja*, *kaphaja*, *sannipataja*, and *raktaja pratishyaya* [2,5]. The nasal mucosa has a rich blood supply, and stimulation of the sympathetic nervous system causes vasoconstriction that results in shrinkage of the nasal mucosa on the other side, while stimulation of the parasympathetic nervous system is responsible for excessive secretion from the nasal mucosa along with dilatation of local vessels. Emotional disturbance also plays a significant role, as the autonomic nervous system innervation of the nasal mucosa is under the control of the hypothalamus [3]. If no treatment is given at an early stage, the condition may become complicated and lead to comorbid conditions like chronic rhinitis, cough, or breathing difficulty and debility [2]. There is no use of antibiotics in acute rhinitis [6]. Antihistamine decongestants are frequently used in cough and cold. However, in some studies, these were not found to be effective in the management of rhinitis [7]. There are limited data regarding the safety of pseudoephedrine and phenylephrine in rhinitis [8]. In Ayurveda, various oral medications are available for the management of this condition. However, it is difficult to administer Ayurvedic medicines orally to children. So, this study has been planned to find an effective way to manage the acute stage of rhinitis that can be administered locally in the nasal cavity. Various Ayurvedic interventions are mentioned in the Ayurveda classics as protocols for the management of *pratishyaya*, including *dhoopana* (nasal fumigation), an intervention that can effectively manage the disease. In this intervention, various herbs are made into a stick known as a *varti* (wick), and its fumes are used for local fumigation of the affected area. It can be considered an Ayurvedic therapy that delivers the medicines directly into the airways, providing relief and protection to the local region [9].

Pratishyaya treatment should be aimed at relieving the *avarodha* (obstruction) created by the dosha. Drugs having *ushna* (hot) and *tikshna* (pungent) properties are indicated in *dhoopana*. The efficacy of steam inhalation of *tulsi*, *vasa*, *nirgundi*, and *nilgiri* has already been shown in respiratory tract infections [10]. So, in this study, *dhoopana* of a polyherbal formulation containing *tulsi*, *vasa*, *nirgundi*, and *nilgiri* will be compared with a steam inhalation containing *arka* of *tulsi*, *vasa*, *nirgundi*, and *nilgiri* in *pratishyaya* in children. *Kashyapa Samhita* (an Ayurveda classical text) is mainly devoted to the Kaumarbhritya branch (Ayurvedic pediatrics) of Ashtanga Ayurveda, and *dhoopana* is described in the treatment protocol of *pratishyaya* [11]. There are many studies regarding the efficacy of oral medication in *pratishyaya* but there is no previous study available regarding the efficacy of local fumigation with medicated fumes in *pratishyaya* in children. Steam inhalation has a known soothing effect on the nasal mucosa in rhinitis. Herbal steam inhalation is more effective as compared to plain water steam inhalation [12], but steam inhalation is quite difficult to administer in children. So, in this study, we plan to compare the effect of polyherbal steam inhalation with polyherbal fumigation in children with *pratishyaya*. The herbs chosen for *dhoopana* were justified in previous studies, as steam inhalation of *tulsi*, *vasa*, *nirgundi*, and *nilgiri* was found to be effective for reducing local inflammation in the nostrils. A detailed description of previous articles and a research gap analysis with justification for this study is given in Table 1.

Table 1. Previous studies and research gap analysis.

Reference	Conclusion	Remark
Memon [13]	*Vyoshadi vati* was found to be effective in reducing signs and symptoms of *pratishyaya* (rhinitis) in comparison with chlorpheniramine maleate in children aged 4-8 years.	Children tend to resist the intake of medicines orally in most cases, especially when they are sick. So, local fumes or steam inhalation could be a better choice.
Tarun and Anup [14]	*Nasya* with *tulasi swarasadi taila* and *haridrakhand* showed 100% results in objective as well as subjective parameters of *pratishyaya*. *Tulasi swarasadi taila nasya* and *haridrakhand* gave effective results in treating *pratishyaya*.	As *tulsi* has an anti-inflammatory effect and was found to be effective in the management of *pratishyaya*, and the *nasya* procedure is contraindicated in the acute stage, fume inhalation can be done with the use of *tulsi* in place of *nasya karma*. Local fume inhalation can provide instant relief for the symptoms of *pratishyaya*.
Rajput and Patni [15]	According to Acharya Charaka, any drug when instilled into the nostrils causes direct action in the brain; hence, it is highly effective in the treatment of various diseases related to the nervous system and supraclavicular region. The *nasya* procedure is indicated in *pratishyaya*. Standardization of *nasyakarma* with Ayurveda and modern scientific parameters with proper documentation is a current need.	*Nasya* is widely used in rhinitis but it is contraindicated in its acute stage. Moreover, it is quite difficult to administer to children. Direct contact with oil in the nostrils sometimes irritates children. In this study, acute cases were mentioned in the inclusion criteria, so local fumes could provide a better approach to the treatment of *pratishyaya*. Moreover, local nasal fumigation is described in the treatment protocol of *pratishyaya*, but no previous study has been done to determine its efficacy in rhinitis.
Kamble et al [16]	Steam inhalation of *tulsi* leaves was found to be more effective in reducing sign and symptoms of cough and cold in adults than steam inhalation of plain water.	*Tulsi* steam inhalation was found to be better than plain steam inhalation in the adult population. This shows that volatile herbs like *tulsi* have better efficacy when given locally in the form of vapors. Steam inhalation is also easier to administer in children. So in this study, *tulsi* was chosen as one of the herbs for fume as well as steam inhalation.
Kumar Dwibedi et al [17]	Initially, there was mild relief in symptoms. Gradually, improvement was seen in signs and symptoms at further appointments. In the last appointment, the patient felt relief and could perceive smells.	Atrophic rhinitis is a chronic stage of *pratishyaya*; hence, a combination of *nasya* and *dhoompana* was given to the patient. *Trikatu dhoompana* was found to be effective in the management of the disease in the chronic stage. Thus, *dhoopana* (nasal fumigation) should only be given to children in the acute stage of *pratishyaya*.
Gowrishankar et al [10]	Phytochemicals from selected plants were found to be effective against protein targets of COVID-19.	In an in silico study, the active components of *vasa*, *nirgundi*, and *nilgiri* were found to be effective against protein targets of SARS-CoV-2. Hence, these herbs were chosen for the intervention as well as the control group.
Swain and Sahu [18]	There was improvement in symptoms of COVID-19 after taking steam inhalation. The severity and duration of infection was reduced after steam inhalation. It was found to be a ray of hope in that pandemic.	This was a nonrandomized, nonclinical trial. The study was performed along with oral medications for COVID-19 without confirming the efficacy of steam inhalation alone. So there is a need for a study of herbs as a single therapy in children. This study is a randomized clinical trial with the use of polyherbal steam inhalation in the control group of children without oral medication.
Berger et al [19]	The intranasal formulation of azelastin and fluticasone propionate was found to be safe for administration in children, and it was well tolerated for 3 months by children with allergic rhinitis.	Epistaxis was reported as a treatment-related adverse effect in both groups, followed by headache and other adverse effects. Herbal procedures are quite safe and effective. Local polyherbal fume administration can be an alternative.
Sebastian and Sujatha [20]	The study showed that steam inhalation with *tulsi* leaves is effective in relieving symptoms of coryza compared to hot water steam inhalation in children aged 6-12 years.	The study was performed in a selected community with a small sample size, and no randomization was done. Steam inhalation was administered for only 3 days. The follow-up time was not mentioned in the article. This study is a randomized clinical trial, and *tulsi* along with *nilgiri*, *nirgundi* and *vasa* will be used for steam inhalation in the control group for 7 days with a follow-up of 28 days.
Macchi et al [21]	A statistically significant improvement was seen in ciliary motility in the first group, who received a nasal wash with sodium hyaluronate in saline solution ($P<.001$).	This was a pilot study with very small sample size. Moreover, the study included patients with recurrent upper respiratory tract infections; there was no specific disease chosen for the study. Aerosol use was indicated in lower respiratory tract infection, as there was a chance of the medicine entering the lungs. In our study, only *pratishyaya* cases will be included, rather than all patients with respiratory tract infections. Polyherbal fumes will be administered in the trial group, which could be a better alternative to aerosols.

Reference	Conclusion	Remark
Baartmans et al [22]	Annually, on average 3 people are admitted to a Dutch burn center for burns resulting from steam inhalation therapy. Most patients are children, and they need skin grafting more often than adults. At burn centers in the Netherlands, 31 patients were admitted with burns caused by steam inhalation therapy in the 1998 to 2007 period.	These data show that steam inhalation can result in burns, especially in children. So, in our study, we plan to find if *dhoopana* can be an alternative.
Murphy et al [23]	Between July 1 and December 31, 2002, 7 children were admitted to the burn unit of a children's hospital in Dublin with scalds sustained during the course of steam inhalation. The children ranged in age from 9 months to 10 years. Techniques involving kettles or bowls of boiling water should be actively discouraged.	The common technique of steam inhalation is risky in children as it may cause burns. So, in our study, we plan to find an easier way to administer herbal effects to the nasal mucosa through *dhoopana*.

Aim

We aim to study the efficacy of polyherbal steam inhalation versus *dhoopana* in children with *pratishyaya*.

Primary Objectives

There are 3 primary objectives: first, to determine the efficacy of *dhoopana* in reducing signs and symptoms of *pratishyaya* compared to polyherbal steam inhalation; second, to study the duration of alleviation of Total Nasal Symptom Score (TNSS); and third, to determine the efficacy of *dhoopana* in the reduction of nasal obstruction in a modified cold spatula test.

Secondary Objectives

There are 2 secondary objectives: first, to study the prevalence of *pratishyaya*, its origin, and its causative factors, such as viruses, bacteria, or allergies; second, to analyze the association between *prakriti* (body constitution) and the prevalence of *pratishyaya* in children.

Hypothesis

The alternate hypothesis is that *dhoopana* has equivalent efficacy to polyherbal steam inhalation in reducing the signs and symptoms of *pratishyaya* in children aged 7-14 years. The null hypothesis is that *dhoopana* does not have equivalent efficacy as polyherbal steam inhalation in reducing the signs and symptoms of *pratishyaya* in children aged 7-14 years.

Trial Design

This will be a randomized, reference, controlled, open-label equivalence clinical study. A total of 70 patients have been recruited for the study.

Methods

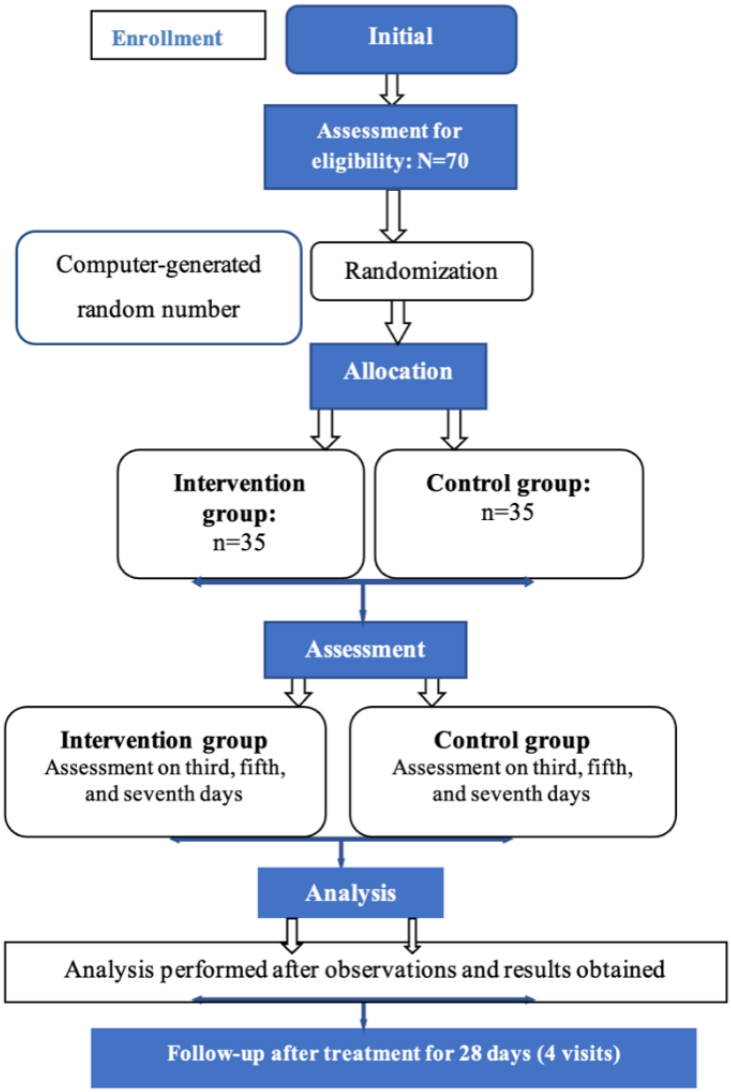
Recruitment

The patients were selected from the outpatient and inpatient departments of the Department of Kaumarabhritya (Ayurvedic pediatrics) of Mahatma Gandhi Ayurveda College, Hospital & Research Centre and from the surrounding region. After initial screening, the patients were randomized using computer-generated random numbers into 2 groups; the control group (polyherbal steam inhalation) and the intervention group (polyherbal nasal fumigation). All baseline parameters were recorded at the start of the study. Both groups underwent treatment for 7 days. All the parameters were recorded on the third, fifth, and seventh days, with a follow-up of 28 days after the treatment period. Patients were advised to drink warm water and stay away from cold and sour items. Patients were given regular counseling and reminders through calls or messages to follow the rules and regulations of the trial.

Guidelines

This study used the Consolidated Standards of Reporting Trials (CONSORT) guidelines; Figure 1 shows a flow diagram of the study.

Figure 1. Consolidated Standards of Reporting Trials (CONSORT) flow diagram.



Grouping and Dosage

Grouping and dosage are described in Table 2.

Table 2. Grouping and dosage.

	Control group (polyherbal steam inhalation)	Intervention group (*dhoopana*; polyherbal nasal fumigation)
Participants, n	35	35
Name and details of the medication	*Arka* is prepared from *tulsi*, *vasa*, *nirgundi*, and *nilgiri*. In participants with mild symptoms, 2.5 ml *arka* is added to 500 ml of water, and in those with moderate to severe symptoms, 5 ml *arka* is added to 500 ml of water for steam inhalation.	*Dhoomvarti* (polyherbal wick) prepared from dry leaves of *tulsi*, *vasa*, *nirgundi*, and *nilgiri*.
Mechanism of delivery	Steam	Fumes
Duration	1 minute for mild symptoms and 1.5 minutes for moderate to severe symptoms.	1 minute for mild symptoms and 1.5 minutes for moderate to severe symptoms.
Route/mode of administration	Nostrils	Nostrils
Frequency	Twice daily	Twice daily

Inclusion Criteria

Children of either sex aged between 7 to 14 years whose parents provide written consent for enrolling their child in the study will be included if they have had the common cold with features of *pratishyaya* for 7-10 days.

Exclusion Criteria

Patients will be excluded if they have had the common cold for more than 10 days or if they have chronic allergic rhinitis, *dushta pratishyaya* (chronic rhinitis with complications), *raktaja pratishyaya* (a type of rhinitis with dominance of the blood element), *sannipataja pratishyaya* (rhinitis with involvement of all 3 elements), or infectious diseases such as tuberculosis. Patients will also be excluded if they have a cleft palate, a deviated nasal septum, or nasal polyps, or if they are hypersensitive to the trial drug or any of its ingredients.

Drug Collection and Authentication

The raw material for the drug was purchased from a reliable source and authenticated and identified by the Department of Dravyaguna and Rasashastra. Details of the raw ingredients are provided in Table 3 and images are shown in Multimedia Appendix 1.

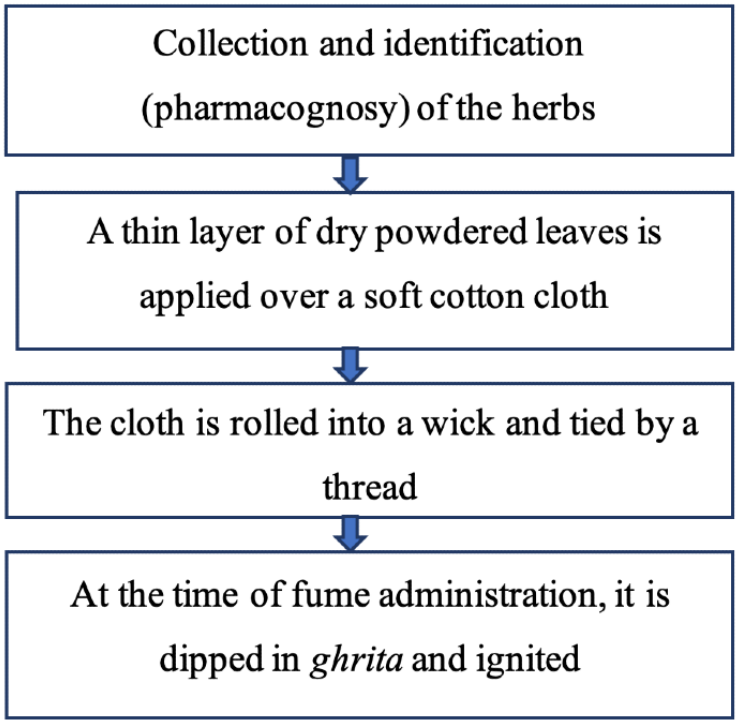
The *dhoomvarti* (polyherbal wick) for nasal fumigation and *arka* (for steam inhalation) from *tulsi*, *vasa*, *nirgundi*, and *nilgiri* leaves were prepared as per the classical methods and standard protocol at the Mahatma Gandhi Ayurveda College and Hospital and were analyzed in a pharmaceutical laboratory. The method of drug preparation is described in Figure 2.

Arka of the leaves of *tulsi*, *vasa*, *nirgundi*, and *nilgiri* was prepared by using a distillation process. Parents of the patients were counseled and trained regarding the administration of *dhoopana* and steam inhalation at their homes.

Table 3. Latin name and family name of the herbs used for nasal fumigation and steam inhalation

Serial No.	Drug	Latin name	Family
1	*Tulsi*	*Ocimum sanctum* Linn	Lamiaceae
6	*Nirgundi*	*Vitex negundo* Linn	Verbenaceae
7	*Vasa*	*Adhatoda vasica* Nees	Acanthaceae
8	*Nilgiri*	*Eucalyptus globules* Labill	Myrtaceae

Figure 2. Method of preparation of dhoomvarti.



Outcomes

The outcomes are designed to compare the efficacy of *dhoopana* and polyherbal steam inhalation on *pratishyaya* with subjective and objective parameters.

Subjective Criteria

Signs and symptoms of *pratishyaya* will be evaluated with the TNSS, illustrated in Table 4.

Table 4. Total Nasal Symptom Score (TNSS).

Symptom and domain	Score
Symptoms	
Rhinorrhoea	
No symptoms	0
Aware but not troubled (mild)	1
Troublesome but does not interfere with normal day-to-day activities or sleeping habits (moderate)	2
Interferes with normal day-to-day activities or sleeping habits (severe)	3
Nasal itching	
No symptoms	0
Aware but not troubled (mild)	1
Troublesome but does not interfere with normal day-to-day activities or sleeping habits (moderate)	2
Interferes with normal day-to-day activities or sleeping habits (severe)	3
Nasal obstruction	
No symptoms	0
Aware but not troubled (mild)	1
Troublesome but does not interfere with normal day-to-day activities or sleeping habits (moderate)	2
Interferes with normal day-to-day activities or sleeping habits (severe)	3
Sneezing	
No symptoms	0
Aware but not troubled (mild)	1
Troublesome but does not interfere with normal day-to-day activities or sleeping habits (moderate)	2
Interferes with normal day-to-day activities or sleeping habits (severe)	3
Additional symptoms as per Ayurveda texts	
Sirashoola **(headache)**	
No headache	0
Occasional headache	1
Frequent headache	2
Continuous headache	3
Aruchi **(loss of appetite)**	
Absent	0
Present	1
Kasa **(cough)**	
No cough	0
Occasional cough	1
Moderate cough	2
Continuous cough with throat and chest pain	3

Objective Criteria

The modified cold spatula test will be used to measure nasal patency in rhinitis. The test is done to study the area of fogging associated with a nasal obstruction and compare the pre- and posttreatment outcomes. The patients are asked to breathe normally over a polished stainless steel plate, and the extent of fogging is marked with a marker pen. The magnitude of fogging is then measured with a transparent graph sheet marked with a central red line at 50 mm on the x-axis, dividing the graph into 2 equal parts with corresponding right and left areas of fogging.

Sample Size

A comparative pilot study was performed with 20 patients, including 10 patients in 2 groups, to evaluate the efficacy of *dhoopana* for rhinitis in comparison with polyherbal steam

inhalation. Based on the results of that study, the minimum sample size for this study was calculated by using the following formula of proportion:

The parameters related to sample size were as follows: α=.05; β=.2; proportion in group 1=0.60; proportion in group 2=0.90; ratio (group 2/group 1)=1; minimum sample size needed for group 1=32; and minimum sample size needed for group 2=32. The minimum total sample size needed was 64, and the minimum total number of patients to be enrolled was 35 in each group (including a 10% withdrawal rate).

Data Collection Tools

This study will use the *Ayurveda Samhitas* (a textbook on Ayurveda), modern texts, and an online search of PubMed and Google Scholar. The polyherbal *dhoomvarti* will be prepared from a powder of *tulsi*, *vasa*, *nirgundi*, and *nilgiri*. The polyherbal *arka* will be prepared from *tulsi*, *vasa*, *nirgundi*, and *nilgiri*. The study will also use a case record form, patient information sheet, and written informed consent form.

Data Analysis

Data will be analyzed by using appropriate descriptive and inferential statistics. Quantitative variables will be analyzed with the Student *t* test and subjective parameters will be analyzed with the Wilcoxon signed test and Mann-Whitney *U* test. Alternate statistical methodologies may be applied if deemed necessary.

Ethical Considerations

The study obtained approval from the institutional ethics committee of Mahatma Gandhi Ayurved College Hospital and Research Centre (MGACHRC/IEC/JULY-2022/522). The committee will decide on the end point and oversee the trial as it progresses. The researchers will assess any adverse events and will report to the ethics committee. Consent from parents and assent from patients was obtained before conducting the trial in the local language while explaining every aspect of the study. The informed consent form included a patient information sheet (part 1) and a certificate of consent (part 2). Data will be anonymized and personal information of the participants will be kept confidential before, during, and after the trial. Physical data will be stored in a protected storage facility with access available only to the researchers. Computerized data will be held in a password-protected hard drive with access available only to the researchers. There was no need to provide any compensation to the patients in the trial. Identification of individual participants and users will not be possible in any images in the manuscript or supplementary files. If needed, prior consent will be obtained from identifiable individuals before the inclusion of such images.

Withdrawal Criteria and Stoppage

No adverse effects of the trial drug were noted during the treatment period. Thus, no cases were excluded from the study. A total of 4 patients, including 2 patients in each group, voluntarily stopped taking treatment during the trial and were counted as withdrawn.

Dissemination

This protocol will be published and disseminated as a thesis on *pratishyaya*. The study protocol provides a detailed overview of the study design, methodology, data collection procedures, data analysis plan, and ethical considerations. By disseminating this protocol, we hope to advance knowledge in the field and facilitate future research.

Results

As of November 2024, we completed the enrollment of 70 patients, with 35 patients in each group. A total of 4 patients voluntarily withdrew from the trial. Data analysis of 66 patients will be completed by February 2025, and we expect the results to be published in March 2025.

Discussion

Dhoopana is mentioned in the Ayurveda classics for the management of acute rhinitis, and we anticipate that it will be found to be equally effective as polyherbal steam inhalation in the management of acute rhinitis in children. Steam inhalation of the herbs that were chosen for this study has been found to be effective in the management of upper respiratory tract infections. Thus, fumes of the same ignited herbs (ie, *tulsi*, *vasa*, *nirgundi*, and *nilgiri*) should work just as well in the management of rhinitis. The disease *pratishyaya* is very common in the pediatric population, but no standardized Ayurvedic therapy is available that can be given locally in the nostrils in its acute stage. Locally given medicines are fast and effective compared to oral medication. Another classical procedure known as *nasya* (nasal instillation of oil) is recommended for rhinitis, and as per previous research, it is effective in the management of chronic and recurrent rhinitis, but as per the Ayurveda classics, it cannot be used in acute rhinitis. The herbs chosen for this study are hot and pungent in nature and can reach the minute *srotasa* (channels of the nostrils); thus, they promise to be beneficial in acute rhinitis. Polyherbal *dhoopana* is safe and easy to administer, and if it is found to be effective, it may be a better alternative to steam inhalation. Thus, it can be used in general pediatric practice for patients with acute rhinitis. A positive outcome of the study will facilitate further studies in a large population with standardization of the procedure for *dhoopana*. In this study, a polyherbal wick was prepared manually, and it takes some time to ignite the herbal powder. In the future, this can be improved by using a pocket-friendly herbal nasal fumigator that ignites the herbs in few seconds without any manual practice. This could be patented and copyrighted later and publicized for the benefit of the population.

Acknowledgments

The experts whose works are cited and discussed in the manuscript are acknowledged by the authors for their significant assistance. The authors also acknowledge the Department of Rasa Shastra (Pharmacology), as well as the staff of the Department of Research, Administration, and Management at Datta Meghe Institute of Medical Sciences for their cooperation and assistance. All authors declared that they had insufficient or no funding to support open access publication of this manuscript, including from affiliated organizations or institutions, funding agencies, or other organizations. JMIR Publications provided article processing fee (APF) support for the publication of this article.

Data Availability

The data sets generated during and/or analyzed during this study are available from the corresponding author upon reasonable request.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Images of intervention.
[DOCX File , 1159 KB - resprot_v14i1e58197_app1.docx]

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Abbreviations

CONSORT: Consolidated Standards of Reporting Trials
TNSS: Total Nasal Symptom Score

Edited by A Schwartz; submitted 08.03.24; peer-reviewed by DKK Fadnavis, S Mandekar, M Lima-Serrano; comments to author 02.05.24; revised version received 26.06.24; accepted 23.12.24; published 21.02.25.

Please cite as:
Kakar M, Rathi R, Balakrishnan D, Rathi B
Evaluation of Comparative Efficacy of Polyherbal Steam Inhalation Versus Polyherbal Nasal Fumigation (Dhoopana) in Children With Rhinitis (Pratishyaya): Protocol for an Open-Label Randomized Controlled Trial
JMIR Res Protoc 2025;14:e58197
URL: https://www.researchprotocols.org/2025/1/e58197
doi:10.2196/58197
PMID:

Protocol

Examining the Implementation of the Italian Version of the Teen Online Problem-Solving Program Coupled With Remote Psychological Support: Protocol for a Randomized Controlled Trial

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Abstract

Background: Pediatric acquired brain injury (ABI) is frequently associated with cognitive and socioemotional alterations. Therefore, targeted rehabilitation to improve everyday functioning, particularly executive functioning (EF), is needed to limit the possible deterioration of cognitive abilities and behavior over time and the associated social and psychological costs.

Objective: In this paper, we present the protocol for a phase-2 randomized controlled trial (RCT) aimed at examining the feasibility and efficacy of a web-based intervention (ie, the Italian version of the Teen Online Problem-Solving [I-TOPS] intervention) to improve problem-solving abilities versus an active-control, web-based intervention (ie, wellness intervention) providing health and wellness content.

Methods: A double-blinded, phase-2 RCT will be conducted to guarantee controls on data quality and findings. In total, 42 adolescents will be recruited from a rehabilitation institute and individually randomly assigned in a 1:1 ratio to receive the I-TOPS intervention or the web-based wellness intervention. Both interventions will include 10 core sessions and will be delivered remotely using a web-based platform. Participants allocated to both interventions and their caregivers will independently complete the learning modules in an everyday setting using their computer. The I-TOPS intervention's core sessions will target the EF domain (eg, planning, emotion regulation, and social skills), while all the contents of the wellness intervention will be aimed at providing psychoeducation on ABI sequelae and supporting health and wellness. Participants assigned to the I-TOPS intervention will also receive bimonthly direct training in problem-solving coupled with remote support from a psychologist. Feasibility data and efficacy outcomes on both adolescents' and parents' functioning will be assessed. Cognitive abilities in the EF domain and behavioral and psychological functioning (ie, internalizing and externalizing symptoms) of the adolescents will be evaluated via performance-based measures, administered remotely using the Google Meet platform, and paper-and-pencil questionnaires; parents' well-being will be assessed through paper-and-pencil questionnaires. Efficacy will be evaluated immediately after training and at 6-month follow-up.

Results: This study started on February 26, 2021, and ended on February 28, 2023. A total of 42 adolescents were enrolled and randomly assigned to the 2 study groups, 34 (81%) completed the intervention and posttreatment evaluation (I-TOPS: n=19 and wellness intervention: n=15) and 31 performed follow-up evaluation (I-TOPS: n=18 and wellness intervention: n=13). Data analysis on feasibility and efficacy will be performed after protocol publication, and the results will be published in the form of a paper in a relevant journal in 2025.

Conclusions: This double-blinded, phase-2 RCT could extend knowledge on the best rehabilitation practices to adopt with the survivors of pediatric ABI by providing evidence-based data currently lacking for the Italian context. If this study yields positive results, a larger, multicenter, phase-3 RCT could be planned and delivered to examine program cost-effectiveness in a larger sample.

Trial Registration: ClinicalTrials.gov NCT05169788; https://clinicaltrials.gov/study/NCT05169788

International Registered Report Identifier (IRRID): DERR1-10.2196/64178

(JMIR Res Protoc 2025;14:e64178) doi:10.2196/64178

KEYWORDS

telerehabilitation; acquired brain injury; executive functioning; pediatric; problem-solving; computer

Introduction

Background

Acquired brain injury (ABI), a condition of either traumatic (eg, traumatic brain injury [TBI]) or nontraumatic origin (eg, stroke, anoxia or hypoxia, and infections or inflammation to the brain), represents one of the leading causes of lifelong disability among children and adolescents [1-4]. Together with physical disabilities, the most common consequences of a pediatric ABI include cognitive impairment, reduced academic and vocational attainment, issues with emotional and behavioral regulation, and social problems, all negatively affecting the quality of life of patients [5-15]. Research has indicated that patients with pediatric ABI may be at high risk for substance misuse, mental health problems, criminal behavior, and unemployment in adulthood [5,9,12,15]. Pediatric ABI also substantially causes stress and burden for caregivers and families because children with these conditions experience neurocognitive, behavioral, and adaptive challenges that require relatives to change their lifestyle and develop additional skills to help their children, which often generates significant physical and emotional burden [16,17]. Therefore, pediatric ABI exerts adverse long-term effects on the individual, their family, and the society [6,9,12,15-17].

Specifically, executive functioning (EF) difficulties represent one of the core deficits of ABI, affecting not only cognitive abilities but also behavioral and social functioning [6,9,13,18-24]. EF deficits have been linked with socioemotional adaptation and psychological well-being, with several patients with these deficits exhibiting externalizing behaviors and temper outbursts [6,9,13,18-24]. Thus, there is a clear need for programs designed to rehabilitate EF during the chronic phase of an ABI. However, studies indicate that many children with ABI fail to receive the recommended treatments for optimal recovery after discharge from the hospitals or rehabilitation centers [25-29]. Research has also reported that numerous children with mental health issues do not obtain adequate support [30]. Barriers to receiving treatment have different origins, ranging from intervention accessibility (eg, geographical barriers and time and economic demands to health care facilities and families), poorly designed and grossly underresourced health services, to patients' and families' readiness to work on issues [26-31]. Therefore, numerous rehabilitation interventions for this population deliverable at a distance (ie, telerehabilitation) have been developed and offered over the years [31-38]. Telerehabilitation has diminished the financial and time burden on families typically associated with traditional rehabilitation, thereby allowing patients to receive higher therapy doses [31,39-41]. In the field of psychology, telerehabilitation has also been found to reduce the stigma of therapy, to have similar clinical outcomes to traditional face-to-face interventions, and to improve treatment utility and satisfaction [31,39-41].

In the United States, in the mid-2000s, Wade et al [42] developed a technology-assisted intervention for pediatric patients with TBI and, subsequently, with ABI, with the aim to address EF in everyday settings. The program targets problem-solving within the family context, combining the problem-solving framework by D'Zurilla and Nezu [43] and D'Zurilla et al [44] with the collaborative family problem-solving model by Robin and Foster [45]. The Teen Online Problem-Solving (TOPS) program was originally designed with the specific purpose of providing a contextualized treatment that addressed EF, self-regulation, and communication challenges in everyday settings. The web-based format of the intervention had the objective of increasing patients' participation in outpatient rehabilitation and improving retention rates. The TOPS-contextualized approach is in contrast with training programs that involve only drill-based exercises, which often suffer from a lack of generalization of the effects [37].

The TOPS program includes self-guided, web-based sessions that the child and their family complete at home and bimonthly videoconferences with a psychologist with expertise in cognitive behavioral therapy [42]. The sessions provide training in the steps of problem-solving, teaching adolescents and families to apply them to everyday challenges with organization and planning, social interactions, and emotion control. Metacognitive strategies to promote self-monitoring and self-regulation are also taught. Both the child and the family are required to complete the web-based learning modules, including reading or listening to the didactic information and performing exercises to reinforce understanding of what they read.

In randomized controlled trials (RCTs) of the TOPS program conducted in the United States, families have evaluated the web-based modules of the intervention as helpful, the length and structure as feasible, and the overall program as easy to follow and useful [46,47]. In addition, the web-based program was found to be convenient and beneficial as face-to-face therapy [48]. Regarding efficacy, previous studies have demonstrated the beneficial effects of the TOPS program on children (eg, EF and psychological well-being and behavior at home, school, and other settings); parents (eg, levels of

depression and psychological well-being); and even parent-child conflicts [37,42,46,48-52]. In view of this success, recent guidelines acknowledged TOPS as an evidence-based treatment and a standard of care for executive dysfunction and behavioral issues following TBI in the United States [36].

In Italy, there is a great need to develop rehabilitation interventions accessible to large cohorts of patients with ABI, considering the substantial distance of many families from rehabilitation centers and, in some cases, the presence of geographical barriers (eg, living in remote rural areas, mountains, and islands), which make it difficult for many patients to receive treatments in the chronic phase [31,53]. At present, in Italy, telerehabilitation for cognitive and behavioral functions is still at an embryonic phase. The lack of remote interventions for young children with neurological conditions in this country has been highlighted by a review published in 2020 [53], reporting very limited research on the topic, with only one intervention for children with ABI conducted up to 2019 [54]. Importantly, no intervention focusing on everyday EF was detected. In 2020 and 2023, two papers on an RCT of our research group on the effects of a drill-based remote intervention for children with ABI were published, but also in this case, no focus on EF was given [55,56]; no other intervention delivered in Italy was found up to 2023 [57]. Nevertheless, the area of remote interventions is a matter of great interest for the Italian health care system, as suggested by the publication of 2 relatively recent documents on the following topics: the Italian State-Regions agreement on telemedicine delivery published in 2020 [58] and the guidelines for home assistance published in 2022 by the Italian Ministry of Health [59]. These documents report the national guidelines for the provision of remote services and identify the key elements required for the delivery of treatments at a distance.

To increase rehabilitation opportunities for young patients with ABI and embrace the push toward remote interventions in Italy, we translated and adapted the original American TOPS program to create an Italian version of the TOPS (I-TOPS) intervention [31]. The usability of the I-TOPS intervention and its potential positive effects on adolescents with ABI in Italy should be rigorously tested by conducting an RCT, with the aim to inform the Italian health care system on standardized methods to promote recovery and well-being among this population. A clear evaluation of the clinical impact and cost-effectiveness of the program should be provided to support recommendations for effective behavioral and neuropsychological interventions.

To this end, a single-center, double-blinded, phase-2 RCT will be conducted, comparing an experimental group receiving the I-TOPS (ie, I-TOPS intervention group) intervention with an active control group receiving a modified version of the program (ie, wellness intervention group), having the same structure but omitting problem-solving–related content. The sample size of the study was established through power analysis by considering data from a previous meta-analytic study on the effects of the original American TOPS program [37]. This paper describes the trial protocol; the steps required to conduct the study, including study procedures (ie, setting, participants' characteristics, sample size calculation, randomization and blinding, intervention and active control characteristics, and outcomes selected); and a discussion of the clinical implications of the study.

Objectives

In summary, the study objectives are to (1) examine I-TOPS intervention feasibility in a sample of adolescents with ABI aged 11 to 19 years—we will examine different feasibility outcomes taken from previous studies on remote cognitive rehabilitation interventions for pediatric patients with ABI, considering both the feasibility of the training (eg, accessibility, training adherence, technical smoothness, and training satisfaction) and the feasibility of study and procedures (eg, participation willingness, participation rates, assessment procedures, assessment timescale, and loss to follow-up) [54,60]—and (2) examine I-TOPS intervention efficacy—before training, after training, and at the 6-month follow-up, we will administer questionnaires and performance-based measures to participants and parents in the 2 study groups to assess neurocognitive and psychological or behavioral functioning of children as well as the psychological well-being of parents.

Methods

Trial Design

We will conduct a single-center, 2-arm, parallel-group RCT. The trial will apply a pre-post design, with a baseline preintervention assessment (T0), a postintervention assessment immediately after the 6-month intervention period (T1), and a long-term follow-up assessment conducted 6 months after the end of the intervention (T2). Participants will be randomly assigned to groups in a 1:1 ratio to receive the I-TOPS or the wellness intervention. The wellness intervention presents the same structure as the I-TOPS intervention but omits contents related to problem-solving. No change to the I-TOPS or wellness intervention content will be made during the trial; therefore, both interventions will be delivered in their initial Italian version. Eventual failures or system downtimes will be recorded and considered for the evaluation of the feasibility of the training, but no changes in functionality will be made. The trial was registered on ClinicalTrials.gov (NCT05169788) on December 23, 2021.

Study Setting

The I-TOPS and wellness interventions will be delivered remotely using a web-based platform including web-based learning modules. Participants will complete the intervention in an everyday setting, generally at home using a computer, as the program is not compatible with tablets and mobile phones. Every 2 weeks, a psychologist located in the rehabilitation center (ie, Scientific Institute IRCCS E. Medea in Bosisio Parini, Lecco, Italy) will contact patients and families using the Google Meet videoconference platform to provide remote monitoring, content discussion, and support on the problem-solving process for the I-TOPS intervention and remote monitoring and content discussion only for the wellness intervention.

Demographic, clinical, and outcome data will be collected and stored at the Scientific Institute IRCCS E. Medea.

Eligibility Criteria

The inclusion criteria for the study, in accordance with those of the studies on the original American TOPS program [42,46,49-52], are as follows: a diagnosis of nonprogressive ABI (eg, TBI, stroke, brain inflammation or infection, and anoxia or hypoxia) in the chronic phase (ie, at least 1 year after the event); ages between 11 and 19 years at the time of the recruitment; full-scale IQ ≥70; proper comprehension and speaking abilities in the Italian language; having a PC and access to the internet in the everyday setting, and adolescent and family familiarity with basic computer and internet literacy to manage emails, access to the internet and websites, and video calls; and at least one parent or guardian living with the adolescent available to participate in the intervention.

Exclusion criteria, in accordance with those of the studies on the original American TOPS program [37,42,46,48-52], are as follows: presence of preinjury or comorbid conditions, such as sensory impairments and global developmental delay; a history of abuse; a history of psychiatric hospitalization; and receiving concomitant psychological intervention.

Participant Recruitment

The staff members responsible for the study (AB and CC), in conjunction with the referring physicians, will identify potentially eligible participants by reviewing medical records related to pediatric ABIs at the Scientific Institute IRCCS E. Medea. Families of all potentially eligible patients or the patients themselves, if of age, will be met face-to-face in the clinic or contacted by phone by a psychologist of the research team and provided with details about the aims and methods of the study. Parents and adolescents will be given the opportunity to ask questions about the study and to confirm whether they are interested in participating. No information on group allocation, and thus, on differences between the I-TOPS and the wellness intervention will be provided to limit user expectations and biased results; only general information on the structure of the program and its duration and aims will be discussed. If families are interested in participating, eligibility criteria will be checked with the parent to confirm suitability for the research and ascertain whether both parents or which parent will participate with the adolescent during the intervention. A summary of the informed consent will also be provided. To achieve adequate participant enrollment, research assistants will contact all adolescents meeting the inclusion criteria with up-to-date contact information until the target sample size is reached.

Randomization and Blinding

After completion of the informed consent and baseline measures, participants will be randomly assigned into one of 2 groups: G1, receiving the regular I-TOPS treatment, or G2, receiving the active control training, namely, the wellness treatment. In detail, the randomization will be conducted by a researcher of the Institute, independently from the research staff responsible for recruiting participants. Randomization of patient assignment to the groups will follow a coin flip procedure using the randomization tool of Microsoft Excel: an automated number will be randomly associated with any recruited patient and determine assignment to G1 (0-0.49) or G2 (0.50-1). No stratification will be used. The independent researcher will give the staff members responsible for the study (AB and CC) a sealed envelope containing the participant's group assignment to keep it concealed from the research staff. This is to avoid selection bias and to prevent the research staff from subverting the allocation sequence. In turn, the research staff will give this envelope to the psychotherapists supervising the interventions, who will contact parents of enrolled adolescents to provide information regarding the next study steps on the basis of the group allocation. Indeed, to allow for clinical supervision, treatment fidelity, and patient interactions, the supervising psychotherapist will be required to receive group allocation information. Other research staff, participants, and testers will remain blinded to group assignment. Given these considerations, this study will constitute a double-blinded RCT. Emergency unblinding will be used only in front of reasonable request by the patient or the referring physician due to clinical reasons.

Interventions

This study will have 2 treatment arms, that is, the I-TOPS (G1) and wellness (G2) interventions, described subsequently in Textbox 1. Participants will not have to pay or will not be paid to access the allocated intervention.

For both interventions, before starting the training, a psychologist, who will follow training administration, will contact the families via telephone and discuss how to access the treatment sessions on the interventions' website and how to connect to Google Meet calls. No recommendations on timing, frequency, or intensity of use will be provided; the only requirement will be the completion of each session within a 2-week window. Prompts to use the training will be provided via emails automatically sent by the program; however, participants will choose the frequency (ie, weekly, bimonthly, or monthly) of reminders by selecting a specific option included in the program website. In addition, bimonthly meetings with the psychologist will review content and promote adherence. To this aim, the psychologist will ensure flexibility and coordinate the timing of the sessions to allow families to have time for other commitments and holidays or breaks to be built into the schedule.

No possibility to modify allocated interventions for each trial participant will be given, but each adolescent could discontinue the intervention at any study time due to personal, family, medical, or other reasons.

Textbox 1. Training sessions of the Italian version of the Teen Online Problem-Solving (I-TOPS) intervention and wellness intervention.

I-TOPS intervention

- Session 1 (*Inizio: essere positivi*; Getting started, staying positive, and handling stress): after an introduction on the I-TOPS program and its purposes, the session explains how it is important to develop and maintain a positive attitude in everyday life to better solve problems. The psychologist should review the differences between a positive versus negative approach to problems with the family, emphasizing why it is important to have a positive problem-solving orientation. The family should be encouraged to talk about how they feel when they have problems.
- Session 2 (*Problem-solving*; Problem-solving): the session introduces a 5-step strategy (ie, FAREI, which represents the corresponding acronym to the strategy ABCDE of the original version of the Teen Online Problem-Solving [TOPS] intervention) to solve practical and organizational problems; the 5 steps of problem-solving are as follows: A (ie, aim or focus on a goal), B (ie, brainstorm or analyze all the possible solutions), C (ie, choose a plan), D (ie, do or implement the plan), and E (ie, evaluate what works and what does not work). The psychologist helps the adolescent to apply the strategy by using examples.
- Session 3 (*Organizzarsi*; Getting organized): the session expounds the cognitive changes that occur following an acquired brain injury (ABI), for example, difficulties in memory and attention; the psychologist asks the teenager and the parent about problems with thinking or learning that they feel the teenager is having because of the ABI and about the strategies that they use to compensate for these difficulties. The psychologist helps the family to apply the F.A.R.E.I. strategy learned in session 2 to solve the everyday problems.
- Session 4 (*Lavorare con la scuola*; Working with the school): the session aims to provide parents with information regarding their rights as well as the rights of their adolescent in the education system, with materials and ideas to become advocates for their adolescent, and to create an optimal learning environment while respecting the school's ideas. In addition, parents are taught strategies to better communicate and work with teachers and are required to solve problems on this topic during the web-based session with the psychologist.
- Session 5 (*Mantenere il controllo*; Staying in control): the session describes the possible behavioral and emotional problems following ABI. The psychologist discusses with the adolescent and their caregivers their own problems to allow them to find a solution. During this session, the adolescent learns the 5-step SMART strategy (which is the same as the one reported in the original TOPS program) useful to empower them to manage their own behavior during social interactions. The 5 steps to stay in control are as follows: S (ie, stop and think), M (ie, monitor your behavior), A (ie, appraise and look at how others are reacting), R (ie, reflect), and T (ie, try a new or different behavior). The psychologist helps the adolescent to apply the strategy in the everyday setting.
- Session 6 (*Gestire la rabbia*; Controlling your anger): the session offers a 6-step strategy to manage anger (ie, SPACCA, which represents the corresponding acronym to the strategy STARRS of the original version of the TOPS intervention) and suggests how to become a good communicator by using *iMessages*. The 6 steps to control anger are as follows: S (ie, stop), T (ie, think about what is happening), A (ie, accept the situation), R (ie, relax), R (ie, reframe or look at the situation differently), and S (ie, solve). The psychologist discusses with the family why a person may have more problems with anger after ABI and helps the adolescent to apply the strategy in the everyday setting.
- Session 7 (*Ascoltare, parlare e leggere i segnali non verbali*; Verbal and nonverbal communication): the session helps the adolescents to focus on verbal and nonverbal communication skills and encourages them to focus on nonverbal signals from communication partners and their own nonverbal communication. The adolescent learns strategies for effective verbal communication. The psychologist supervises the exercises done by the adolescents on the web platform and helps them to identify some situations of everyday life in which the learned abilities could be implemented to improve social communication.
- Session 8 (*Comportamento sociale e di gruppo*; Social behavior and problem-solving): the session focuses on possible everyday difficulties in group settings, romantic relationships, web-based communication, and family context. The psychologist discusses with the adolescent and the family how friendships and social activities could change after an ABI and asks the adolescent to identify social situations that are challenging for them and to apply the strategies learned in sessions 5 and 6 to better deal with others.
- Session 9 (*Prendersi cura di sè*; Taking care of you): the session focuses on the relationship between sleep, nutrition, hydration, physical exercise, and cognitive functioning and wellness following an ABI; it also explains the consequences of feeling stressed and suggests different strategies to manage stress. The psychologist discusses with the family members their own habits and helps the adolescents to use the strategies presented in the session to face difficulties of everyday setting and to maintain an adequate routine to support wellness.
- Session 10 (*Conclusione: mettere insieme i pezzi*; Moving forward and planning for the future): this session recaps the 3 main strategies showed in previous sessions (FAREI, SMART, and SPACCA) and introduces a fourth strategy (FOCUS) devoted at helping adolescents to understand the possible steps to effectively ask for help whenever necessary in view of potential future problems in the everyday setting. This strategy is made of F (ie, flexibility when dealing with something), O (ie, optimism), C (ie, creativity to think about other ways to deal with something), U (ie, use your own resources), and S (ie, support or ask for help). The psychologist helps the adolescent to exercise this fourth strategy to use it in the everyday setting after the end of the training.

Wellness intervention

- Session 1 (*La strada verso il recupero*; Recovery and planning for the future): the session introduces the wellness intervention and focuses on the teenager's global difficulties and worries following an ABI. The psychologist provides psychoeducation on ABI sequelae and encourages the adolescent and their caregivers to describe their personal experience of the injury and related emotions and concerns.
- Session 2 (*Fare fatica è normale*; Acquired brain injuries: possible consequences): the session describes the cognitive changes that can occur following ABI, for example, difficulties in memory, attention, and executive functioning (EF) and includes video testimonials of adolescents with ABI discussing such difficulties. The psychologist encourages the teens and their caregivers to describe their personal experience of the injury and its consequences. The content is aimed at providing psychoeducation on ABI sequelae specifically related to the area of cognition.
- Session 3 (*Essere positivi*; Staying positive and handling stress): the session explains how it is important to hire and maintain a positive attitude in everyday life, but this is not specifically related to the problem-solving process, instead to wellness, reducing perceived stress. The psychologist investigates the family's use of humor in daily life and encourages them to talk about how they feel and how they react when problems occur.

- Session 4 (*Lavorare con la scuola*; Working with the school): the session aims at providing parents with information regarding their rights as well as the rights of their adolescent in the education system and with materials and ideas to become advocates for their adolescent and to create an optimal learning environment for their adolescent while respecting the school's ideas.
- Session 5 (*Prendersi cura di sè*; Taking care of you): the session focuses on the relationship between sleep, nutrition, hydration, exercise, and cognitive and physical functioning following ABI. The psychologist investigates with the adolescent and their caregivers their habits in these areas. The aim is to support health and wellness.
- Session 6 (*Gestire lo stress*; Managing your stress): the session explains the consequences of feeling stressed on health and suggests some strategies to manage stress. The psychologist investigates how the adolescents usually cope with stress and helps them to learn the strategies to manage stress and to experiment them in daily life. The aim is to support health and wellness.
- Session 7 (*Il sonno*; Sleep): the session shows the possible sleep changes following ABI and gives advice to improve sleep quality to support health and wellness. The psychologist investigates the adolescent's sleeping habits and, if necessary, helps them to improve sleep quality. The aim is to support health and wellness.
- Session 8 (*Dopo la scuola superiore*; After high school): the session offers the adolescent an overview on the opportunities provided by the Italian system in terms of education and work activities after high school, with a primarily psychoeducational focus. The psychologist helps the adolescents to think about what they would like to be when they grow up and what paths they could follow.
- Session 9 (*Emozioni di chi si prende cura*; For parents: family coping): the session shows the possible emotional difficulties of caregivers of adolescents with ABI and offers strategies for managing stress within the family context. The psychologist reviews with the caregivers their unique responses to the injury, acknowledging that responses are as unique as they are, with a focus on normalizing their emotional reactions.
- Session 10 (*Parlare con i vostri ragazzi*; Talking with your teenager): the session helps the parents to become good listeners and good communicators to improve their communication with the adolescents and the families to support a calm family environment and overall family wellness. The psychologist engages the parents in role-playing to allow them to improve their communication abilities.

I-TOPS Intervention (ie, Experimental Intervention Group)

The qualitative data on the process of adaptation of the original TOPS program to the Italian context (ie, I-TOPS) are extensively reported as a case study in a paper published in 2021 [31]. In summary, the adaptation process comprised focus groups with parents of adolescents with TBI to understand the needs of Italian patients and their families; after a literacy translation of the original program into the Italian language, they were asked their opinions on the relevance and clarity of the program content. The main suggestions were related to the scripted videos, with recommendations to emphasizing nonverbal aspects of communication that are integral to the Italian culture. Furthermore, a clearer depiction of the consequences of negative behaviors in the videos was required. The translation of the original TOPS program text from the English language to the Italian language was completed by 3 different psychologists with expertise in the field of brain injury and cognitive behavioral therapy. Translations were subsequently produced by 1 bilingual expert via forward-backward methods, and discrepancies were discussed and resolved. The final text was checked by adolescents with TBI, their parents, physicians, and adolescents of a local school class. Any suggested changes were accepted if they did not alter the meaning of the original sentence. This process required 5 months of work, during which further content revisions were made to improve ease of comprehension and flow in the Italian language.

The regular version of the I-TOPS intervention consists of 10 core sessions focused on problem-solving, EF, behavioral strategies, and social skills and 10 supplemental sessions. Before starting the program, the psychologist will meet with the adolescents and their family to learn about the specific issues occurring in their everyday setting with respect to organization or planning, social interactions, and emotion control that they want to work on during the intervention. Thus, although the I-TOPS program is delivered according to a defined protocol and content, the problem-solving will focus on personalized, everyday issues that the adolescents and their families have identified. The 10 core modules consist of self-guided didactic content regarding the steps of problem-solving and strategies for managing everyday challenges, brief videos modeling these skills, and exercises to support implementation. The adolescents and their families will complete a new module approximately every 15 days. Each web-based session will take 30 to 45 minutes to complete depending on the adolescent's level of attention. The parent or parents will work with the adolescent to complete each module. The program will not provide any feedback on the activities completed. After the family has completed and reviewed the contents of each session, the trained psychologist will conduct a video meeting of approximately 1 hour with the adolescent and the parent to review the web-based content and practice the problem-solving skills, focusing on a problem identified by the family related to the intervention content from the web-based learning modules (ie, organization or planning, social interactions, and emotion control). Ideally, video meetings should be provided bimonthly, but this period can be slightly adjusted according to family commitments. Completion of all 10 sessions is expected to take each family 5 months. Supplemental sessions will be recommended if their specific content is determined to be potentially beneficial in addressing the ongoing problems of the adolescent or the family identified at the baseline assessment. Therefore, considering supplemental sessions (a maximum of 2 supplemental sessions will be scheduled for each adolescent and family), we anticipate that participants will take approximately 6 months to complete the program.

Wellness Intervention (ie, Active Control Training)

The active control wellness intervention was developed by translating the original TOPS program contents related to health and wellness into the Italian language, usually included in

supplemental sessions, or contents included in original core sessions related to psychoeducation on TBI. In addition, in this case, the translation of the original TOPS program text from the English language to the Italian language was completed by 3 different psychologists having expertise in the field of brain injury and cognitive behavioral therapy. Translations were subsequently produced by 1 bilingual expert via forward-backward methods, and discrepancies were discussed and resolved.

Patients included in the wellness intervention will complete the treatment according to the same schedule as patients of the experimental group but will not receive direct intervention on EF nor support with respect to the problem-solving process. This control treatment focuses on health and wellness but omits contents on problem-solving, EF, behavioral strategies and social skills, and goal setting. The wellness intervention consists of 10 core sessions and 3 supplemental sessions to provide adolescents and their families with a program having the identical structure to the original I-TOPS intervention. The wellness intervention represents an active control training. No feedback will be automatically provided on the activities completed by the program. Bimonthly meetings of a brief duration (ie, about 15 minutes each) with the psychologist will focus on promoting knowledge regarding the consequences of ABI and on healthy lifestyle behaviors to improve wellness and will have the goal to sustain compliance. Completion of all 10 sessions and potentially supplemental ones (a maximum of 2 supplemental sessions will be scheduled for each adolescent and family) is expected to take each family a total of 6 months, similar to the experimental TOPS program. The active control group allows us to control for the placebo effects associated with being involved in a rehabilitation treatment and to isolate the effects of problem-solving training in the I-TOPS intervention.

Therapist Training

The I-TOPS intervention and the wellness treatment will be delivered by psychologists with expertise in psychotherapy. To ensure fidelity and quality assurance, all psychologists will receive training in recruitment strategies, interviewing techniques, questionnaire administration, and delivery of the I-TOPS and wellness interventions before beginning the program implementation; instructions for delivering each session are detailed in a treatment manual written by the TOPS program developer SLW and her research staff.

Treatment Fidelity

In relation to the I-TOPS intervention, psychologists will receive weekly supervision from a qualified psychotherapist with a master's in clinical psychology, a specialization in cognitive behavioral psychotherapy, and qualification in clinical neuropsychology to ensure treatment fidelity and quality assurance.

With respect to the wellness intervention, a supervising psychotherapist will conduct a random review of the sessions conducted by the psychologists every 2 weeks to ensure fidelity. The main topic of discussion will be how to focus on the ABI consequences without directly teaching problem-solving strategies to manage those consequences.

Data Collection

Following completion of the consent process, sociodemographic information (eg, age, sex, and socioeconomic status); details of past medical history; concurrent medication; the adolescent's age at the time of injury; and injury severity, measured using the Glasgow Coma Scale [61] will be collected from each patient's referring physician. Family compositions will be collected from parents via telephone for outpatients or directly in the clinic for hospitalized patients who are close to discharge.

At baseline (T0), after treatment (T1), and at 6-month follow-up (T2), adolescents and parents will be asked to complete study outcome measures, including questionnaires on cognitive and behavioral functioning of adolescents, and the psychological well-being of parents and adolescents will undergo remote cognitive performance–based evaluations. Questionnaires will be sent to adolescents and families in a sealed envelope; after completing them, adolescents and parents will be required to return them to the research staff using an envelope with a postmark included in the sealed envelope within 2 weeks. To promote participant retention, support from a member of the research team could be given for questionnaire fulfillment, if needed. In addition, performance-based measures on adolescents' cognitive functioning will be remotely administered, thus removing practical barriers to patient retention in the study, such as difficulties in transportation and reaching research centers.

Feasibility Outcomes

Outcome measures to assess study feasibility will be taken and adapted from previous studies on telerehabilitation interventions for adolescents with ABI, with the aim to use a priori–defined criteria and allow comparisons [54,60]. These measures have been developed for a previous study [60] based on the relevant literature on pilot feasibility studies [62,63]. A total of 9 measures will be used: 4 to assess the feasibility of the I-TOPS or the wellness intervention (ie, accessibility, training adherence, technical smoothness, and training motivation) and 5 to evaluate the study design and procedures (ie, participation willingness, participation rates, assessment procedures, and assessment length and loss to follow-up).

With respect to the feasibility of the I-TOPS or the wellness intervention, the outcomes outlined in Textbox 2 will be considered.

In relation to the feasibility of study design and procedures, the outcomes outlined in Textbox 3 will be considered.

Textbox 2. Outcomes to be considered regarding the feasibility of the Italian version of Teen Online Problem-Solving (I-TOPS) or wellness intervention.

- Accessibility: number and percentage of participants who ask for further instructions to understand training content and session-related tasks when at home. This criterion refers to understanding how to access the training, how to enter a session, how to perform and save exercises, and how to print specific materials. The criterion for success: 90% of families understand training content and session-related tasks when at home, after the explanation of sessions' content and activities by the psychologist. For all families, the explanation of the content of sessions will be performed during each scheduled web-based meeting (ie, at the end of each session, the psychologist will briefly explain the content of the following one, also indicating to families the web-based activities they are expected to do for the next meeting), with instructions repeated if a family asks for further clarification. If ≥3 explanations are needed, requiring other remote calls, the criterion will be considered to not have been satisfied. The criterion for success was 100% in the paper presenting the original version of the feasibility criteria [60] and in a previous study of our research group [54], both focusing on remote cognitive interventions having a drill-based format. However, for this study, it was reduced to 90%, given the complexity and multiple requirements of navigating and completing content in the I-TOPS intervention.
- Training adherence: number and percentage of the 10 core sessions completed during the scheduled training period (ie, expected time for completion of the 10 core sessions is 5 months) by each patient, including dropouts. No data on the number of log-ins or average session length will be recorded, as, for both treatments, these data do not provide significant information on better training use and are not considered to be associated with improving target abilities. The criterion for success: average 80% of treatment core sessions is completed after 5 months by each treatment group; the remaining 20% (ie, 2 core sessions) should be completed in a maximum 1 further month (ie, 2 extra weeks for each session). To be adherent, participants needing an additional month to complete the training need to have agreed in advance with the psychologist to postpone sessions due to valid reasons (such as holidays or other family plans). The average completion rate per treatment group in the scheduled time frame, calculated as the sum of the percentage of sessions completed by each participant divided per the total number of participants, is considered.
- Technical smoothness: number and percentage of participants who encounter technical issues with the training material (eg, the platform does not work) that persist for 2 or more weeks, thereby generating a training interruption and possibly influencing total training duration. The criterion for success: all participants will be able to perform the training without technical issues; dropouts are included in the calculation, considering only sessions performed.
- Training satisfaction: training satisfaction will be assessed through a satisfaction questionnaire created ad hoc for the original Teen Online Problem-Solving program and already used in previous studies on its feasibility (Multimedia Appendix 1) [46,47]. The questionnaire assesses perceived helpfulness and usability of the program and improvements as a result of treatment, and for this study, it was translated into the Italian language. Item responses include 1 (ie, strongly disagree), 2 (ie, disagree), 3 (ie, agree), and 4 (ie, strongly agree) on a Likert scale. In particular, 5 items pertain to perceived changes in one's problem-solving abilities and psychological wellness, 10 items pertain to satisfaction with the overall program (ie, program helpfulness and enjoyment and relevance of contents), and 2 items focus on the website ease of use. The questionnaire generates a total score, with higher scores indicating greater perceived satisfaction. A total score of ≥57 reflects a positive outcome in terms of satisfaction. The criterion for success: 80% of participants have a neutral or positive global score on the questionnaire.

Textbox 3. Outcomes to be considered in relation to the feasibility of the study design and procedures.

- Willingness to participate: number of participants who accept to partake in the study among those who were contacted for study enrollment. The criterion for success: 75% of eligible participants agree to take part in the study; the criterion is considered on the whole group, as referred to prerandomization data.
- Participation rates: number and percentage of enrolled participants who complete ≥1 session of the interventions, not abandoning the study after baseline measurements and before the start of the training. The criterion for success: 80% of participants who agreed to partake actually participate in the study.
- Assessment procedures: number and percentage of participants for whom outcome data are collected without any problems (eg, missing data and technical issues of assessment tools) on the 3 assessment time points (ie, baseline [T0], after treatment [T1], and 6-month follow-up [T2]). The criterion for success: 90% of the outcome measures for each participant are collected at each time point.
- Assessment timescale: number of participants whose follow-up data are collected within a week after training completion, for posttraining assessment, and within 2 weeks after the 6-month period from training end, for follow-up evaluation. The criterion for success: for all participants, the interval between training end and immediate posttraining evaluation is ≤7 days; for the 6-month follow-up, the assessment is performed in a range of 0 to 14 days from the first day of the 6 months subsequent to training end. This criterion is calculated only for participants performing posttraining and follow-up evaluations, excluding dropouts.
- Loss to follow-up: number of patients who fail to complete all outcome measures at posttraining assessment and 6-month follow-up. The criterion for success: less than 20% of participants enrolled fail to complete all outcome measures on both posttraining assessment and 6-month follow-up. This criterion does not refer to the presence of evaluations with missing data for each participant, for which the criterion "assessment procedures" already provides such information.

Efficacy Outcomes

A total of 9 outcome measures will be used to test preliminary evidence of training efficacy. Specifically, 7 self-assessed outcome measures (ie, 5 questionnaires for parents and 2 questionnaires for adolescents), 2 performance-based tasks assessing social cognition taken from a standardized neuropsychological battery, and a virtual reality–based assessment of everyday setting EF will be used. Questionnaires will be sent to patients and families in a sealed envelope; after completing them, participants will be required to return them to the research staff using an envelope with a postmark included in the sealed envelope within 2 weeks. The performance-based subtests assessing social cognition and the virtual reality–based assessment will be administered remotely using the Google Meet videoconference platform.

A detailed description of outcome measures is provided in Textbox 4. The sample of this study will include adolescents aged 11 to 19 years, but some measures and questionnaires have been standardized for populations having a lower maximum age range; however, they will be adopted for this study as no other measures with the same characteristics are available in the Italian language. The individual measures affected by this problem are clearly described in Textbox 4.

All outcome measures will be administered at T0 (ie, preintervention assessment), T1 (ie, immediately after the 6-month intervention), and T2 (ie, 6 months after the end of the intervention).

For the questionnaire outcomes, approaches to missing individual items will follow the guidelines for missing item procedures indicated in the manual for each questionnaire. If no guidelines for individual missing items are available, the mean of the completed items will be used to replace missing items if ≤10% are missing.

A summary of outcome measures to test training efficacy is presented in Textbox 5.

Textbox 4. Description of outcome measures.

- Behavior Rating Inventory of Executive Function Second Edition (BRIEF-2)−parent form [64]: the BRIEF-2–parent form questionnaire is aimed at assessing executive functioning (EF) behaviors of children and adolescents (aged 5-18 years) in everyday life by considering their parents' perspectives. The questionnaire is composed of 63 items referred to 9 different clinical scales (ie, inhibit, self-monitor, shift, emotional control, initiate, working memory, plan or organize, task-monitor, and organization of materials) and 3 validity scales (ie, inconsistency, negativity, and infrequency). BRIEF 2–parent form is administered to parents, who rate the frequency of executive problems of their children on a 3-point Likert scale. Raw scores on the global scale range from 63 to 189. The *t* scores (mean 50, SD 10) are used to evaluate the level of EF behaviors relative to normative samples. Higher scores indicate a worse outcome. As this questionnaire covers the age range of 5 to 18 years, scores of adolescents of 19 years have been standardized by considering norms for adolescents of 14 to 18 years.
- BRIEF 2–self-report form [64]: the BRIEF 2–self-report form questionnaire is aimed at assessing self-reported EF in everyday life of adolescents aged 11 to 18 years. It is composed of 55 items belonging to 7 clinical scales (ie, inhibit, self-monitor, shift, emotional control, task-monitor, working memory, and plan or organize) and 3 validity scales (ie, inconsistency, negativity, and infrequency). Raw scores on the global scale range from 55 to 165. The *t* scores (mean 50, SD 10) are used to interpret the level of EF compared to normative sample. Higher scores represent a worse outcome. As this questionnaire covers the age range 5 to 18 years, scores of adolescents of 19 years have been standardized by considering norms for adolescents of 14 to 18 years.
- Child Behavior Checklist 6 to 18 (CBCL 6-18) [65]: the CBCL 6 to 18 is aimed at assessing psychological adjustment and behavioral functioning of children and adolescents aged 6 to 18 years, as rated by parents. The questionnaire includes 113 items. The scores of this instrument considered for this study are total problems, internalizing problems, and externalizing problems. Raw scores of the Total Problems Scale range from 0 to 226 and are converted to *t* scores (mean 50, SD 10) to interpret the level of behavioral functioning compared to normative sample. Higher scores indicate a worse outcome. As this questionnaire covers the age range 6 to 18 years, scores of adolescents aged 19 years have been standardized by considering norms for adolescents aged 12 to 18 years.
- Youth Self-Report 11 to 18 (YSR 11-18) [65]: YSR 11 to 18 is aimed at assessing self-reported psychological adjustment and behavioral functioning of adolescents aged 11 to 18 years. The questionnaire includes 112 items. The scores of this instrument considered for this study are total problems, internalizing problems, and externalizing problems. Raw scores of the Total Problems Scale range from 0 to 224 and are converted to *t* scores (mean 50, SD 10) to interpret the level of behavioral functioning compared to normative sample. Higher scores represent a worse outcome. As this questionnaire covers the age range 11 to 18 years, scores of adolescents aged 19 years have been standardized by considering norms for adolescents aged 11 to 18 years.
- Beck Anxiety Inventory (BAI) [66]: the BAI is a 21-item questionnaire aimed at assessing state and trait anxiety in adults. In this study, the questionnaire is administered to parents to evaluate their psychological functioning. The total score is calculated as the sum of the 21 items (4-point Likert scale, ranging 0-3), with a minimum score of 0 and a maximum score of 108. Higher scores indicate a worse outcome. Specifically, a score of 0 to 21 indicates low levels of anxiety, a score of 22 to 35 indicates moderate levels of anxiety, and a score of 36 to 108 indicates potentially concerning levels of anxiety.
- Symptom Checklist 90 (SCL-90) [67]: the SCL-90 is a self-report questionnaire for adults aimed at measuring psychiatric symptom intensity on 9 different subscales (ie, somatization, obsessive-compulsive, interpersonal sensitivity, depression, anxiety, anger-hostility, phobic anxiety, paranoid ideation, and psychoticism). The 90 items included in the questionnaire are scored on a 5-point Likert scale (ranging 0-4), indicating the rate of occurrence of the symptoms during the last 7 days. In this study, the questionnaire is administered to parents to assess their psychological well-being. The Global Severity Index (GSI) is considered, for which the score is reported as a ratio of the sum of all items to the number of items scored. Higher scores indicate higher psychiatric symptom intensity; consistent with recommendations [65], an average score corresponding to ≥1 on the GSI enters the clinical range.
- Parenting Stress Index (PSI)–Short Form [68]: PSI–Short Form is a 36-item questionnaire aimed at assessing levels of stress associated with parenting in relation to different areas: parenting competence, restrictions on life introduced by parenting, parental conflict, depression, and social support. The 36 items of the questionnaire are scored on a 5-point Likert scale. The global score (PSI-total) is considered for this study, for which clinical cutoff is established at 90. Higher scores indicate higher distress.
- Jansari assessment of Executive Functions for Adolescents (JEF-A) [69]: JEF-A is a computerized assessment based on nonimmersive virtual reality aimed at evaluating everyday EF in adolescents aged 10 to 18 years. It is a performance-based assessment administered to adolescents. Participants are asked to plan, set up, and run a birthday party through the completion of 16 tasks resembling real-world activities. JEF-A tasks evaluate 8 constructs related to EF: planning, prioritization, selective thinking, creative thinking, adaptive thinking, action-based prospective memory, event-based prospective memory, and time-based prospective memory. All tasks are scored on a 3-point scale: 0 for failure, 1 for a partial or nonoptimal completion, and 2 for satisfactory completion. The scores for the 2 tasks for any particular construct are summed (ie, maximum of 4 possible), and this score is converted to a percentage of achievement for this construct. In addition to the 8 individual module scores, an average total percentage is computed for the whole assessment. The final raw score ranges from 0 to 32. Higher scores and percentages indicate a better EF. Although this instrument has been tested on adolescents with acquired brain injury (ABI) who are aged 10 to 18 years, in this study, we adopted it for participants aged 19 years as well to ensure comparability and a task in line with tasks related to such an age instead of administering to those adolescents the task for adults involving a multiple errand task based around a business office [70].
- A Developmental Neuropsychological Assessment-2 (NEPSY-2; Theory of Mind and Affect Recognition subscales) [71]: the Theory of Mind and Affect Recognition subscales of NEPSY-2 are performance-based subtests administered to adolescents and aimed at evaluating their social perception and emotion recognition skills. Theory of Mind subscale–part A measures understanding of mental functions and other people's perspectives, and its raw scores range from 0 to 17; Theory of Mind subscale–part B examines the ability to match basic emotions (eg, happy, sad, angry, afraid, and disgusted) to specific situations, and its raw scores range from 0 to 8. The Affect Recognition subscale tests the ability to recognize emotions in facial expressions, and its raw scores range from 0 to 35. Raw scores are converted into scaled scores (mean 10, SD 3) based on age norms ranging from 1 to 19. Higher scores indicate better outcomes. As this battery covers the age range 3 to 16 years, scores of adolescents aged 17 to 19 years have been standardized by considering norms for adolescents aged 11 to 16 years.

Textbox 5. Outcome measures to test training efficacy administered to adolescents and parents.

Cognitive outcomes

- Jansari assessment of Executive Functions for Adolescents (JEF-A; performed by the adolescent) [69]
- A Developmental Neuropsychological Assessment-2 (NEPSY-2; performed by the adolescent) [71]
- Behavior Rating Inventory of Executive function 2 (BRIEF 2-self-report form; related to self-functioning. filled by the adolescent) [64]
- Behavior Rating Inventory of Executive function 2 (BRIEF 2-parent form; related to the adolescent, filled by the parent) [64]

Behavioral or psychological outcomes

- Youth Self-Report 11 to 18 (YSR 11-18; related to self-functioning, filled by the adolescent) [65]
- Beck Anxiety Inventory (BAI; related to self-functioning; filled by the parent) [66]
- Child Behavior Checklists 6 to 18 (CBCL 6-18; related to the adolescent, filled by the parent) [65]
- Parenting Stress Index (PSI; related to self-functioning, filled by the parent) [68]
- Symptom Checklist-90 (SCL-90; related to self-functioning, filled by the parent) [67]

Sample Size and Power Calculation

A previous meta-analysis on the effects of the original American TOPS program on the various outcomes found a small-to-medium average effect size (Hedges g=0.37) [37]; however, high variability was found among the effect sizes of the different studies analyzed. This led us, to be conservative, to estimate a small effect size of f=0.2 for the evaluation of the power calculation in the present study. Power analysis was conducted using G*Power3 Software (Heinrich-Heine-Universität Düsseldorf) [72,73]. Assuming a correlation of 0.50 between repeated measures and setting the α level at P<.05, a sample size of 21 participants per group will be required to obtain 80% of power with our 2 group- and 3 time-point- design. Therefore, a whole sample of 42 participants will be required to be included in the study. Attrition was not considered in performing power calculation, as adherence rates will be a core outcome of this study, which is pioneering for the Italian context and, therefore, will be aimed at collecting data on feasibility. Therefore, any eventual dropouts will be accounted for in statistical analyses using intention-to-treat analysis procedures.

Data Analysis Plan

All randomized adolescents will be included in the analyses, irrespective of adherence to treatment in the I-TOPS or wellness intervention. No imputation of a missing baseline or follow-up data will be performed. The t tests and chi-square analyses will be performed to compare the I-TOPS (ie, experimental) and wellness (ie, control) intervention groups on continuous and dichotomous variables, respectively. Similar analyses will be performed to examine baseline differences between patients who will complete the study and those who will drop out. Frequencies and means related to feasibility outcomes will be calculated. Analyses will be performed using SPSS (version 29.0.1.0; IBM Corp) [74].

Efficacy outcome measures will be separately entered into linear mixed effect models with “time” (baseline vs immediately after treatment vs 6-month follow-up) and “treatment” (regular I-TOPS vs wellness intervention) and their interaction as fixed factors and “intercepts” and “participants” as random factors. In case of differences in any clinical or demographic variables between groups at baseline, those measures will be included in the analyses as covariates. Mixed model analysis allows flexible modeling of the pattern of change over time and uses all the data for a given participant, even if that participant is not seen at all assessments, allowing us to retain participants with missing assessments. Significant interaction effects (ie, time and group) or group effects will be analyzed by post hoc tests. The significance threshold will be set at <.05. No interim analysis will be planned.

Safety Reporting

The risks associated with participating in this trial are considered minimal. The exclusion of adolescents with photosensitive epilepsy reduces the possible risks associated with the prolonged use of a technological device. The interventions, both the original I-TOPS and the wellness interventions, could raise awareness of injury-related cognitive or behavioral problems, which could contribute to conflict between family members. Family communication and problem-solving in the I-TOPS group might increase family burden. Nevertheless, the purpose of the original I-TOPS program is ultimately to help families cope with these difficulties by teaching problem-solving and communication strategies. In addition, the psychologist supporting the web-based interventions (ie, both original I-TOPS and wellness intervention) is trained to handle any emerging problems. Should any issues arise, the psychologist will have the opportunity to discuss the situation during weekly group supervision meetings with the supervising psychotherapist who is qualified in psychotherapy (a minimum of 2 psychologists is scheduled to deliver the treatments). Thus, there is no requirement to report nonserious adverse events (SAEs) in this study; nevertheless, a monitoring of SAEs will be performed. SAEs may be reported by referring physicians of each patient or researchers, the I-TOPS intervention coaches, participants themselves, or any other informant. Adverse event data will be monitored by the Ethics Committee of the Scientific Institute, IRCCS E. Medea to ensure safety. All suspected SAEs will be reported within 24 hours of discovery to the chief investigator, who will be asked to inform the ethics committee contact person at our Institute. All SAEs will be followed up until resolution.

Ethical Considerations

This study has been approved by the Ethics Committee of Scientific Institute, IRCCS E. Medea (08/21-CE, January 21, 2021). The trial will be conducted in accordance with the protocol and the principles of the 1964 Declaration of Helsinki. Any eventual amendments to the protocol will be submitted to the Ethics Committee of Scientific Institute, IRCCS E. Medea for approval. The principal investigator should make available, on request, relevant trial-related documents for monitoring and audit by the sponsor (Scientific Institute, IRCCS E. Medea) or the relevant research ethics committee.

The informed consent will be obtained face-to-face by staff members responsible for the study (AB and CC) when the adolescents and parents come to the clinic or remotely by using a sealed envelope for those families not able to reach the Institute. The consent process depends on the age of the participants; for participants aged 11 to 17 years, the parents or guardians will provide consent, while participants aged 18 or 19 years will provide their own signed consent. Families will be required to sign the "participant information sheet and informed consent for research participation." Participants will be given the opportunity to express their concerns and declare barriers to participating in the study at the time of enrollment. Participants will have the ability to opt out at any time during the study.

Parents of participants below the age of consent or participants of age will be required to sign a "privacy policy statement and consent." An Institute Data Protection Officer (DPO) will be available, representing a contact point between the Italian Data Protection Authority and the concerned parties. DPO email address is reported on the "privacy policy statement and consent" signed by the parents or the participants. In addition, using the email address of the DPO reported on the "privacy policy statement and consent," participants will have the possibility to provide feedback and express any concerns about the project.

Participants' personal data will be pseudonymized. A unique trial number will be provided to each participant consenting to participate in the study. Each participant will be identified in all study-related documentation by the trial number and initials. A record of names and addresses linked to participants' trial numbers will be maintained by the research team and stored securely. All data will be entered into a password-protected database and encrypted using a stored procedure. Data will be stored for 50 years, except in the case of extension by law, in accordance with information reported in the document on data management for scientific research.

To prevent problems with mislaid usernames and passwords, participants will access the web pages of the allocated training program through links emailed to them by the research team members. Once the program has been completed by the participant, it will be locked to prevent further data entry or change.

The trial database will be designed and maintained by 2 members of the research team responsible for data management (AB and CC); access to the database will be given to eventual research assistants involved in the research project by signaling their name to the specific privacy office of the Institute. Database access by researchers will be password protected.

All data will be collected and managed in accordance with Regulation (European Union) 2016/679 of the European Parliament and of the Council of April 27, 2016, on the protection of natural persons with regard to the processing of personal data and on the free movement of such data and repealing Directive 95/46/EC.

No compensation related to study participation will be provided.

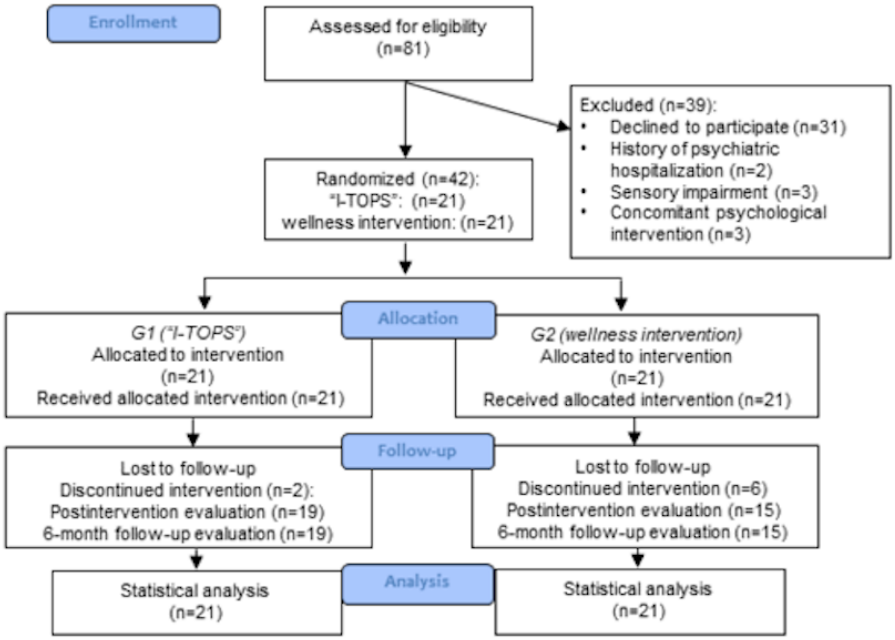
Results

After the approval of the ethics committee, the study started on February 26, 2021, and ended on February 28, 2023. Recruitment started on December 27, 2021, and ended on February 25, 2022. The last patient evaluation was performed on February 22, 2023. A secular event, namely the COVID-19 emergency, fell into the first part of the study period, which could have increased the interest of adolescents and families in participating in a remotely delivered treatment. However, due to the need of the target population to receive neurocognitive treatment in the chronic phase, we consider this fact marginal and not influencing the adherence rate. At study protocol submission in *JMIR Research Protocols*, the study has been concluded; the expected 42 participants were randomly assigned into the 2 treatment groups, and 34 (81%) of them concluded the assigned intervention and underwent posttraining and 6-month follow-up evaluations. The total attrition rate was 19% (8/42).

Figure 1 depicts the CONSORT (Consolidated Standards of Reporting Trials) flow diagram.

After the publication of the protocol, data analysis to test feasibility and efficacy will be performed, and final results are expected to be published in the form of a paper in a relevant scientific journal in 2025. In this paper, demographics associated with digital divide issues such as age, education, gender, family socioeconomic status, and computer or internet literacy will be reported.

Figure 1. CONSORT (Consolidated Standards of Reporting Trials) flow diagram. I-TOPS: Italian version of teen online problem-solving.



Discussion

Principal Findings

This RCT will evaluate the feasibility and efficacy of a web-based training aimed at improving EF and problem-solving abilities (ie, I-TOPS intervention) versus an active control web-based intervention providing health and wellness content (ie, wellness intervention) in adolescents with ABI. Substantial evidence on the feasibility and efficacy of the original TOPS program developed and delivered in the United States has been collected, while this RCT will be the first study providing data for the Italian context using the adapted Italian version of the intervention (ie, I-TOPS).

EF rehabilitation is highly recommended for pediatric patients with ABI to limit the progressive deterioration of behavior over time and to reduce associated social and psychological costs [31,75]. Telerehabilitation represents a new form of service that mitigates issues associated with face-to-face rehabilitation, such as limitations in access or elevated costs for families and hospitals, creating more care opportunities for patients. Until now, in Italy, no specific remote intervention for EF for this population is available [57]. Therefore, the TOPS program, originally developed in the United States to help teenagers with TBI and, subsequently, other types of ABI to improve problem-solving in the everyday setting, has been translated and adapted to the Italian cultural context with the name "I-TOPS." The I-TOPS intervention urgently needs to be administered in a rigorous RCT in Italy, allowing a test of its feasibility, clinical efficacy, and cost-effectiveness. Our research team has already conducted pilot trials on telerehabilitation treatments for children with ABI in recent years and has also concluded and published a phase-2 RCT on the effects of a drill-based cognitive training [55,56]. However, data on the efficacy of the program were promising only for visual-spatial working memory and not for other cognitive domains, including EF or behavioral and psychological measures [55,56]. Therefore, at a clinical level, the need remains to provide patients with a rehabilitation program to improve EF in everyday settings. This research is the first Italian study that will focus on this topic.

We will conduct a phase-2 RCT to guarantee adequate controls on data quality and findings, consistent with recommendations proposed for studies on rehabilitation interventions [75]. This RCT protocol is reported in accordance with the CONSORT-EHEALTH (Consolidated Standards of Reporting Trials of Electronic and Mobile Health Applications and Online Telehealth) checklist (version 1.6.1) [76] (Multimedia Appendix 2), which allows for improving the quality of reports of web-based intervention evaluations. Data from this RCT will help inform future directions for investments in the field of telerehabilitation in Italy.

Strengths and Limitations

The planned study possesses a number of strengths, including the use of an active control group (ie, wellness intervention) instead of a passive one, which allows controlling for placebo effects. Furthermore, although the I-TOPS program involves self-directed, web-based learning modules, the provision of active problem-solving therapy by a trained cognitive behavioral psychologist constitutes a key aspect for the success of this RCT. In support of this, a recent study highlighted the fundamental role of patient-therapist engagement in obtaining good results during the rehabilitation therapy [77]. Finally, the use of the computer, rather than a smartphone, for treatment delivery should allow adolescents to maintain an adequate level of commitment and concentration while performing the I-TOPS intervention, requiring them and their families to carry out the program in a quiet place at home and not in random places (eg, on the beach and means of transportation). However, at the same time, this requirement may restrict treatment access and preclude participation by families who do not have the financial means to buy a computer and the necessary equipment for the

videoconferences. Furthermore, families who go on vacation during the 6-month intervention period will have to plan to bring a computer to continue the program or postpone appointments if they are unable to access a computer, which may cause problems with respect to the treatment schedule. At the same time, the long study duration could cause study adherence issues. Nevertheless, it will be the responsibility of our research team to indicate whether the postponement of the sessions is agreed in advance (ie, for holidays or other justified or warranted engagements of the family) or it is instead linked to other factors associated with feasibility issues (eg, forgetfulness, lack of desire or motivation, and failure to carry out tasks). An accurate examination of the feasibility associated with both the training and study design and procedures will be reported.

To limit the issues related to potential biases associated with subjective measures [37], this study examines efficacy as well by using performance-based measures. Furthermore, it adopts a virtual reality–based assessment [69] requiring adolescents with ABI to do errands typical of the everyday setting, which could provide important information on their actual functioning in activities similar to those of real life. Inclusion of these measures will provide further evidence regarding the utility of the intervention in improving various neuropsychological consequences, and thus, this information could be useful to provide the National Health Care System with recommendations for survivors of pediatric ABI.

In addition, the examination of training and study procedure feasibility will allow investigating the usability of the training and the adequateness and potential replicability of the study design, which could help addressing potential issues to intervention delivery in the clinical context and study replication by future research teams. This could also favor the evaluation of the generalizability of trial findings to the general patient population of adolescents with brain injury, addressing sources of potential bias and imprecision. In the clinical context outside of an RCT setting, the I-TOPS intervention would be delivered in the same exact way as in this study, in terms of content, prompts to use the training and human involvement, which increases the relevance of findings of this study to inform the clinical practice.

Conclusions

If this phase-2 RCT yields positive results, a larger, multicenter, phase-3 RCT could be planned and delivered to examine I-TOPS intervention efficacy and cost-effectiveness in a larger sample. Since 2020, Italy has a network for sharing the best practices related to rehabilitation for pediatric neurological children—Rete Pediatrica degli IRCCS [78]—with an important focus on telerehabilitation. This network could enroll in the phase-3 RCT, particularly given that the institute conducting the phase-2 RCT is part of this network.

If the phase-3 RCT demonstrates efficacy, future work will focus on broader implementation within the Italian health system. Beyond providing clinical benefits to adolescents with ABI and their families, the I-TOPS intervention might reduce longer-term health care service use, thus limiting rehabilitation costs. The program might also have broader societal benefits through improvements in educational and vocational outcomes and reductions in criminal behavior frequently associated with EF impairments following ABI [6,9,13,18-24]. Considering local policy making and treatment delivery, the I-TOPS intervention requires limited economic resources to be implemented due to its web-based format and allows for a centralized psychologist, with expertise in the program and pediatric ABI, to provide treatment throughout the country rather than limited to a single region. Therefore, I-TOPS intervention delivery does not necessarily need individuals with this expertise throughout Italy, especially in rural areas or islands, but could allow clinicians of specialized rehabilitation centers to take charge of a wide range of patients, also reaching those living in remote regions. In addition, with the program being accessible at any time that is convenient for the adolescents and their families, it could be less burdensome than traditional clinic appointments, which often require children to miss school lessons or parents to modify their work schedules. Using I-TOPS intervention materials, the National Healthcare System might routinely provide the program to adolescents with ABI and their families throughout the country using a single central therapist to support the needs of multiple families in disparate locations. The findings from this RCT will be disseminated through publications in peer-reviewed and popular science journals and presentations at scientific conferences with the aim to reach relevant research, clinical, health service, and patient communities.

Acknowledgments

This study was supported by the Italian Ministry of Health (Ricerca Corrente 2022-2024 to SS) and “5 per mille” funds for biomedical research. Study sponsors and funders had no role in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication. The authors would like to thank the principal, teachers, and students of Scuola Superiore Maria Ausiliatrice, Lecco, Italy, for their precious contribution in realizing the videos included in the Italian version of the Teen Online Problem-Solving (I-TOPS) program.

Authors' Contributions

CC, AB, CU, RB, and SLW defined the study design and method. CC, MP, and SLW wrote the manuscript. AB, AJ, FAS, GP, CU, RB, RR, and SS significantly revised the manuscript. CC, MP, and SLW prepared the tables and figures. All authors read and approved the final manuscript.

Conflicts of Interest

SLW is the developer of the original Teen Online Problem-Solving program, which was adapted for the Italian context (Italian version of Teen Online Problem-Solving) by the first author, CC. In this regard, we declare that no conflict of interest exists in data reporting: CC was not responsible for patient enrollment and allocation and was masked with respect to participants' group allocation; SLW did not have access to any information on patients nor to the database. All other authors declare no other conflicts of interest.

Multimedia Appendix 1
Training satisfaction questionnaire.
[PDF File (Adobe PDF File), 476 KB - resprot_v14i1e64178_app1.pdf]

Multimedia Appendix 2
CONSORT-eHEALTH checklist (V 1.6.2).
[PDF File (Adobe PDF File), 97 KB - resprot_v14i1e64178_app2.pdf]

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Abbreviations

ABI: acquired brain injury

CONSORT: Consolidated Standards of Reporting Trials
CONSORT-EHEALTH: Consolidated Standards of Reporting Trials of Electronic and Mobile Health Applications and Online Telehealth
DPO: Data Protection Officer
EF: executive functioning
I-TOPS: Italian version of Teen Online Problem-Solving
RCT: randomized controlled trial
SAE: serious adverse event
TBI: traumatic brain injury
TOPS: Teen Online Problem-Solving

Edited by A Schwartz; submitted 15.07.24; peer-reviewed by M Owens; comments to author 11.10.24; revised version received 15.11.24; accepted 25.11.24; published 21.02.25.

Please cite as:
Corti C, Papini M, Strazzer S, Borgatti R, Romaniello R, Poggi G, Storm FA, Urgesi C, Jansari A, Wade SL, Bardoni A
Examining the Implementation of the Italian Version of the Teen Online Problem-Solving Program Coupled With Remote Psychological Support: Protocol for a Randomized Controlled Trial
JMIR Res Protoc 2025;14:e64178
URL: https://www.researchprotocols.org/2025/1/e64178
doi:10.2196/64178
PMID:

Protocol

Effectiveness of Text Messaging Nudging to Increase Coverage of Influenza Vaccination Among Older Adults in Norway (InfluSMS Study): Protocol for a Randomized Controlled Trial

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Abstract

Background: The coverage of influenza vaccination among older adults in Norway is insufficient, especially in some immigrant groups. To improve public health, there is a need for an intervention that can increase influenza vaccination coverage. Further, interventions tailored to reduce potential barriers among immigrants can reduce health inequities.

Objective: InfluSMS aims to determine if SMS nudging increases vaccination coverage among those aged 65 years or older (1) in Norway's general population; (2) among immigrants born in Poland; and (3) among immigrants born in Ukraine; and evaluate the impact of SMS nudging in Norwegian versus in the official language of the native country of immigrants born in Poland or Ukraine.

Methods: InfluSMS is a pragmatic randomized controlled trial conducted among people aged 65 years or older residing in Norway. Influenza vaccination coverage is the main outcome, measured in control and intervention arms for each of the 3 populations listed earlier. In all 3 populations, the control arm is standard care, that is, no individual reminder for influenza vaccination. All populations have an intervention arm that will receive an SMS nudge in the Norwegian language. In addition, the Polish and Ukrainian immigrant populations include a second intervention arm that will receive an SMS nudge in Polish or Ukrainian, respectively. In the general population, at least 23,485 individuals will be randomized to the SMS intervention arm while the rest of the population constitutes the control arm. In each of the 2 immigrant populations, we will randomize all eligible individuals 1:1:1 into the 3 arms. The intervention will take place at the start of the 2025-2026 influenza season. All eligible individuals will be passively followed up through the National Immunisation Registry, SYSVAK, from which individual influenza vaccination status 3 months after the SMS nudge will be collected. Coverage rates between arms within each population and effect sizes between the populations will be compared. The cost-effectiveness of SMS nudging will also be assessed.

Results: The inclusion of participants will start in the third quarter of 2025, and the registry data will be available in the first quarter of 2026. Coverage rates of each strategy and coverage differences between strategies will be presented.

Conclusions: SMS nudging is a scalable, inexpensive, and nonintrusive intervention that could be integrated into the national influenza vaccination program if the trial shows it effectively increases influenza vaccination coverage among older adults.

Further, the trial will establish whether language is a barrier to influenza vaccination uptake among recent immigrant groups that have low influenza vaccination coverage, and to what extent this potential barrier can be diminished by SMS nudging in the official language of their native country.

Trial Registration: ClinicalTrials.gov NCT06486766; https://clinicaltrials.gov/study/NCT06486766

International Registered Report Identifier (IRRID): PRR1-10.2196/63938

(JMIR Res Protoc 2025;14:e63938) doi:10.2196/63938

KEYWORDS

influenza vaccination; coverage; uptake; behavioral nudging; vaccine hesitancy; randomized controlled trial; undervaccination; migrant health; mobile health; mHealth; smartphones; eHealth; SMS

Introduction

Background

Seasonal influenza has a high disease burden worldwide and may cause up to 5 million severe cases and 645,000 deaths annually [1]. Vaccination against influenza is generally safe and may be effective in reducing influenza-like illness and associated conditions [2-4]. It is a widely recommended public health intervention [5,6], especially for groups experiencing a disproportionately high influenza burden such as older adults, who have a higher risk of severe disease, hospitalization, and mortality [7,8]. However, influenza vaccination coverage generally falls far below the 75% target set by the World Health Organization [9], thus many older adults that could have benefitted from vaccination remain unprotected. Furthermore, vaccine hesitancy, defined as a "delay in acceptance or refusal of vaccination despite availability of vaccination services" [10], is widespread for influenza vaccination [11]. The World Health Organization has defined vaccine hesitancy as one of the 10 current threats to global health [12].

Several immigrant groups have shown a relatively low vaccination coverage in their adopted country and a relatively high burden of vaccine-preventable disease [13,14]. This may partly be related to differences in vaccine hesitancy, which may differ between countries [15,16]. It may also be associated with more limited access to vaccination among some immigrant groups, for instance, if immigrants do not understand the language in their adopted country. Whatever the reason, efforts are needed to narrow the gap in vaccination coverage and to promote public health as well as health equity. Tailored interventions addressing acceptability and access barriers faced by immigrants may be useful to achieve this end [14,17].

Vaccine hesitancy is a complex phenomenon that has several psychological components [18,19] that may be influenced by public health interventions that facilitate action and reduce barriers to uptake [20,21]. Behavioral nudges may improve compliance with the use of primary health care services [22], including influenza vaccination uptake among older adults [23]. However, the effectiveness of nudging varies substantially by mode, content, and population [24]. Nudging by reminding older adults to vaccinate against influenza has proven effective in increasing coverage but with far higher effectiveness for reminders sent by ordinary mail [25] than by a governmental electronic letter system [26]. SMS text message nudging may improve childhood vaccination [27], COVID-19 vaccination among health system employees [28], and influenza vaccination among patients due for a routine primary care visit [29]. However, a recent systematic review of randomized control trials (RCTs) on text messaging for improving vaccine uptake shows that very few trials have addressed influenza vaccination among older adults [30].

Norway's influenza vaccination program recommends vaccination to people aged 65 years or older, as well as to other risk groups and health care personnel. Each municipality organizes local vaccination of risk groups. Vaccination is typically available at general practitioner's offices, health clinics, and pharmacies, and is currently offered at an out-of-pocket cost ranging from NOK 150 to 500 (US $14 to $47). In general, vaccination at general practitioners requires the vaccinee to schedule an appointment, while vaccination at pharmacies can be drop-in or scheduled. There is no individual invitation, reminder, or scheduling for vaccination organized by the influenza vaccination program. COVID-19 vaccination is also recommended to the same age group at the same time of year. The same vaccination conditions apply to all residents of Norway, regardless of their citizenship or legal residency status.

InfluSMS is designed as a pragmatic, multiarmed, superiority RCT embedded in the Norwegian influenza vaccination program. In this trial, we aim to determine if sending a smartphone SMS nudge to be vaccinated against influenza can improve vaccination coverage in the general population aged 65 years or older in Norway, and further, to determine the impacts on vaccination coverage associated with providing an SMS nudge in the official language of the native countries of immigrants born in Poland or Ukraine. The Norwegian setting is well suited to conduct an RCT on SMS nudging among older adults, including in selected immigrant groups because there are nationwide administrative and health registries that can be used for this purpose.

An RCT on SMS nudging for influenza vaccination among older adults is warranted because the coverage is insufficient and because evidence on the effectiveness of this intervention is lacking [23,30]. Moreover, most older adults in Norway have a smartphone, thus an SMS intervention is likely to reach most of the eligible population. It is also a relatively nonintrusive and inexpensive intervention that is highly scalable, which thus could function as part of a national influenza vaccination program.

On average the influenza vaccination coverage among older individuals in Norway is 64%. However, the coverage among

some immigrant groups is much lower. Immigrants born in Poland and Ukraine have especially low coverage rates with only 19% and 3% vaccinated in the 2023-2024 influenza season, respectively (Table 1). Poles and Ukrainians are the 2 largest immigrant groups in Norway. As of March 2024, there were 110,000 and 66,000 immigrants from Poland or Ukraine, respectively, accounting for 2.0% and 1.2%, of the entire Norwegian population. Even though the age profile of immigrants from Poland and Ukraine is younger than for some other country backgrounds, they still account for many older adult individuals (Table 1), and this demography is likely to increase in the coming years. Furthermore, Poles and Ukrainians are relatively recent immigrants and may as such have a limited proficiency in Norwegian. If this language barrier hinders their uptake of services, it could potentially be reduced by providing nudges in the official language of their native country.

Table 1. Nationwide coverage[a] of influenza and COVID-19 vaccine among individuals aged 65 years or older[b] during the 2023-2024 influenza season in Norway, stratified by country background[c].

	Total population	Influenza vaccine[d], n (%)	COVID-19 vaccine[e], n (%)
All	1,020,728	656,990 (64.4)	555,745 (54.4)
Born in Norway	941,657	623,598 (66.2)	530,923 (56.4)
Born in Sweden	7129	4520 (63.4)	3976 (55.8)
Born in Denmark	5966	3820 (64.0)	3372 (56.5)
Born in United Kingdom	4606	2888 (62.7)	2594 (56.3)
Born in Germany	3991	2000 (50.1)	1783 (44.7)
Born in Poland	3888	740 (19.0)	520 (13.4)
Born in Ukraine	3843	119 (3.1)	72 (1.9)

[a]Norwegian Immunisation Registry SYSVAK [31] data, extracted May 31, 2024.

[b]Age on December 31, 2023 (born 1958 or earlier).

[c]The most common country backgrounds among individuals aged 65 years or older.

[d]Received at least 1 dose of influenza vaccine between September 1, 2023, and May 29, 2024.

[e]Received at least 1 dose of COVID-19 vaccine between September 1, 2023, and May 29, 2024.

Poles and Ukrainians in Norway also had a very low uptake of the COVID-19 vaccine, both during [32] and after (Table 1) the pandemic, showing that low uptake of adult vaccines in these populations is not limited to influenza vaccination. Thus, interventions that may overcome vaccine hesitancy, which is prominent in Ukraine and Poland [15,16], as well as potential access barriers such as language, are likely to have a general relevance for vaccine uptake.

A recent systematic review highlighted language and tailored text message nudges for improving vaccine uptake as understudied [30]. We are not aware of any studies that have investigated the effectiveness of SMS nudging for influenza vaccination in several languages among immigrant populations.

Objectives

The primary objectives of the InfluSMS trial are to establish whether (1) influenza vaccination nudging by SMS in the Norwegian language increases influenza vaccine coverage compared to standard care, among the Norwegian population aged 65 years and older; (2) influenza vaccination nudging by SMS in Polish or Ukrainian language increases influenza vaccine coverage compared to standard care, among older adults of Polish or Ukrainian background, respectively; (3) influenza vaccination nudging by SMS in Norwegian language increases influenza vaccine coverage compared to standard care, among older adults of Polish or Ukrainian background, respectively; and (4) influenza vaccination nudging by SMS in Polish or Ukrainian language increases influenza vaccine coverage more than nudging by SMS in Norwegian language among older adults of Polish or Ukrainian background, respectively.

For primary objectives 1-3, we hypothesize that SMS nudging will increase coverage. If this hypothesis is not confirmed, the interventions investigated here are futile from a public health perspective, and the remaining study objectives will not be investigated. For primary objective 4, we hypothesize that an SMS in the official language of the native country of each immigrant population will be more effective in increasing coverage than an SMS in Norwegian.

The secondary objectives are to establish whether (1) the effect of SMS nudging in the Norwegian language differs by country background; (2) the effect of SMS nudging in the official language of their native country differs between older adults of Polish or Ukrainian background; (3) SMS nudging for influenza vaccination is cost-effective compared to standard care; (4) SMS nudging for influenza vaccination influences coverage of COVID-19 vaccination; and (5) the time to vaccination differs by the comparisons described in the primary objectives.

Secondary objectives 1-4 are exploratory and have no hypotheses. For secondary objective 5, we hypothesize that SMS nudging will shorten the time elapsed to vaccination.

Methods

Participants

Overview

All Norwegian residents have a unique personal identification number, which is used in health and administrative national registries and can be used to merge data across different registries. In this study, we identify all eligible individuals based on information available from the National Population Register and the Norwegian Immunisation Registry SYSVAK.

The trial has 3 separate populations of individuals who are aged 65 years or older and who reside in Norway, namely (1) the entire Norwegian population (except immigrants born in Poland or Ukraine); (2) immigrants born in Poland; and (3) immigrants born in Ukraine.

Inclusion Criteria

- Aged 65 years and older (age at the end of 2025, ie, born in 1960 or earlier).
- Resident in Norway and have a valid ID number on September 1, 2025.
- Have a smartphone number in the common contact register.

Exclusion Criteria

- Have received the 2025 influenza vaccine prior to the SMS nudge dispatch date.
- Have emigrated or died before SMS nudge dispatch date.

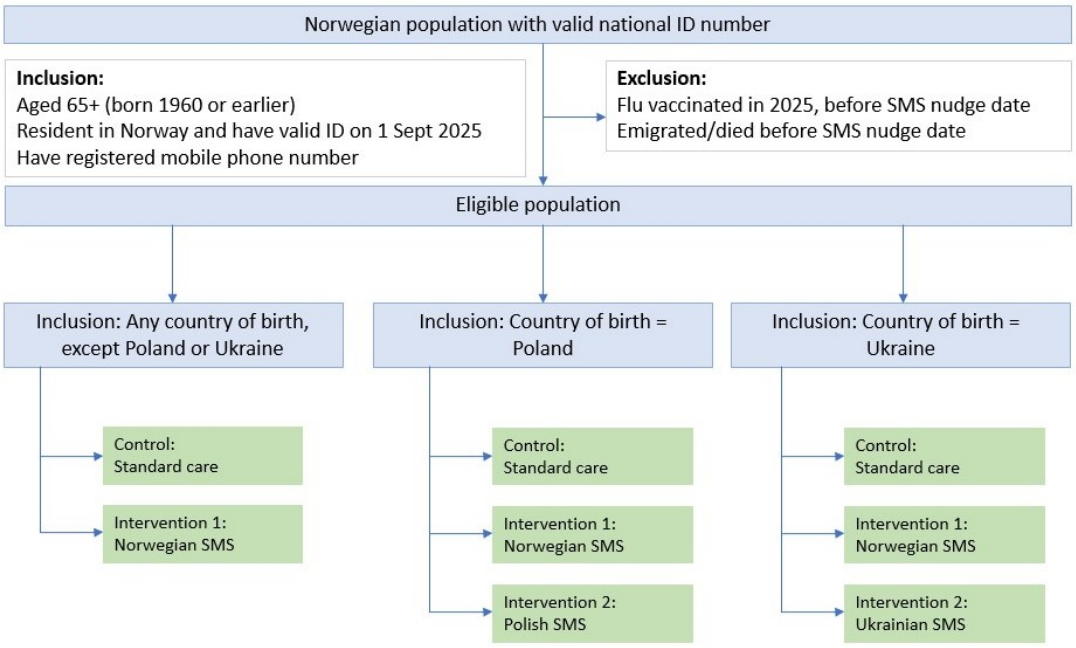
Interventions

Participants in the intervention arms receive an SMS reminder for influenza vaccination in Norwegian, Polish, or Ukrainian. Participants in the control arm do not receive an SMS reminder for influenza vaccination, which is “standard care” in Norway. A description and overview of the InfluSMS study arms and participant flow are shown in Table 2 and Figure 1.

Table 2. InfluSMS study arms.

Study arm	Description	Population
Control	Standard care: Individuals do not receive an SMS reminder for influenza vaccination.	• General population • Immigrants born in Poland • Immigrants born in Ukraine
Intervention 1	Norwegian nudge: Individuals receive an SMS in Norwegian language at the start of the influenza season; to remind them they are recommended to get the influenza vaccine	• General population • Immigrants born in Poland • Immigrants born in Ukraine
Intervention 2	Polish or Ukrainian nudge: Individuals receive an SMS in the official language of their native country (ie, Polish or Ukrainian) at the start of the influenza season, to remind them they are recommended to get the influenza vaccine	• Immigrants born in Poland • Immigrants born in Ukraine

Figure 1. InfluSMS participant flowchart.



Outcomes

The primary outcome measure is having been vaccinated against influenza during the 3 months following the SMS dispatch date in the 2025-2026 influenza season (yes or no, for each individual), as registered in the Norwegian Immunisation Registry SYSVAK [31]. Notification of influenza vaccination to SYSVAK is obligatory for vaccine administrators and does not require patient consent. Follow-up during this trial is passive and does not require any effort from the participants.

Effects will be assessed by influenza vaccination coverage, that is, percent uptake, which will be compared between strategies. SMS nudging will take place at the earliest timepoint at which vaccines for the upcoming influenza season become widely available across the country, which usually is around week 42. All SMS nudges will be dispatched within 1 week. Each individual will be followed up through SYSVAK for 3 months after their SMS dispatch date. We end follow-up at 3 months because we expect that the potential effect of an SMS nudge will be exhausted by then, and because most vaccinations in the influenza vaccination program will have occurred by the end of this period.

Time to influenza vaccination, that is, the number of days elapsed between the SMS dispatch date and the influenza vaccination date (as registered in SYSVAK), is a secondary outcome measure.

We will also address coverage of COVID-19 vaccination as an outcome in the exploratory analyses.

Sample Size

Primary Objective 1: General Population in Norway

We will identify all individuals in the National Population Register that fulfill the eligibility criteria, and among those, make a random selection to receive the Norwegian nudge (intervention 1). We power for a 1% point minimal detectable increase in uptake in the SMS arm compared to the control arm in the general population because the intervention is relatively inexpensive and might be cost-effective even with low effectiveness on coverage. To achieve this minimal detectable increase with a baseline uptake rate of 60%, a power of 0.8, and a 1-sided α of .05, we need to randomize 18,788 individuals to intervention 1. However, based on available statistics, some 20% of individuals may have received the influenza vaccine before the scheduled trial start date and will be excluded from the trial after randomization. We thus need to randomly sample at least 23,485 individuals aged 65 years or older from the entire Norwegian population (except those born in Poland or Ukraine) to be allocated to intervention 1 to be able to detect an increase of 1 percentage point (23,485×80/100=18,788). The control group will be the rest of the Norwegian population that fulfills the eligibility criteria. Currently, there are circa 1.1 million persons aged 65 years or older who reside in Norway. We use this large group as a control because it gives the study high power, the inclusion of individuals receiving standard care carries no cost, and it will provide real-world data on the entire older adult population in Norway.

Primary Objectives 2-4: Immigrants Born in Poland or Ukraine

To maximize power among individuals born in Poland or Ukraine, we will include all eligible individuals and randomly assign them 1:1:1 to each of the 3 study arms. The number we will be able to include in the trial will most likely be higher in 2025 than in 2023 (Table 1) due to the age structure in these immigrant populations and due to new migration. Based on current national demographic statistics, we anticipate there will be some 6000 individuals aged 65 years or older from each immigrant group at the start of the trial. However, some 10% may be excluded due to not having a registered phone number, and a further 1% and 6% (Table 1) may be excluded due to influenza vaccination before the scheduled SMS dispatch date among the Ukrainian and Polish immigrant populations, respectively. Thus, we expect to be able to randomize 5346 Ukrainian immigrants, giving 1782 individuals in each study arm. With a baseline uptake rate of 3% (Table 1), a power of 0.8, and a 1-sided α of .05, this gives a minimal detectable coverage increase of 2 percentage points, adjusted for 3 pairwise comparisons. Similarly, we expect to be able to randomize 5076 Polish immigrants, giving 1692 individuals in each study arm. With a baseline uptake rate of 19% (Table 1), a power of 0.8, and a 1-sided α of .05, this gives a minimal detectable coverage increase of 4% points, adjusted for 3 pairwise comparisons.

In conclusion, the minimal detectable coverage increases of this trial fall within the range of effect sizes reported for other modes of nudging investigated in neighboring countries that share a similar influenza vaccination policy. Specifically, a recent study from Denmark reported that nudging by electronic letters increased coverage by approximately 1% points [26], while a recent study from Finland reported that nudging by ordinary mail on average increased coverage by approximately 6% points [25].

Stratified Analyses

We will also perform analyses stratified by sex, broad categories of age, years of residency in Norway, and household composition. These analyses will have lower power to detect the differences indicated earlier because the sample size in each stratum will be lower than for the overall population.

Recruitment

The study uses data from all residents in Norway who meet the eligibility criteria. The data is retrieved from complete nationwide registries that contain routinely collected information. Therefore, recruitment and follow-up are entirely registry-based and do not require any action by the participants.

Assignment of Interventions

Assignment of treatment arm (control, intervention 1, and intervention 2) will be randomized, automated, and concealed. The identities of the participants will not be decipherable by the data managers.

We will use an external service provider to identify the eligible study population, perform the random selection and randomization procedures, and dispatch the SMS. The provider will be selected through a tendering process. All data

management by the service provider will be done in close collaboration with and under the supervision of the project group. Data management, random selection, and randomization procedures will be performed with reproducible code that includes documented and adequate software functions, preferentially in R programming (R Foundation for Statistical Computing). For the Norwegian population, individuals in intervention arm 1 will be randomly selected from the whole eligible population, while the remainder of the eligible population will serve as the control arm. Similarly, we will use complete random assignment to treatment arm for the Polish and Ukrainian populations. Examples of R functions that serve these purposes are sample_n (from the *dplyr* package) and complete_ra (from the *randomizr* package). Random selection and randomization procedures will be performed after the assessment of the exclusion criteria. The project group will inspect the randomization code before dispatching the SMS.

Blinding

The outcome measure of the trial is based solely on routinely collected data and those reporting or registering this information will not be aware of whether a vaccinated individual has received an SMS nudge. Thus, the trial is blinded to the outcomes assessor. Moreover, treatment allocation is randomized and computer-generated, there is no interaction between the InfluSMS project team and study participants, and the InfluSMS researchers work with deidentified data and do not know the identity of any participant in the dataset. Due to the inherent characteristics of the intervention, treatment allocation cannot be blinded for participants.

Data Collection

The external service provider will be asked to prepare a key file that includes all individuals born in 1960 or earlier in the Norwegian population, with associated individual information including the individual national ID number, the household ID, a randomly generated study ID unique for each individual, and categorical variables indicating treatment arm and exclusion status. This key file will be shared with the National Population Register and SYSVAK. All registries involved will merge requested variables from their registry to this file by the national ID number, and forward the resulting file, excluding the national ID number, to the InfluSMS team. Using the study ID, InfluSMS researchers will then merge the deidentified files from the registries. The key linking the national ID numbers and the study ID numbers will be kept by the service provider and will never be accessible to the InfluSMS team. The procedure is illustrated in Figure 2.

Table 3 lists the variables that will be used in the trial. Note that the national ID will only be used to generate the dataset.

Figure 2. InfluSMS data flow and deidentification of registry data.

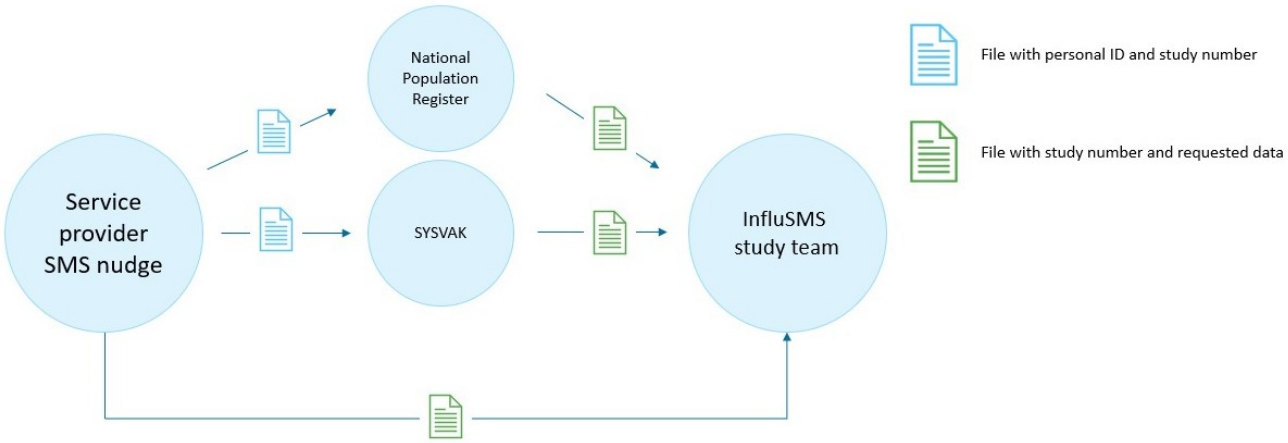


Table 3. List of variables collected or generated in the trial.

Variable	Reason for inclusion
National Population Register	
National ID	Used to identify eligible individuals and link to study ID. Not shared with InfluSMS project group
Household composition	Variable identifying whether eligible individuals live in the same household, to enable sensitivity analyses
Year of birth	Potential confounder (age)
Sex	Potential confounder
Vital status, with date	Exclusion of individuals who died or emigrated
Country of birth	Determine if born in Poland or Ukraine
Immigration date	Determine time living in Norway (potential confounder)
SYSVAK	
National ID	Used to identify eligible individuals and link to study ID. Not shared with InfluSMS project group
Date of vaccination	Determine if date of vaccine was before/after nudge, and impact of vaccination
Disease against which the vaccine protects: • Influenza • COVID-19	Determine who received each vaccine, to calculate vaccination coverages
External service provider	
National ID	Used to identify eligible individuals and link to study ID. Not shared with InfluSMS project group
Demography: • General population • Born in Poland • Born in Ukraine	Study populations
Randomized, and received intervention (SMS): • Yes • No	Identify control or intervention groups
Date SMS was sent	Start of intervention
SMS language: • Norwegian • Polish • Ukrainian	Type of intervention
Excluded from study: • No • Yes, with code for reason	Quantify exclusions
SMS sending errors: • Yes: error in sending • No: no known error	Quantify errors with intervention or infrastructure

Data Management

All data management and analyses will be scripted in R code so that each step can be reproduced and quality assured. Range and other logical data checks will be performed for quality assurance. Programming will be validated by several team members. Data and scripts will be used and stored in a high-security data zone that will be accessible only to team members via login.

Statistical Methods

All individuals randomized will be analyzed, except individuals who die or emigrate during follow-up, who will be excluded from the analyses. We expect exclusions to be evenly distributed between treatment arms due to the randomized design.

Additionally, we anticipate a low proportion of excluded individuals given the relatively short follow-up time of the trial. According to official statistics [33], we can expect approximately 2800 deaths and 100 emigrations per month among the nearly 1.1 million persons aged 65 years or older residing in Norway, which accounts for 0.3% of this population.

As recommended for binary RCT outcomes [34], coverage differences between treatment arms will be expressed on absolute and relative scales, that is, as percentage point differences and as relative risks, with associated 95% Wald CIs. The primary focus will be on absolute scale analyses because they may be most informative for public health decision-making. Absolute estimates will be derived from linear regressions [35], while relative estimates will be derived from generalized linear models with a log-binomial link function [36]. Overall interactions (specifically secondary objectives 1 and 2, where differences between treatment arms will be compared between country backgrounds) will be assessed by likelihood ratio tests and, if significant, further analyzed by the participation differences between factor levels of the variables that interact.

We will compare the time to vaccination (ie, the number of days elapsed between the SMS dispatch date and the influenza vaccination date) between trial arms by the Kaplan-Meier method and the log-rank test.

We assume the registry data for randomized individuals to be close to complete and thus will not impute missing values.

As sensitivity analyses, we will exclude households consisting of at least two or more people aged 65 or older. Comparing the results of these analyses with the main results will indicate whether there may be spillover effects of the SMS interventions within households. Moreover, it will exclude persons living in nursing homes, who may experience easier access and less autonomy regarding influenza vaccination. In exploratory analyses, we will also address the potential effects of SMS nudging for influenza vaccination on the coverage of COVID-19 vaccination. We will use the same statistical methods for these sensitivity and exploratory analyses as described for the main analyses.

We will develop a decision analytic model that can evaluate the potential cost-utility of each nudge compared to standard care and each other. The model will be based on coverage differences observed in the trial and will incorporate implications of increased coverage on the spread of influenza and its consequences for the use of health care resources. Data on reduced influenza from increased uptake will be based on effect estimates of vaccination from the best available scientific evidence. Costs associated with the intervention as well as with increased uptake of the vaccine will be recorded in detail during the project phase. Direct medical costs related to the downstream use of health care services will also be incorporated into the model. The cost-utility analysis will be based on Norwegian guidelines [37], conducted according to standard principles for health economic evaluation [38], and reported according to current guidelines [39].

Data Monitoring

The trial does not pose any harm to participants; thus, the project does not have a data monitoring committee or plans for auditing of trial conduct. Similarly, there will be no interim analyses before the end date of follow-up and no stopping guidelines for the trial.

Ethical Considerations

We have submitted the project for initial evaluation to the Regional Committees for Medical and Health Research Ethics, who recently determined that the project does not fall under the jurisdiction of the Health Research Act [40] (reference #787321). We will thus apply for exemption from the duty of confidentiality from the Health Directorate. The rationale for this decision was that the objective of the research is not to gain new knowledge on health and disease as such, with reference to paragraphs 2 and 4a of the Health Research Act. The application was considered by the REK sør-øst B committee.

This study cannot be performed based on informed consent. Exemption from the duty of confidentiality gives a permit to access and merge the personal registry data without obtaining informed consent. We have conducted several similar registry-based studies. It is our experience that exemption for the duty of confidentiality is granted for studies of this nature, that have large potential public health benefits and no direct consequence for participants [41-44]. The registries own their data and will grant the project data access based on the permits we supply in our data application (ie, exemption from the duty of confidentiality).

Smartphone numbers will be accessed through the Contact and Reservation Register, in which every Norwegian citizen who has logged into a Norwegian public service using an electronic ID is registered. Individuals can opt out of the register, and those who have done so will not receive an SMS as part of this study. About 95% of the adult Norwegian population is part of the Contact and Reservation Register. Opting out will not be considered in the analyses in this pragmatic trial because access to smartphone numbers would be through the same register if SMS reminders were part of the influenza vaccination program. We expect that the drop-out rate will be similar across treatment arms due to the randomized design.

We will submit the protocol and approvals together with a dedicated data protection impact assessment for assessment by the data protection officer at the National Institute of Public Health. The data protection officer oversees data processing in research projects to ensure it is in accordance with applicable data protection laws. The main principles regarding data protection and confidentiality in the project are described in the Data Collection and Data Management sections.

In case of protocol amendments, all stakeholders that have granted approvals to the project, as well as Clinicaltrials.gov, will be notified. None of the project members have any financial or other conflicting interests to declare.

Data access is contingent on the specific permits described above. Thus, data are only accessible to project members. To advise the project, users of Polish, Ukrainian, and Norwegian

origin will be part of the project group. We will also have focus groups with users from each nationality to help formulate acceptable and adequate SMS nudges.

Dissemination

We plan to publish the protocol and the findings of the trial in international peer-reviewed scientific journals. Authorship will be granted according to the Vancouver Convention. Professional writers will not be used.

The findings will also be presented at national and international conferences. To inform the public, we will publish information about the trial on a project web page. Information aimed at the public will mainly be in Norwegian. Further, we will present the project to various stakeholder groups, notably the main user groups of the study (organizations for older adults and immigrant groups) and public health organizations.

Results

As of July 3, 2024, the project has received funding for protocol development from Foundation Dam (grant SDAM_FOR-558766) and we are in the process of obtaining permits, agreements, and access to the infrastructure needed to conduct the trial. Inclusion of participants will start in the third quarter of 2025 and the outcome registry data will be available in the first quarter of 2026. We plan to publish the results during the fourth quarter of 2026.

The results will be reported according to the Consolidated Standards of Reporting Trials (CONSORT) statement on eHealth [45,46]. We will present the baseline characteristics of the 3 study populations, and describe the coverage by treatment arm and population, for strata of age, sex, and duration of residency. We will present the absolute and relative coverage differences between the treatment arms as described in objectives 1-4. In addition, we present comparisons of effect sizes between populations as described in secondary objectives 1 and 2, on absolute and relative scales. The primary focus will be on absolute scale analyses for the coverage analyses (primary outcome measure). We also compare the time to vaccination between treatment arms (the secondary outcome measure). All effects are presented with 95% CIs. We also present the likelihood ratio test *P* value for interaction terms. Table shells for the analyses described earlier can be found in Multimedia Appendix 1. The main findings may also be illustrated in the figures.

Discussion

This pragmatic RCT will provide insights into the effectiveness of SMS reminders in improving influenza vaccination coverage among older adults, which was specifically mentioned as a knowledge gap in a recent review on this topic [23]. The trial will estimate the effectiveness in the older adult population in Norway at large, and among older adult immigrants from Poland or Ukraine, which are large immigrant populations that have a particularly low influenza vaccination coverage in Norway. For the immigrant populations, the trial will also address whether the language of their adopted country may represent a barrier to influenza vaccination uptake that can be reduced by SMS nudging in the official language of their native country. If SMS nudging is effective, it is a strategy that may be feasible for implementation in a nationwide influenza vaccination program because it is scalable, inexpensive, and non-intrusive. Since influenza vaccination protects against influenza and its sequelae, a higher influenza vaccination coverage will benefit society through lower health care costs, as well as the individuals who get vaccinated through direct protection against influenza.

Strengths of this trial include the use of data on nearly all individuals aged 65 years or older residing in Norway, whose health and administrative data are captured in nationwide registries without any loss to follow-up. This eliminates selection and response biases associated with surveys, ensures high quality of the main outcome measure of the trial, that is, influenza vaccination coverage, and yields results that are valid at the national level. Further characteristics that contribute to the high internal validity of this study include the randomized design, no experimenter bias, and standardized procedures for all participants. This trial also has high external validity since it is conducted in real life and will thus yield data that will be entirely representative of how these interventions would work should they become part of an adult vaccination program. Moreover, the results are likely to be of relevance internationally, both as a proof of concept of whether SMS interventions might be effective in increasing adult vaccination coverage and more directly for the immigrant groups addressed here, which likely experience similarly low coverage, for similar reasons, in other adopted countries. The trial will also establish the feasibility of implementing an SMS nudging intervention using the infrastructure available in Norway, for instance in terms of timely access to the necessary health and administrative registry data. Novelty is another strength of the study since we are not aware of other trials with similar interventions and objectives. The trial will also be informed by users, which may enhance its relevance to the populations targeted by the interventions.

The trial also has several limitations, most of which relate to the number of Polish and Ukrainian immigrants we will be able to randomize. First, the number of persons in the immigrant groups who are aged 65 years or older in the 2025-2026 influenza season is a moving target that will be influenced by the influx and outflux of people by that time, as well as the exact underlying age distribution of these immigrant populations. Second, our estimates of the fraction of people missing a registered smartphone number are based on statistics for the whole Norwegian population, and we do not know whether this fraction may be different for the Polish and Ukrainian sub-populations. Third, the minimum detectable effect size for the Polish and Ukrainian populations is approximately 4% and 2% points, respectively. This may be a limitation because even smaller effect sizes might be of public health interest for an inexpensive intervention. Finally, even though we will initiate the trial at the very start of the influenza season, some people will already have been vaccinated by this point, and they will be excluded from participation in the trial. The number of excluded individuals will depend on national vaccine distribution logistics and the epidemiology of influenza in the trial season, which are beyond our control.

The current influenza vaccination program lacks an individual cue to action, which could potentially be more effective than a general recommendation that lacks personalization or direct communication. Sending SMS nudges for influenza vaccination is one way to make individual contact that is likely to reach a very large proportion of the eligible population. If sending SMS reminders is effective, even small effect sizes may benefit public health and be cost-effective. Furthermore, nudges tailored to immigrant groups that have very low uptake of influenza vaccine may reduce inequalities in the use of this preventive health care service and, thus, in health. Insights from the interventions investigated in the current trial can extend to other vaccination contexts and be of international relevance.

Acknowledgments

The authors wish to thank Suzanne Campbell from the National Immunisation Registry SYSVAK for providing background coverage estimates, and Folkehelseforeningen for administrative support and endorsement for project funding. The project was funded by Foundation Dam (grant SDAM_FOR-558766). The funder did not have any role or authority in the study design; collection, management, analysis, and interpretation of data; writing of the report; or decision to submit the report for publication.

Data Availability

The datasets generated in this study are not publicly available because the participants have not consented to it. The data are available from the corresponding author upon reasonable request with permission from the relevant Norwegian authorities.

Authors' Contributions

BTH, LEØ, and HM conceived the study. BTH acquired funding for the study and is the principal investigator. BTH and HM wrote the original draft of the manuscript. All authors contributed to the development of the methodology of the study, critically reviewed manuscript drafts, and approved the final version of the manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Table shells for statistical analyses.
[DOCX File , 27 KB - resprot_v14i1e63938_app1.docx]

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Abbreviations

CONSORT: Consolidated Standards of Reporting Trials
RCT: randomized controlled trial

Edited by A Schwartz; submitted 03.07.24; peer-reviewed by B Eshrati; comments to author 31.10.24; revised version received 14.11.24; accepted 29.11.24; published 25.02.25.

Please cite as:
Hansen BT, Klungsøyr O, Labberton AS, Sääksvuori L, Rydland KM, Ødeskaug LE, Wisløff T, Meijerink H
Effectiveness of Text Messaging Nudging to Increase Coverage of Influenza Vaccination Among Older Adults in Norway (InfluSMS Study): Protocol for a Randomized Controlled Trial
JMIR Res Protoc 2025;14:e63938
URL: https://www.researchprotocols.org/2025/1/e63938
doi:10.2196/63938
PMID:39998878

Protocol

Testing a Dashboard Intervention for Tracking Digital Social Media Activity in Clinical Care of Individuals With Mood and Anxiety Disorders: Protocol and Design Considerations for a Pragmatic Randomized Trial

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Abstract

Background: Mood and anxiety disorders are prevalent mental health diagnoses. Numerous studies have shown that measurement-based care, which is used to monitor patient symptoms, functioning, and treatment progress and help guide clinical decisions and collaboration on treatment goals, can improve outcomes in patients with these disorders. Including digital information regarding patients' electronic communications and social media activity is an innovative approach to augmenting measurement-based care. Recent data indicate interest and willingness from both mental health clinicians and patients to share this type of digital information in treatment sessions. However, the clinical benefit of systematically doing this has been minimally evaluated.

Objective: This study aims to develop an electronic dashboard for tracking patients' digital social activity and a protocol for a pragmatic randomized trial to test the feasibility and efficacy of using the dashboard in real-world clinical care of patients with depression or anxiety disorders.

Methods: We developed a personalized electronic dashboard that tracks patients' electronic communications and social media activity, visualizes data on these interactions through key graphics and figures, and provides a tool that can be readily integrated into routine clinical care for use by clinicians and patients during treatment sessions. We then designed a randomized trial to evaluate the feasibility and effectiveness of using the electronic dashboard in real-world care compared to treatment as usual. The trial included patients aged ≥12 years with a mood or anxiety disorder who were receiving treatment in outpatient psychiatry clinics in the Johns Hopkins Health System and the Kennedy Krieger Institute. The primary outcome includes changes in patient-rated depression symptoms. Secondary outcomes include changes in patient-rated anxiety symptoms and overall functioning. Exploratory analyses examine the impact of the intervention on measures of therapeutic alliance and the detection of clinically actionable targets.

Results: We successfully developed an electronic dashboard for tracking patients' electronic communications and social media activity, and we implemented a protocol for evaluating the feasibility and efficacy of using the dashboard in routine care for mood

or anxiety disorders. The protocol was approved by the Johns Hopkins University School of Medicine Institutional Review Board. In this study, we report the technological, ethical, and pragmatic considerations in developing the dashboard and testing it in a real-world setting.

Conclusions: The integration of an electronic dashboard to monitor digital social activity in mental health care treatment is novel. This study examines the feasibility and effectiveness of the dashboard and the challenges in implementing this protocol. The lessons learned from developing and implementing the study will inform ongoing discussions about the value of gathering collateral information on patients' digital social activity and how to do so in a way that is acceptable and clinically effective.

Trial Registration: ClinicalTrials.gov NCT03925038; https://clinicaltrials.gov/study/NCT03925038

International Registered Report Identifier (IRRID): DERR1-10.2196/63279

(JMIR Res Protoc 2025;14:e63279) doi:10.2196/63279

KEYWORDS

digital mental health; mental health; dashboards; psychiatry; measurement-based care; electronic communication; social media; depression; anxiety; personal health information

Introduction

Background

Mood and anxiety disorders are among the most common mental health disorders in the United States, and they are associated with significant morbidity, mortality, and overall impairment in functioning [1]. These disorders are prevalent across the lifetime, with an onset often in adolescence, and evidence suggests that their rates are increasing in this age group in the United States [2]. A tragic outcome of depression and anxiety is suicide, which has increased by 30% since 2000 and is a leading cause of death in individuals aged between 10 and 34 years [3].

There are treatments for mood and anxiety disorders, but these are not always effective. In a meta-analysis of 38 studies of patients with depression and anxiety receiving outpatient mental health therapy, >40% did not show a reliable change in symptom improvement [4]. Barriers to effective treatment include patient adherence to the treatment model, session attendance, and the alignment between patients' needs and clinicians' therapeutic modalities [5]. There is clearly an urgent need to provide improved mental health care and develop new approaches to treat patients with mood and anxiety disorders.

Measurement-based care (MBC) is a promising but underused approach to providing more effective care for patients with mood and anxiety disorders [6]. MBC refers to the systematic use of measurement tools to monitor patient symptoms, functioning, and treatment effects in care to guide clinical decision-making and promote collaborative treatment planning [7]. A wealth of evidence shows that, when properly implemented, MBC can significantly improve patient outcomes; however, clinicians have been slow to adopt MBC in routine practice [8]. MBC traditionally entails the regular collection of patient-rated or, less frequently, clinician-rated outcome measures during treatment. A significant barrier to adopting MBC is the burden on both patients and clinicians to collect the outcome measures during busy clinical encounters [7]. The emergence of digital technologies, such as smartphones and wearables, has the potential to dramatically broaden the scope of MBC by offering new sources of collateral information that can be more readily leveraged to achieve the goals of MBC [9]. Digital information from these devices can provide valuable insights into a patient's course of illness in real time beyond the point of care [10], and the information can be "passively" collected, which reduces the burden on patients and providers and facilitates downstream use as part of a more expansive approach to MBC [9].

A variety of information relevant to mental health can be gleaned from digital devices [9]. A particularly rich source of digital information is available from social media [10] and other forms of electronic communication, such as SMS text messages [11], collectively referred to as digital social activity in this study. Our social activity is crucial in shaping our mental health, and electronic communication and social media platforms have transformed the way people communicate and interact with one another daily. Indeed, they are typically the predominant form of communication, especially among adolescents and young adults [12,13].

A growing body of research has examined the potential for obtaining useful clinical insights into mental health from digital social activity. Multiple studies have shown that quantifiable signals derived from the language used and activity on different social media platforms are associated with and can be used to develop computational models that distinguish individuals with depression [14-17], postpartum depression [17], schizophrenia [18-20], posttraumatic stress disorder [21], and other serious mental illnesses [22,23]. Other studies have developed models that can predict clinically salient changes in the trajectories of mental illness, such as relapse leading to hospitalization in patients with psychotic disorders [22], the emergence of suicidal ideation or attempts [24,25], the occurrence of binge drinking [26], and clinical responses to antidepressant treatments [27]. Many earlier studies were limited by a reliance on self-report or inferences drawn from data available on social media platforms to establish "ground truth" about mental health end points. In addition, these studies typically analyzed data from only 1 social media platform, while individuals regularly engage with multiple platforms [28]. More recent studies have validated models using clinically documented samples with data from electronic health records [16,20], and another recent study specifically addressed the challenges of developing generalizable models based on diverse social media data sources [29].

Together, these studies suggest that it is possible to reliably monitor digital social activity for actionable collateral information, sparking interest in using such information to improve clinical care for patients with mental illnesses.

Several recent surveys have found that clinicians ask about their patients' electronic communications and social media activity [30-32], and they believe that using this information is helpful in providing more effective treatment [32]. Both clinicians and patients have reported that they are comfortable with using and discussing social media and digital data in mental health therapy [31,33,34]. However, one study found that adult patients were less willing to share more personal data, such as their location or private communications, compared to less personal data, such as screen state (ie, phone screen on or off) and motion data [34]. Another study found that therapists were concerned about whether patients' online posts would accurately reflect their mood, while patients did not want their use of social media and content to be the sole focus of their therapy sessions [31]. In a different study, adolescent patients at risk of suicide, whose social media activity was being monitored by their therapists, expressed concern about the balance between privacy and safety, with some reporting that they may be less likely to seek peer online support [35].

Despite the promise, it remains unclear whether systematic monitoring of digital social activity in routine care of patients with mood or anxiety disorders is acceptable and feasible. Moreover, it has not been shown whether doing so is effective in improving patient outcomes. One group has reported on the design and development of an electronic dashboard for displaying the results of computational analyses of patients' digital social activity that can be used by clinicians and patients [36,37]; however, the use of this dashboard has not been formally tested in clinical practice. Another group has taken a simpler approach to incorporating collateral information from patients' digital social activity and tested this approach in an unblinded randomized trial [38]. They found that integrating insights about patients' social media use in clinical care is feasible; however, there was no significant difference in mental health outcomes between the intervention and treatment as usual (TAU) arms [38]. More research is needed to better understand the appropriate role of systematically monitoring digital social activity in routine clinical care of patients with mental illness.

Objectives

This study was initiated to address the aforementioned need. In this study, we report on the development of an electronic dashboard for tracking patients' digital social activity and a protocol for a pragmatic randomized trial to test the feasibility and efficacy of using the dashboard in real-world clinical care of patients with depression or anxiety disorders. We describe our guiding conceptual model and the decisions we made in designing the dashboard and protocol to test the dashboard, and we discuss the challenges we confronted and the solutions we implemented to launch the trial. The systematic monitoring of patients' digital social activity in clinical care is not only novel and promising but also presents several important challenges. This study informs discussions about translating the promise into clinical reality and sets the stage for reporting trial results in a subsequent paper, which will ultimately contribute to the evidence base on whether monitoring digital social activity in clinical care is warranted.

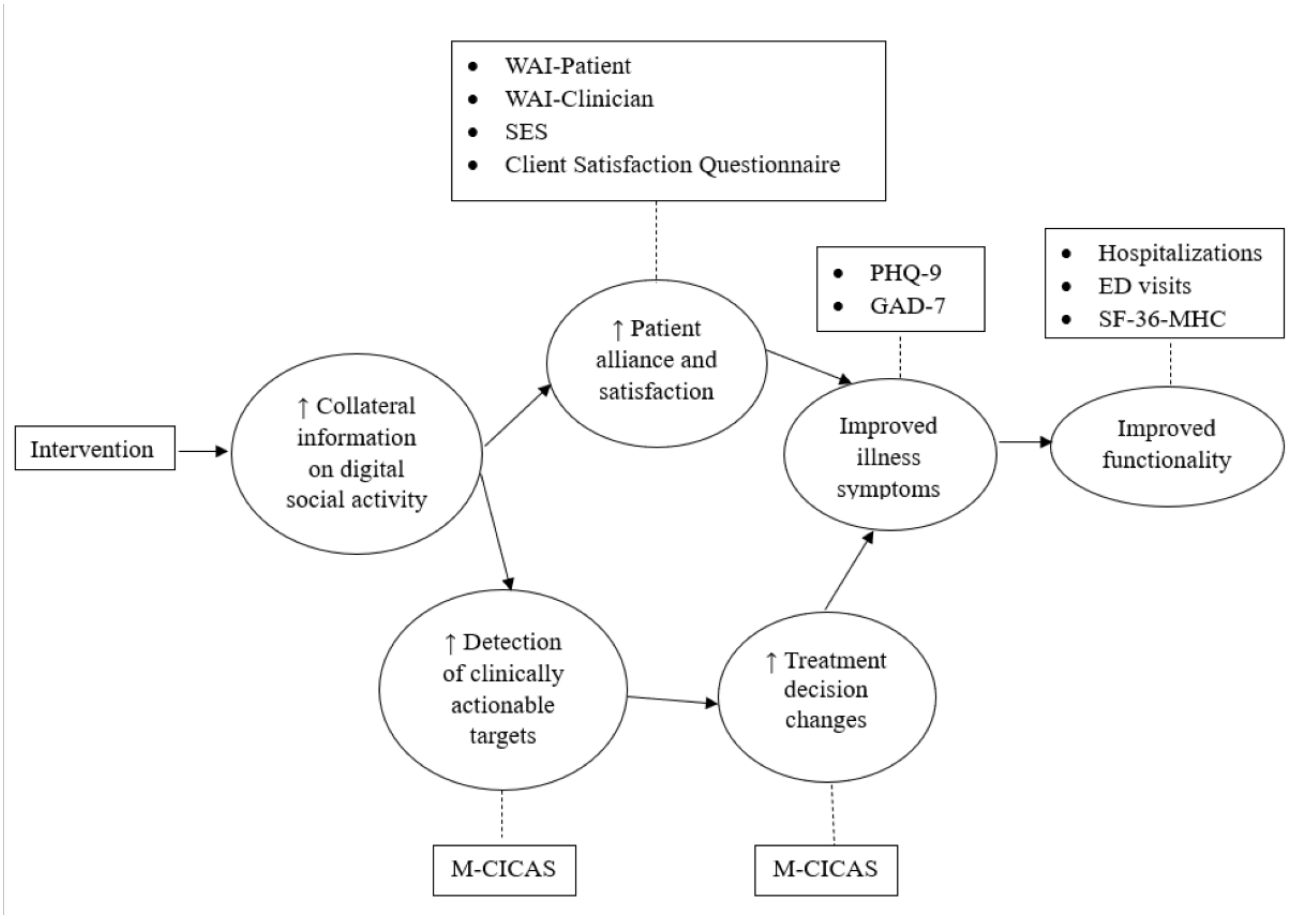
Methods

Conceptual Model

The conceptual model that guided our development and testing of a digital social media intervention in patients with depression or anxiety is shown in Figure 1.

It is grounded in the principles of MBC. We have an expansive view of MBC, which posits that systematically monitoring multiple sources of collateral information, in addition to patient- and clinician-rated outcomes measures, throughout the course of treatment can significantly improve clinical outcomes. In this case, the intervention is designed to gather collateral information about the patient's digital social activity, which growing evidence suggests can provide important real-time insights into the patient's mental health status. We hypothesize that such an intervention may improve downstream clinical outcomes through 2 mediating pathways. In the first pathway, routinely gathering collateral information on the patient's digital social activity may lead to better detection of clinically actionable targets. Clinically actionable targets may include the early detection of signals that the patient's course of illness is starting to worsen or of interpersonal struggles that may precipitate declines in the course of illness. Earlier detection of these clinically actionable targets can lead to more rapid treatment adjustments to address emerging issues before they become more intractable problems. The treatment adjustments may involve a wide variety of interventions, including changes in medication; frequency and duration of clinical visits; the focus of psychotherapy; and outreach to parents, the school, or other responsible parties in the patient's social support network. In the second pathway, the digital social media intervention may improve the therapeutic alliance by fostering more informed and open communication between the patient and clinician, and a substantial body of evidence indicates that a strong therapeutic alliance is crucial to the success of psychiatric treatment [39]. The conceptual model hypothesizes that through these 2 mediating pathways, the intervention may improve more proximal clinical outcomes on clinical symptomatology, which, in turn, leads to improvements in more distal outcomes, such as overall functioning. It is possible that routinely collecting information about the patient's digital social activity may lead to the false positive detection of clinically actionable targets, leading to unnecessary and perhaps harmful changes in treatment. Another possibility is that data collection may disrupt the therapeutic alliance between the patient and clinician by raising concerns over privacy and engendering distrust, which together could ultimately lead to worse clinical outcomes. These are empirical questions about the impact of the proposed intervention that need to be tested and are the focus of our randomized pragmatic trial.

Figure 1. Conceptual model of the mediating pathways by which an intervention designed to monitor patients' digital social activity may impact proximal and distal patient outcomes. ED: emergency department; GAD-7: Generalized Anxiety Disorder-7; M-CICAS: McLean Collateral Information and Clinical Actionability Scale; PHQ-9: Patient Health Questionnaire-9; SES: Session Experience Scale; SF-36 MHC: Short Form-36 Health Survey Mental Health Component; WAI: Working Alliance Inventory.



Electronic Dashboard

Overview

We developed an electronic dashboard to present information about our patient participants' digital social activity for review by their treating clinician in collaboration with the participants during routine clinical encounters. The creation of each personalized dashboard involves 4 steps. First, data from different social media and electronic communication platforms used by the participants, which they have identified for release, were collected using a commercially available app called Bark. Second, the gathered data were transferred to and processed at Johns Hopkins University. Third, the data were analyzed and translated into a set of key graphs and figures that can be rendered in an electronic dashboard format. Fourth, a patient-specific dashboard was delivered to the treating clinician. For each of these components, we implemented steps to ensure the privacy and security of the data as they were gathered and processed, which are detailed in the Data Collection and Data Processing sections.

Data Collection

Data from the patient participants' digital social activity were collected using Bark [40]. Bark is a commercially available app that is designed for use by parents or caregivers to monitor and manage their children's online activity by scanning >30 social apps, web browsers, emails, and SMS text messages. It provides alerts based on algorithms trained to detect online threats, such as cyberbullying, and offers personalized insights and recommendations regarding how to address these alerts. The app works with both iOS and Android mobile devices, but differences exist in how the app accesses certain communication platforms. Apple has stricter controls to prevent third-party apps' direct access to monitor iOS devices. Therefore, to access text messages on iOS devices, users install an app on a desktop computer, and text messages from the iOS device are "manually" transferred to the desktop via a cord connection and uploaded to Bark when the desktop is connected to the internet.

In partnership with Bark leadership, we modified the app for use in this research project by shutting down all features, including alerts, except those related to gathering data from participant activity on SMS text messages, email, and various social media platforms. As a result, the Bark app was used in our study as a data collection tool rather than an analytic tool. Textbox 1 shows the data types and platforms that are monitored by the app.

Textbox 1. Overview of data types and platforms monitored by Bark.

Data type and data sources

- Email: AOL, Comcast, Gmail, iCloud, Outlook, and Yahoo
- Search engine: Microsoft Edge (Android), Firefox (Android), Google Chrome (Android), and Safari (iOS)
- Social media: Instagram, Twitter, Snapchat, Facebook, Pinterest, Reddit, Tumblr, and TikTok
- Text messaging: GroupMe, SMS text messages (Android and iOS), iMessage (iOS), Gmail Chat, WhatsApp, Discord, and Kik
- Miscellaneous: Google Drive (documents and comment or reply), iCloud Notes (iOS), YouTube (comment), and OneNote

Data Processing

Bark executes queries to their internal database at regular intervals (approximately every 30 min) that identify newly captured digital traces from all active participants in the study. These queries generated JSON-formatted data files, which were then automatically uploaded to a password-protected access point on Amazon Web Services Simple Storage Service (AWS S3). Data files were transferred through an encrypted https or transport layer security connection from AWS S3 to a remote network drive hosted at Johns Hopkins University using a scheduled job that executes hourly on a remote server. Microsoft Active Directory was used to restrict network drive access to a subset of study team members on a need-to-have basis. The study team did not provide Bark with any information about patient participants except for the unique signup codes. Data collected by Bark were not shared with guardians in the case of minor participants.

Bark does not apply any exclusion criteria to preemptively filter data uploaded to AWS S3. Instead, the study team used an intermediate processing stage to discard data that lacked natural language text, were unlikely to contain clinically relevant information (eg, promotional emails), or were of a nature that would be likely deemed too invasive by study participants. Images, videos, geolocation tags, and internet use (not including search engine queries) fell into the latter group. Text from the remaining data was passed through a toolkit, which replaced personally identifiable information (ie, phone numbers, social security numbers, zip codes, email addresses, and names) with grammatically appropriate synthetic alternatives [41].

Dashboard Generation

The research team developed several algorithms to analyze the electronic communication data (ie, messages) gathered via the Bark app and, in turn, created a patient participant–specific dashboard that highlighted patterns of patient electronic communication use relevant to their mental health. The choice of the information displayed on the dashboard was primarily based on previous empirical observations recorded in the literature regarding relationships among digital activity, language use, and mental health status (ie, anxiety and depression), and certain visual elements (ie, distribution of platforms used by the participant and the total number of messages sent) were included to contextualize the analyses. Some measures of use were included on the dashboard to facilitate clinician engagement with patient participants (eg, use by platform). Broadly, the type of information displayed to clinician participants about patient participants fell into the following 3 general categories: use statistics, content, and measures of content.

Use Statistics

The dashboard presented information regarding the frequency at which the patient participant had recently used electronic communication. To contextualize the information contained within the dashboard, digital cards located at the top of the dashboard indicated the number of messages a patient participant sent and received during the past week (with comparisons to a running weekly average), a list of platforms (eg, SMS text messages and Discord) used to send messages, and an indicator of the platform most frequently used to send messages [42,43]. To identify possible sleep disturbances or irregularities, a bar graph presented the daily distribution of messages sent during the daytime (6 AM to midnight) and late at night (midnight to 6 AM) over the past 7 days [44,45]. To provide an indication of social connectedness, a second bar graph displayed a weekly distribution of messages sent and received during the past 90 days [46]. A final bar graph displayed the weekly distribution of platforms used to send messages during the past 90 days, which was included primarily to engage participants and provide grounding to existing digital measurement tools (eg, iOS Screen Time).

Content

Language from messages sent by the patient participant during the past 7 days was displayed in multiple forms throughout the dashboard. First, to provide a general summary of the patient participant's communication patterns over the previous week, a word cloud displayed the 40 most frequently used words across all digital platforms, with the size of each word dependent on its use frequency. Second, to capture recent thoughts, interests, and personal challenges, search engine queries were semantically clustered using an external knowledge base derived from Wikipedia and then listed within a table [47,48]. To highlight specific psychologically relevant themes, all messages were processed by the Linguistic Inquiry and Word Count (version 2007) toolkit [49]. The most frequently used words for a set of predefined themes were identified as psychologically relevant in previous literature [16,50-54] and representative messages for those themes were displayed. These themes included the following: positive emotion, negative emotion, anxiety, anger, sadness, family, friendship, work, health, achievement, leisure, home, money, and death. Representative messages for each theme were those that contained the highest number of thematically relevant words. Importantly, as a privacy measure, representative messages were hidden behind a pop-up window until patient participants granted their clinician verbal

permission to view them. In all the aforementioned cases, common "stop words," such as articles and pronouns, were excluded from consideration.

Measures of Content

Several numeric measures were also extracted from the content described earlier and visualized in the dashboard. A bar graph showed the proportion of messages sent over the previous 7 days that contained each theme from the Linguistic Inquiry and Word Count toolkit. To facilitate temporal comparisons, a heat map displayed this same measure computed weekly over the previous 90 days. A second heat map displayed the proportion of messages, aggregated weekly over the previous 90 days, containing different forms of pronouns (eg, personal vs impersonal and first person vs third person). The inclusion of the pronoun measures was based on multiple previous studies identifying correlations between the use of certain pronoun forms and mental health status [55-57].

Dashboard Delivery

Electronic dashboards for each patient participant were updated nightly using an automated script and stored as HTML in a password-protected relational database. Code hosted on a web server behind the Johns Hopkins University firewall was used to retrieve and display dashboards to the clinicians treating patient participants. Multiple guardrails were in place to control access to patient participant dashboards by the treating clinicians. The clinicians were allotted permission in our study's Microsoft Active Directory group and connected to the Johns Hopkins University virtual private network to access the dashboard's landing page. Upon reaching the dashboard's landing page, treating clinicians were prompted to authenticate themselves using Johns Hopkins single sign-on (with 2-factor authentication). A cookie generated by the single sign-on authentication procedure was used throughout the dashboard to ensure that clinicians could only access dashboards for their own patient participants. The list of appropriate patient participants (including a participant ID and name) was shown to the clinician to facilitate navigation around the dashboard.

Data Privacy

We worked closely with our technology team to implement several solutions that helped preserve the privacy of the data collected through the Bark app. We developed a coding system for patients to log into the Bark app so that Bark would not have direct access to any personally identifying information about the patients who were under our care and participating in the study. In addition, we transferred and processed all the collected data to servers behind the Johns Hopkins University firewall that could only be accessed by approved study team members using Johns Hopkins University's standard 2-factor authentication procedures. To further protect the privacy of the data collected through the app, we implemented a pipeline that minimized manual review of the data to only what was necessary to process the data and use it clinically. In addition, we instructed clinicians to review the appropriate dashboards only when they met with their patients, and at that time they could address any potential concerns that emerged from the collected data. We informed patients that the collected data would not be monitored in real time, so they were aware of the procedures.

Randomized Trial

Overview

Motivated by our conceptual model, we hypothesized that providing clinicians with an electronic dashboard of their patients' digital social activity before routine clinical encounters would aid the dialogue and exchange of relevant collateral information during those encounters and thereby improve patient outcomes. The goal was to test this hypothesis in a randomized pragmatic trial comparing patients who received care augmented by the electronic dashboard versus patients who received TAU. The primary research questions to be addressed by the trial were as follows: (1) Is the use of the electronic dashboard in routine care feasible and acceptable to both patients and their clinicians? and (2) Does the use of the electronic dashboard in routine care improve outcomes for patients with depression or anxiety disorders? The outcomes to be examined are described subsequently.

Study Sample

The study was carried out in outpatient psychiatry clinics across the Johns Hopkins Medical Institution and the Kennedy Krieger Institute, which is affiliated with but separate from the Johns Hopkins Medical Institution. We focused on clinics that use a collaborative care model in which patients see a psychiatrist for medication-assisted care as well as a master's level therapist or doctoral-level psychologist for ongoing psychotherapy. Both clinicians and patients were recruited to participate in the study. We first recruited clinicians in the selected clinics to participate in the study and then sought to enroll patients on their case rolls. Patients aged ≥12 years with a mood or anxiety disorder receiving ongoing care were eligible. To be pragmatic and stay as close to the real world as possible, there were no exclusion criteria other than if the treating clinician determined the patient was not able to provide informed consent. In addition, all patients who met the inclusion criteria were eligible, regardless of their current mental health status and scores on patient or clinician rating scales.

Study Procedures

All patient participants downloaded the Bark app and went through the process of connecting their social media and electronic communication platforms to the app. To promote trust and participation in the study, we allowed patients to decide which platforms to connect to the Bark app. While patients retained final control of the decision, we explained to them that their most frequently used apps would provide the most relevant information. Patients were randomized within strata formed by treating clinicians in a 1:1 ratio with blocks of size 2 to either the dashboard intervention or TAU. The purpose of stratified randomization in blocks was to promote balance in the number of patient participants in the 2 treatment arms seen by each clinician, thereby reducing the impact of differences between treating clinicians on comparisons of patient outcomes between the 2 arms. For patients in the intervention arm, the electronic dashboard was delivered to the treating clinician before scheduled clinical visits. The clinician and patient

collaboratively decided when and how to use the dashboard in the session during each clinical encounter. For patients in the TAU arm, the clinician did not receive a clinical dashboard for review. After the initial visit to download the Bark app, there were no more study-specific research visits. To be pragmatic and stay as close to the real-world setting as possible, patients continued to be seen by their clinician as clinically indicated. The first regularly scheduled clinic visit with their clinician after the patient consented and downloaded the Bark app was considered the study's baseline visit. Patients were then followed through their clinical care for up to 6 months, and all study measures were completed during their regularly scheduled clinic visits.

Study Measures

Both the patient and clinician participants completed measures throughout the study follow-up. The measures were selected to address the primary research questions and (based on our conceptual model) to tap into potential mediating constructs. Table 1 provides the schedule of measures during the study follow-up.

Table 1. Schedule of participant measures.

Measures	Baseline	Every clinic visit	Every 3 months[a]
Patient and clinician			
Consent	✓		
Demographics	✓		
Patient			
CSQ[b]	✓		✓
SF-36 MHC[c]	✓		✓
WAI-SR[d]	✓		✓
SES[e]		✓	
PHQ-9[f] and GAD-7[g]		✓	
Patient questionnaire			✓
Clinician			
MFAS[h]	✓		
M-CICAS[i]		✓	
EDMH[j]		✓	
WAI-SRT[k]	✓		✓
Clinician questionnaire			✓

[a]These measures were collected every 3 months, coinciding with the nearest regularly scheduled clinic visit.

[b]CSQ: Client Satisfaction Questionnaire.

[c]SF-36 MHC: 36-Item Short Form Health Survey Mental Health Component.

[d]WAI-SR: Working Alliance Inventory-Short Revised.

[e]SES: Session Experience Scale.

[f]PHQ-9: Patient Health Questionnaire-9.

[g]GAD-7: Generalized Anxiety Disorder-7.

[h]MFAS: Monitoring and Feedback Attitudes Scale.

[i]M-CICAS: McLean Collateral Information and Clinical Actionability Scale.

[j]EDMH: Electronic Data and Mental Health.

[k]WAI-SRT: Working Alliance Inventory-Short Revised-Therapist.

Patient Measures

To measure proximal outcomes on mental health symptoms, participants completed the Patient Health Questionnaire-9 (PHQ-9) [58] and Generalized Anxiety Disorder-7 (GAD-7) [59] at the baseline and every subsequent clinic visit during follow-up. The PHQ-9 is a 9-item measure of current depressive symptoms ranging from 0 to 27, with higher scores representing greater levels of depression. The GAD-7 is a 7-item measure of current anxiety symptoms that ranges from 0 to 21, with higher scores representing greater levels of anxiety. In addition, to measure more distal outcomes on overall mental health–related quality of life, participants completed the Short Form-36 Health Survey Mental Health Component (SF-36 MHC) at baseline and every 3 months, coinciding with their nearest regularly scheduled clinic visit. This 13-item mental

health component scoring ranges from 0 to 100, with higher scores indicating higher mental health–related quality of life [60]. We selected these measures as our primary (PHQ-9) and secondary (GAD-7 and SF-36 MHC) outcomes because they are brief, making them pragmatic to collect, and they are widely used with well-established psychometric properties for measuring important clinical outcomes that, based on the conceptual model we hypothesized, will improve with the proposed intervention.

To measure the overlapping constructs of therapeutic alliance and patient satisfaction, participants completed the Working Alliance Inventory-Short Revised (WAI-SR) and Client Satisfaction Questionnaire at baseline and every 3 months, coinciding with their nearest regularly scheduled clinic visit. The WAI-SR is a 12-item measure of the goal, task, and bond aspects of the therapeutic alliance, and each item ranges from 1 to 5, with higher scores indicating greater alliance [61]. The Client Satisfaction Questionnaire is an abbreviated 8-item measure of patient satisfaction with clinical therapy sessions, and each item ranges from 1 to 4, with higher scores reflecting greater satisfaction [62]. In addition, to further measure therapeutic alliance after every clinic visit, patients completed the Session Experience Scale. This is a 4-item scale that assesses key dimensions of effective therapeutic relationships [63]. Finally, at the end of the study follow-up, patients completed the patient questionnaire, which was a 4-item open-ended measure of the patient-clinician relationship that we developed to assess patient perception of the therapeutic relationship with their clinician and whether discussions about electronic communication had occurred and whether this was helpful.

Clinician Measures

At baseline, clinicians completed the Monitoring and Feedback Attitudes Scale. This is an 18-item measure of clinician attitudes toward treatment tracking and the usefulness of incorporating individualized progress measures. It is scored on a 5-point Likert scale, with higher scores indicating more positive attitudes [64]. To measure clinician perspectives on the therapeutic alliance, they completed the WAI-SR-Therapist at baseline and every 3 months, coinciding with the patient's nearest regularly scheduled clinic visit. This is a 10-item version of the WAI-SR, and each item is rated on a 0 to 5 scale, where higher scores represent a higher alliance [65]. In addition, at every clinic visit, clinicians completed the McLean Collateral Information and Clinical Actionability Scale (M-CICAS) and the Electronic Data and Mental Health (EDMH) Questionnaire. The M-CICAS [66] collects information on the collateral sources of information reviewed, clinical actions taken, and shared decisions made between a clinician and a patient in a clinical session. The EDMH Questionnaire is a 6-item assessment of electronic communication that was completed by clinicians after sessions with patients randomized to the dashboard arm. It includes three Likert-rated questions: (1) Did review of electronic communications affect topics discussed in sessions? (2) How helpful was the review of this information to patient care? and (3) How likely is the clinician to recommend reviewing electronic communication to other clinicians? The questionnaire also includes 3 open-ended questions to gather more context about responses to the first 3 questions. Finally, at the end of the study, clinicians completed the clinician questionnaire, which is a 2-item open-ended survey to measure the use of dashboard-prompted electronic communication in discussion and the usefulness of the dashboard on patient care. We developed the EDMH Questionnaire and clinician questionnaire, but these have not been validated. They were included to gather additional qualitative data on the experience of using the dashboard in clinical care for exploratory analyses.

Data Management

The PHQ-9 and GAD-7 were collected as part of an MBC program that has been implemented in our clinics. As part of this program, patients completed the PHQ-9 and GAD-7 before every clinic visit through the Epic electronic health record as part of routine care. All other measures were collected remotely at the scheduled times via text with a link to questionnaire forms developed in a REDCap (Research Electronic Data Capture; Vanderbilt University) database that is maintained by approved study team members at Johns Hopkins University. These data are to be joined and processed for downstream analyses after removing all patient identifiers except for dates of service.

Statistical Analysis

The primary outcome of the trial is the difference in depressive symptoms measured by the PHQ-9 total score over the course of follow-up between the dashboard intervention and TAU arms. Secondary outcomes include differences in anxiety symptoms measured by the GAD-7 total score and in the more distal outcome of functioning, as measured by the SF-36 MHC. Because the PHQ-9 and GAD-7 were collected at each clinic visit and the SF-36 MHC at baseline and end of the study, there are repeated measures over time for each scale within individual patients. We plan to use random effects linear regression models to test for differences in scores on these measures between the 2 treatment arms. We will include fixed effects terms for the treatment arm as well as for time. Furthermore, we will consider including fixed effects terms for potential confounders, such as demographics (eg, age, sex, and race), and clinical factors, such as primary diagnosis and the number of clinic visits as an indicator of clinical severity. We will also include random effects for individuals to account for the correlation in outcome measures within repeated measures of the same individual as well as for clinicians, if indicated, to account for the potential clustering effects of treatment within clinicians. The primary statistical test of interest will focus on the fixed effects term for treatment, which will provide an estimate of the mean differences in the outcome measures between the 2 treatment arms, controlling for time. We will consider different functional forms of the time covariate and use the one that provides the best fit to the data on changes in score over time. Given that patients will be enrolled in the study regardless of their current mental health status and scores on these outcome measures, we consider the model in which we control for time to be the most appropriate test of differences between the treatment arms. However, we may consider examining interactions between treatment and time to see whether changes in the scores over time differ between the 2 treatment arms. We will use the conventional threshold of $P<.05$ to declare differences statistically significant.

In additional exploratory analyses, we will examine whether there are differences between the 2 treatment arms in measures of therapeutic alliance and detection of clinically actionable targets, both of which we hypothesize, based on our conceptual model, may mediate the therapeutic effect of the intervention. These analyses will provide important evidence as to whether the proposed intervention actually engages the targeted mechanisms of action. In particular, we will test whether there are differences between the 2 treatment arms on scores on the WAI-SR (which measures therapeutic alliance for both patients and clinicians) and the M-CICAS (which captures information about the detection of clinically actionable targets and whether subsequent treatment adjustments were made). For the WAI-SR score, which is a quantitative measure and was captured every 3 months, we will use the same modeling approach as statistical modeling for the primary and secondary outcomes. For the M-CICAS, which was captured after every clinic visit, we will tally the number of times issues related to the patient's social media activity or electronic communications were discussed in the clinical encounter and the number of times treatment adjustments were made. We will again use the same modeling approach as described earlier, except that we will use random effects logistic regression models to carry out separate tests of differences in the probability of these events occurring over time between the 2 treatment arms. Furthermore, we will use $P<.05$ as the threshold to declare findings significant even though multiple tests will be carried out because these analyses will be exploratory.

Finally, we will conduct a series of analyses to assess the feasibility and acceptability of the intervention. We will use several different approaches to do this. First, we will provide descriptive statistics on how many clinicians and patients whom we approached agreed to participate and the reasons why some declined. We are particularly interested in learning whether clinicians and patients decline due to concerns about privacy in sharing personal information obtained from their social media and electronic communication activity or due to the burden of collecting and sharing this information during busy clinical encounters. Second, we will examine descriptive statistics regarding which social media and electronic communications platforms patients agreed to share to assess whether patients were selective about what information they voluntarily provided. Third, we collected a qualitative survey from clinicians to describe the main themes on whether they found systematically discussing social media and electronic communications during treatment helpful, and, if so, what they found most useful.

Sample Size

We estimate that the study has 80% power to detect differences in the primary outcome measure described earlier between the 2 treatment arms with a Cohen *d* effect size of at least 0.5, given the prespecified sample size of 100 and at least 3 repeated outcome measures. We selected a planned sample size of 100 to balance pragmatics and novel treatment intervention, while ensuring a large enough sample size to detect clinically meaningful differences.

Ethical Considerations

The study protocol was approved by the Johns Hopkins University School of Medicine Institutional Review Board (#00184638). We obtained informed consent from both patients and clinicians who participated in the study, ensuring voluntary participation and understanding of objectives, procedures, and potential risks of the study. We obtained assent from patients who were aged <18 years and consent from their guardians. All personal data collected were anonymized and stored in encrypted electronic databases, accessible only to the research team members. To compensate participants for their time and effort, patients received US $100 at randomization and another US $100 at the completion of the study. Participants who shared iOS text data were compensated US $50 because of the extra work required from the participants to share these data. Therapists received US $100 for enrolling 5 patients, US $200 for enrolling 10 patients, and US $250 for enrolling ≥15 patients.

Results

The study was initiated in April 2019, but progress was delayed due to the onset of the COVID-19 pandemic. Data collection has been completed, and the study results will be reported in a separate manuscript. The study is registered on ClinicalTrials.gov (NCT03925038).

Discussion

Challenges

Overview

The goals of this study were to create an electronic communication dashboard and evaluate its use in routine mental health treatment for patients aged ≥12 years with mood or anxiety disorders. The integration of a dashboard to monitor social media use in routine mental health care is novel and promising. With the explosion in the use of electronic communications, it is increasingly relevant to consider social media activity in the therapy setting to aid in treatment planning. However, there are important challenges that merit consideration in deciding how to best achieve this and testing whether doing so is acceptable and effective. In this study, we report the decisions we made to address these challenges in designing and testing such an intervention. The challenges generally fall into 3 categories: technological, ethical, and pragmatic.

Technical Challenges

The most immediate questions to tackle are technological, including how to monitor social media and electronic communications and how to extract and present the information from these data for routine use in clinical care. Regarding the first question, we decided to collaborate with a private start-up company and use the Bark app as a tool for monitoring patients' digital social activity. Our patients typically use several social media and electronic communications platforms, and we wanted to simultaneously track as many as possible to obtain a more comprehensive picture of their digital social activity. The Bark app offers the best out-of-the-box solution that meets our needs for monitoring the widest array of platforms and working with

both the iOS and Android operating systems, which are widely used by our patients. However, there are challenges in working with Bark. The app was not designed for our use case; therefore, we worked with the company to make certain modifications, to make it suitable for our purposes. To give an illustrative example, we had to shut down all alerts from the app, especially ones that promoted the product, because we did not want to be seen as endorsing it commercially. In addition, there are unavoidable challenges to making connections with the different social media and electronic communication platforms through the Bark app that are beyond its control. The iOS and Android operating systems each present their own challenges to work with, but Apple devices, in general, have stricter controls in place. Bark has implemented certain workarounds to these controls, such as for capturing SMS text messages; however, these solutions can add extra burden to patients in using the app, and it is important to learn whether this impacted their willingness to engage with the intervention. Moreover, different social media and electronic communications platforms are constantly evolving their rules and application programming interfaces for third-party access to their data, which could potentially disrupt the connections made by our patients through the Bark app. We will learn what impact, if any, this had on fidelity to the intervention throughout the course of the study. Finally, our incentives are not always aligned when working with Bark. They are a commercial enterprise and understandably motivated to focus on developing a product that will appeal to their target customers, which are parents. By contrast, we wanted to use a tool that can be seamlessly integrated into clinical care and would appeal to both our patients and their clinicians. There is clearly some but not complete overlap in our interests, and it is an open question whether working with the Bark app is sustainable beyond the life of this study.

Regarding a solution to digest and present information about the patient's digital social activity, we decided to develop a custom electronic dashboard. Bark has developed its own algorithms to analyze social media activity data and present alerts of concerning behavior to parents. However, we chose not to use Bark's alerts because their algorithms are proprietary, and we could not clinically validate them. As there were no other options that met our needs at the time, we decided to develop our own approach. As part of future work, we will conduct a qualitative assessment to gather stakeholder feedback on the dashboard, which can inform the next generation of development.

Ethical Challenges

The next set of challenges to consider are ethical challenges. A major concern is how to ethically manage personal information often exchanged on social media and other electronic communication platforms. This concern is especially heightened because we were dealing with patients as young as 12 years, and we were processing potentially sensitive information about their mental health through a third-party commercial app. We worked closely with our technology team to develop several solutions to securely gather and store data in a way that protected the privacy and confidentiality of our patients. However, these solutions raised competing concerns about how to manage scenarios where collected data might contain information that a patient was at risk of harming themselves or others. In weighing the competing concerns about privacy against responding to actionable findings revealed by the collected data, we decided to err on the side of privacy. We sought to inform patients when they joined the study that the information gathered through the Bark app was not monitored in real time and would be reviewed when they met with their clinicians. The clinicians were able to directly address any concerns about the risk of harm to the patient or others that emerged from reviewing their digital social activity during clinical sessions.

Furthermore, there was concern that social media and electronic communications may reveal information about third parties who did not consent to be in the study, such as friends, families, or acquaintances. To address this concern, we used automated procedures to anonymize the content by replacing identified names with fictitious substitutes. While no procedures for scrubbing identifiers in text are 100% effective, this step helps to minimize the chances of inadvertently revealing third-party identities. Consistent with this thinking, we also opted not to analyze data from videos or pictures. The videos and pictures are likely a rich source of information about a patient's mental health status; however, we decided to forgo such information again in favor of caution in protecting the patient's privacy.

Pragmatic Challenges

The final set of challenges to consider are pragmatic challenges. It is one thing to implement procedures that ensure the intervention is ethically sound, but it is another thing to ensure patients and providers are comfortable using those procedures. We anticipate that trust is an important factor in the adoption and success of the intervention. To respect the patient's choice and promote trust, we chose to let participants select which social media and electronic communications platforms they connected to the Bark app. We recognize that some patients may have decided not to connect to certain platforms they regularly use because they were uncomfortable sharing their activity on these platforms, and, as a result, we may have missed important information that is highly relevant to their mental health. However, we reasoned the potential risk was worth the benefit of giving patients control over participation in the study and building trust with the intervention. We sought to explain to the patients during the log-in process the value of sharing their commonly used platforms to encourage more complete engagement. Similar reasoning motivated our decision to mask any specific content (ie, SMS text messaging) that was extracted from the social media and electronic communication platforms and displayed on the dashboard. Moreover, we wanted to give patients a measure of control over how the intervention was used and allow them to decide when clinicians could review the content. Finally, we decided to let the clinicians and patients decide collaboratively whether and when to use the dashboard during the clinical encounter. We trained the clinicians on how to interpret and use the information on the dashboard, but we let them make the decisions with their patients on how it was used in actual care. We understand that this may result in variability across clinicians on how the intervention was used, but we opted to be pragmatic and give the clinicians and patients control over the use of the intervention to foster greater buy-in.

Limitations

In addition to the challenges detailed earlier, there are several limitations to the study that will be important to consider when interpreting the findings that come from it. First, the dashboard we developed and tested is a first-generation product, which may have important limitations in functionality. For example, it is unable to distinguish sarcasm or specific kinds of speech, such as slang, that may be important to correctly interpret social interactions. In addition, it does not include nontext forms of communication, including images or emojis, which can be rich sources of information. It is possible that the functional limitations may negatively impact the efficacy of the intervention. It will be important in future work to continue improving the dashboard to address these functional limitations and achieve the full potential of its clinical utility. Second, there is potential for selection bias in the study participants and their sharing of social media and electronic communication data. Moreover, for those who agreed to participate, their use of social media may have been influenced if they knew it was being regularly monitored. These considerations may skew the findings and limit their generalizability. Information gathered during the conduct of the study from those who do and do not agree to participate may help inform the extent to which these biases influence the results.

Conclusions

We anticipate that this study will be an important step in advancing the use of novel tools for monitoring digital social activity in routine clinical care to improve outcomes for patients with mood or anxiety disorders. We will learn whether using such tools is acceptable and feasible and whether there is evidence that doing so provides clinical benefits. In addition, we will learn what works and what does not work when using this intervention approach, which will crucially inform how to improve upon it for real-world implementation.

Acknowledgments

This work was supported by a generous grant from the Once Upon a Time Foundation. The authors would like to thank Dr Raina Merchant and her team at the University of Pennsylvania and Dr Ipsit Vahia and his team at McLean Hospital for the many productive discussions about the conceptual model and design considerations for this intervention study.

Data Availability

The datasets generated and analyzed during this study as well as the code for the dashboard will be available from the corresponding author upon reasonable request.

Conflicts of Interest

MD receives consulting fees from Good Analytics and Bloomberg LP.

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Abbreviations

AWS S3: Amazon Web Services Simple Storage Service
EDMH: Electronic Data and Mental Health
GAD-7: Generalized Anxiety Disorder-7
MBC: measurement-based care
M-CICAS: McLean Collateral Information and Clinical Actionability Scale
PHQ-9: Patient Health Questionnaire-9
REDCap: Research Electronic Data Capture
SF-36 MHC: Short Form-36 Health Survey Mental Health Component
TAU: treatment as usual
WAI-SR: Working Alliance Inventory-Short Revised

Edited by T Leung; submitted 24.06.24; peer-reviewed by C Rohleder, D Benrimoh; comments to author 30.07.24; revised version received 03.09.24; accepted 02.01.25; published 05.03.25.

Please cite as:
Nesbitt B, Virgadamo D, Aguirre C, DeCamp M, Dredze M, Harrigian K, Lhaksampa T, Meuchel JM, Meyer AM, Walker A, Zirikly A, Chisolm MS, Zandi PP, Miller L
Testing a Dashboard Intervention for Tracking Digital Social Media Activity in Clinical Care of Individuals With Mood and Anxiety Disorders: Protocol and Design Considerations for a Pragmatic Randomized Trial
JMIR Res Protoc 2025;14:e63279
URL: https://www.researchprotocols.org/2025/1/e63279
doi:10.2196/63279
PMID:40053788

Protocol

Efficacy of a Supervised Exercise Program on Pain, Physical Function, and Quality of Life in Patients With Breast Cancer: Protocol for a Randomized Clinical Trial

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Abstract

Background: Breast cancer is the second most common cancer in women worldwide. Treatments for this disease often result in side effects such as pain, fatigue, loss of muscle mass, and reduced quality of life. Physical exercise has been shown to effectively mitigate these side effects and improve the quality of life in patients with breast cancer.

Objective: This randomized clinical trial aims to evaluate the efficacy of a 12-week supervised exercise program on pain, physical function, and quality of life in female patients with cancer.

Methods: This randomized, double-blind clinical trial will recruit 325 participants, divided into an intervention group receiving the exercise program and a control group receiving standard care recommendations. Outcome measures, including pain (assessed via the Brief Pain Inventory), physical function (Disability of the Arm, Shoulder, and Hand Questionnaire), and quality of life (European Organization for Research and Treatment of Cancer QLQ-C30 and European Organization for Research and Treatment of Cancer QLQ-BR23), will be evaluated at baseline, immediately post intervention, and 12 weeks post intervention. Statistical analysis will involve repeated measures of ANOVA and MANOVA to determine the significance of the intervention's effects across time points.

Results: Recruitment and data collection will commence in February of 2025, and data analysis is scheduled for completion at the end of 2025. No results are currently available

Conclusions: Physical exercise is anticipated to play a significant role in alleviating pain, enhancing physical function, and improving the quality of life in female patients with cancer. This study will provide robust evidence to support the integration of supervised exercise into standard care protocols for this population.

Trial Registration: ClinicalTrials.gov NCT06618690; https://clinicaltrials.gov/ct2/show/NCT06618690

International Registered Report Identifier (IRRID): PRR1-10.2196/63891

(JMIR Res Protoc 2025;14:e63891) doi:10.2196/63891

KEYWORDS

breast cancer; exercise; quality of life; muscle strength; pain; efficacy; protocol; physical exercise; fatigue; loss of muscle; physical function; randomized clinical trial; patients with cancer

Introduction

Background

The World Health Organization (WHO) defines breast cancer as a pathology in which cells present in the breast reproduce uncontrollably and form tumors [1]. It is the second most common type of cancer worldwide, with an incidence in 2022 of 2.3 million. Similarly, in 2022, its mortality rate ranked fourth in the world with a rate of 669,418 [2]. Women are the most affected by this disease, with only 0.5% to 1% of cases in men [1].

Genetic mutations play a key role in cancer development. Mutations in *BRCA1* and *BRCA2* increase the risk of breast [3], ovarian, and prostate cancers, while *TP53* is linked to multiple cancers like breast and colon due to its role in cell cycle regulation [4]. *PTEN* mutations are found in breast and thyroid cancers [5], and APC is associated with colorectal cancer [6]. *MLH1* and *MSH2* mutations cause Lynch syndrome, increasing colorectal cancer risk [7]. *KRAS* mutations are common in lung, colon, and pancreatic cancers [8].

Other causes of the disease are diverse: on the one hand, advanced age at motherhood and late menopause are also considered risk factors. On the other hand, breastfeeding, physical exercise and not consuming alcohol are considered protective factors against the disease [9,10].

Treatment will be selected according to the characteristics of the tumor. Generally, it is based on neoadjuvant or adjuvant chemotherapy, radiotherapy, surgery, and hormonal therapy [11].

The prognosis of the disease has improved due to early diagnosis and therapeutic advances. The mortality rate, in turn, has decreased significantly [12,13]. Because of this increase in survival, scientific society is becoming interested in the treatment of the side effects that these patients may suffer, which include both physical and psychological symptoms [14]. Associated physical symptoms that may appear include lymphedema, decreased movement and strength of the upper limb, decreased mobility and strength of the upper limb [15], pain [16], bone loss [17], and sarcopenia [18].

These side effects have a direct impact on the health-related quality of life of patients with cancer [14]. The WHO defines quality of life as the individual's perception of his or her social and cultural way of life, as well as his or her expectations and goals. This is a very open concept that encompasses different aspects of the person from physical health, psychological state, level of independence, social relationships, and personal beliefs [19]. Quality of life measurement is frequently used in breast cancer studies to evaluate the effectiveness and outcomes of treatments [20].

Exercise and Breast Cancer

It has been observed that patients with breast cancer present atrophy of the skeletal muscle apparatus, which is associated with the mitotoxic effects of chemotherapy. Anthracyclines, substances that play a leading role in chemotherapy against breast cancer, have an affinity for the inner membrane of the mitochondria, the place where the body's energy is produced; therefore, this mechanism explains fatigue, atrophy, and muscle pain [21,22].

Various treatments are currently being studied to alleviate these side effects, including therapeutic exercise. Exercise provides short- and long-term benefits to reduce the symptoms that may appear during treatment in each patient. Here, therapeutic exercise specialists play an important role in helping patients overcome their fear and improve their physical abilities [23]. The American College of Sports Medicine says exercise is associated with improved survival after developing cancer [24].

The health professionals in charge of applying this type of therapy must evaluate each patient individually and adapt the exercise prescription to each one of them. The ideal type of exercise for these patients is one that includes a combination of aerobic and resistance exercise, the intensity of each of these parts will be determined by the characteristics of the patient [25,26].

There is evidence that professionally supervised physical exercise has positive results compared to unsupervised exercise. Research has shown evidence that it positively influences decreases anxiety, depressive symptoms, and fatigue, improves quality of life and physical function, and there is no risk of exacerbating upper limb lymphedema. Even people who have already developed lymphedema can perform resistance exercises. In 2000, Harris and Niesen-Vertommen [27] were the first to start strength studies with people with lymphedema, as the existing recommendations so far were the rest of the affected limb [27-30].

The objective of this project is to develop a randomized clinical trial to determine the efficacy of a supervised exercise program on pain, physical function, and quality of life in female patients with cancer.

Methods

Hypothesis

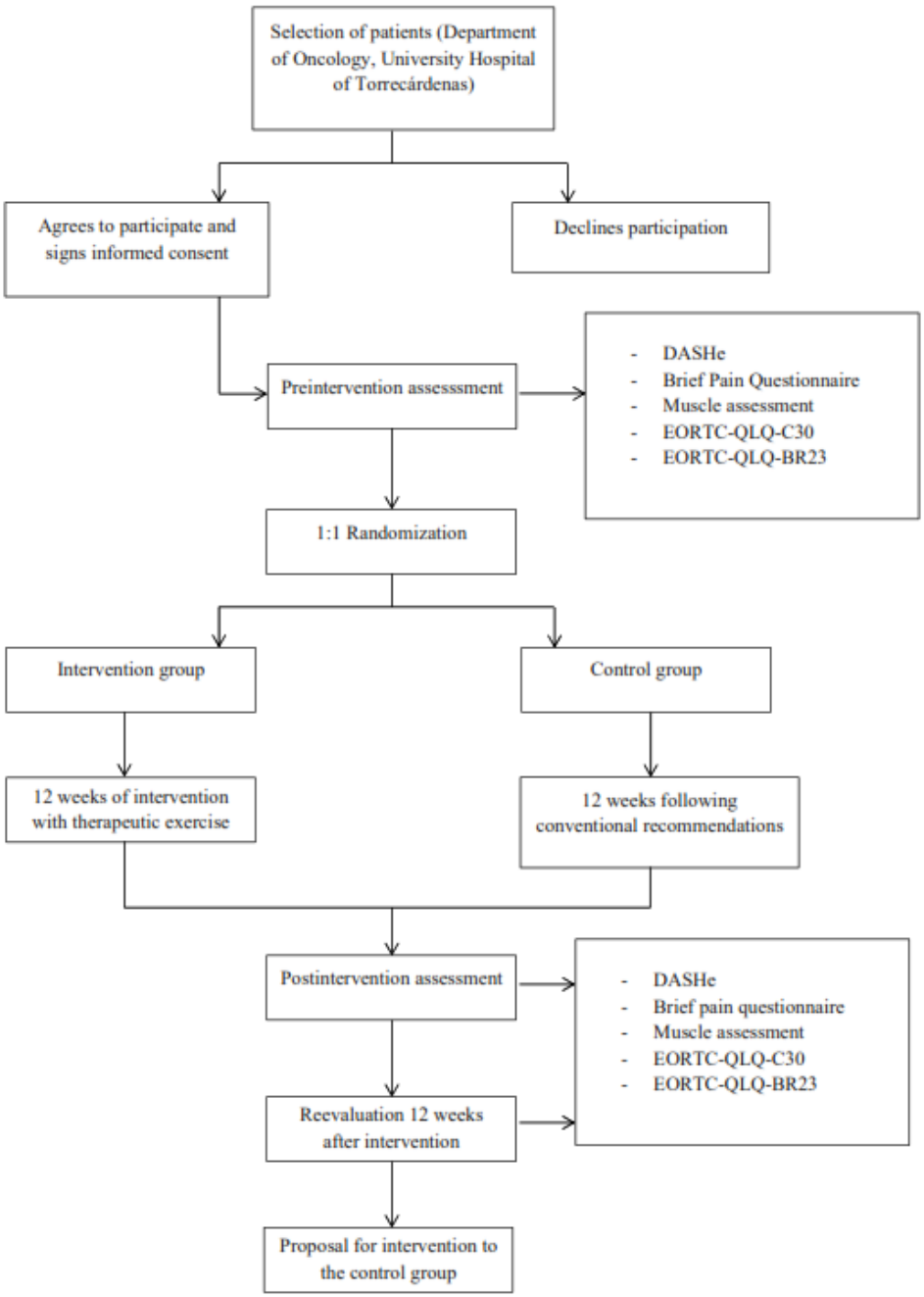
- A supervised exercise program reduces pain and improves physical function and quality of life in female patients with cancer compared to a control group not receiving the exercise program.
- The beneficial effects of the supervised exercise program are maintained over time at least 12 weeks after the end of the program.

Study Design

This study will be a single-blind, randomized clinical trial. To determine the efficacy of a therapeutic exercise program on the different dimensions of quality of life, physical function, and pain in patients with cancer. Once the participants have been recruited, they will be randomly assigned to 2 groups (intervention group and control group). Three assessments will be made: initial assessment, assessment after the end of the intervention, and assessment 12 weeks after the end of treatment. The intervention group will follow a 12-week therapeutic exercise plan, and the control group will follow the usual recommendations for this type of patient. After this last

assessment, the participants in the control group will be offered the intervention. (Figure 1). Approval will be sought from the ethics committee of the University Hospital of Torrecárdenas.

Figure 1. Untitled.



Study Population

The participants will be recruited through the oncologists of the University Hospital of Torrecárdenas. The inclusion criteria will be the following: women aged between 45 and 65 years (age range with the highest incidence in Spain), with oncologic treatment completed less than 3 months ago, without metastasis, without pathologies that contraindicate exercise, and who have agreed to sign the informed consent form. The exclusion criteria will include: not attending scheduled sessions to instruct on the exercises to be performed, being part of other studies, undergoing another type of therapy, and pregnant patients.

The selected age range of 45 to 65 years for participants is based on epidemiological data indicating that this demographic encompasses the highest incidence of breast cancer in Spain. This range ensures a representative sample for evaluating the intervention's efficacy while excluding populations less likely to face similar diseases and treatment dynamics. Additionally, menopause is included as an independent variable in the analysis due to its significant influence on both physiological and psychological responses to breast cancer treatment and exercise interventions. Hormonal changes associated with menopause can affect musculoskeletal health, fatigue levels, and overall quality of life, making it a critical factor to consider when evaluating the intervention’s outcomes on pain, physical

function, and quality of life [31]. By accounting for these variables, the study aims to provide a nuanced understanding of how menopausal status may modulate the benefits of supervised exercise in patients with cancer.

Sample

To calculate the sample size, the QuestionPro software (QuestionPro Inc) was used [32]. It consists of software that, among other functions, incorporates a sample calculator for research.

Based on breast cancer morbidity data in the province of Almeria for 2022, published by the National Institute of Statistics [33], the calculation assumed a moderate effect size of 0.5, based on prior research on exercise interventions in similar populations. To ensure sufficient sensitivity to detect meaningful differences, the significance level (α) was set at .05 (2-tailed), and the study power (1–β) was set at 80%. Considering these assumptions, an initial sample size of 280 participants was determined. However, recognizing the potential for participant dropout, which is common in exercise-based trials, we accounted for an estimated attrition rate of 15%. To compensate for this and maintain statistical power, the final sample size was adjusted to 325 participants.

This approach ensures that the study is adequately powered to detect significant differences between the intervention and control groups for the primary outcomes. If further specifics or expanded parameters are required, we are happy to provide additional details. This explanation aims to address editorial concerns and clarify the robustness of our calculation methodology.

In the beginning, an attempt will be made to recruit the estimated size of participants; if this cannot be done, a smaller sample size will be used, assuming a decrease in the confidence level of the results.

Randomization

All participants have the same probability of belonging to either group. Assignments will be randomized with a 1:1 ratio using the OxMaR software (OxMaR Inc) in its Spanish version [34].

Measuring Tools for Evaluation

Disability of the Arm, Shoulder, and Hand Questionnaire

Self-administered and validated questionnaire in Spanish, the original questionnaire was first published in 1996 [35]. This measuring instrument assesses the impact of processes occurring in the upper limb. This questionnaire consists of 30 items and 2 optional modules. The score obtained is transformed to a scale from 0 to 100, where higher scores show a worse result. It shows a high internal consistency (Cronbach α=0.96) [36].

Brief Pain Questionnaire

This questionnaire is a pain assessment instrument used to measure pain intensity and its impact on the patient's daily life; the original questionnaire was developed at McGill University in 1971, with an internal consistency of 0.7 [37]. The questionnaire used in the study was validated in Spanish in patients with neoplastic pain. It consists of 11 items on a Likert-type scale from 0 to 10 (where 0=no pain and 10=worst possible pain) and 15 additional items that assess the impact of treatment on pain relief. It presents a high internal consistency, with Cronbach α being higher than 0.7 in all dimensions (0.89 for pain intensity and 0.87 for impact on daily life) [38].

Muscle Assessment

Muscle strength will be assessed using a 1 maximum repetition (MR) protocol for the chest press in the horizontal plane and the leg press, as this is the most commonly used muscle assessment test in similar studies, according to the meta-analysis by Hasenoehrl et al [39]. One RM is defined as the maximum weight at which only 1 repetition can be performed [40].

For the evaluation, we will start with an initial warm-up series with 6 repetitions, the initial weight will be 2.5 kg and 18 kg for the upper and lower limbs, respectively. According to the perceived effort of each participant, we will start with an approximate weight for the one RM test, until it increases according to tolerance to find out the 1 RM weight of each participant. This is the strategy followed by Brown and Schmitz [41]. The assessment of the upper limb will be performed unilaterally in order to objectively evaluate the difference between the affected and healthy upper limb, as was done by Hagstrom et al [42]. Thus, we will start with 1.25 kg for each upper limb.

EORTC-QLQ-C30 Quality of Life Questionnaire

A questionnaire was created by the European Organization for Research and Treatment of Cancer (EORTC) to assess the quality of life in patients with cancer. The organization provides the questionnaire translated into several languages, including Spanish. It consists of 30 Likert-type questions that assess various aspects of quality of life, including the ability to perform activities, symptom control, general perception of health, and other relevant aspects such as difficulty breathing, insomnia, anorexia, constipation, diarrhea, and economic impact [43].

The EORTC-QLQ-C30 presents in most of the studies performed a good internal consistency (Cronbach α=0.7 for most of the scales). This questionnaire, based on a specific formula, obtains results on a scale from 0 to 100, where a higher score indicates a better quality of life. The scores for each question within each dimension (physical, emotional, and social functioning) are summed [44]. Within this questionnaire, there are specific modules that complement it for some types of cancer, for breast cancer they have created the EORTC QLQ-BR23 [44].

EORTC Quality of Life Questionnaire, QLQ-BR23

This questionnaire is a specific module for breast cancer that complements the previous questionnaire. Two main aspects are assessed here: functional scale (body image, sexuality, and concern for the future) and symptom scale (breast symptoms, arm, and side effects of treatment). It presents in most of the studies carried out a good internal consistency (Cronbach α=0.7) [44]. Like the general module, this questionnaire has a score from 0 to 100, where they are transformed according to a formula by specific dimensions.

Ethical Considerations

In this study, clinical investigations involving medical devices are conducted on human participants. In order to safeguard the integrity, well-being, and privacy rights of the participants, the study is carried out in accordance with the guidelines set forth by the Declaration of Helsinki of the World Medical Association (64th General Assembly, Fortaleza, Brazil, October 2013), the Council of Europe Convention on Human Rights and Biomedicine, Good Clinical Practice standards, Royal Decree 1090/2015 of December 4, which regulates clinical trials with medicinal products, the Research Ethics Committees for Medicinal Products and the Spanish Registry of Clinical Studies, and Royal Decree 1591/2009 of October 16th, which regulates medical devices [45,46].

The study protocol will be submitted to the Bioethics Committee at the University Hospital of Torrecárdenas for review and approval in February 2025, during the preparatory phase. Ethical approval will be obtained before the initiation of any participant recruitment or data collection activities, in compliance with ethical standards. Recruitment is scheduled to begin in February 2025, contingent on receiving ethical approval. The ethical approval number will be provided in the final manuscript once it is obtained.

Before the study commences, explicit informed consent will be requested from participants via a digital form, clearly explaining the study's objectives and participation details (Multimedia Appendix 1). Participants will have the ability to opt out at any stage without consequences. For any secondary data analyses, it will be confirmed that prior institutional review board–approved consent covers reuse without requiring additional consent. Compliance with Spanish Organic Law 3/2018 of December 5, 2018, on the Protection of Personal Data and the guarantee of digital rights [47], will also be ensured. Participant privacy will be rigorously protected, and all collected data will be anonymized or deidentified to prevent the disclosure of personal information. The data will be securely stored and used exclusively for this research project and any resulting publications. If any identifiable data is included in images or supplementary materials, explicit consent will be obtained and the necessary documentation will be submitted as supplementary files.

Participants will not receive any financial compensation for their participation in the study. However, they will be provided with detailed information about the study's objectives, potential benefits, and their rights as participants to ensure transparency and fairness in the research process. These measures ensure that the study adheres to the highest ethical standards and prioritizes participant safety, confidentiality, and informed consent in compliance with national and international research ethical regulations.

Intervention

The proposal will be carried out in the intervention group (group 1), while the control group (group 2) will undergo the conventional recommendations indicated for this type of patient.

A supervised training plan will be carried out for 12 weeks with a frequency of 3 sessions per week with a duration of 60 minutes, an ideal estimate according to the meta-analysis of Montaño-Rojas et al [48]. In first 2 weeks, the group exercises will be performed to familiarize the participants with the exercises and then each participant will perform them at home with a review every 2 weeks to assess the increase of the load.

The exercises and loads included in this treatment plan have been designed and modified based on previous clinical trials [39,49-51]. The training plan will work the upper limbs, lower limbs, and trunk. All sessions begin with a general warm-up, which will be previously instructed to the participants, in which the heart rate will be increased (Multimedia Appendix 2). After a 2-minute break, the specific block of each session will begin (Textbox 1 and Multimedia Appendix 2). All exercises will be performed with dumbbells, elastic bands, and a ball. We will consider the age of each participant, making minor adjustments to the initial exercise program as needed.

Three sets of all exercises will be performed with 10-12 repetitions at 50%-60% 1 MR (previously calculated for each participant in each of the exercises) with 1 minute of rest between sets. Finally, we will conclude with general stretching previously instructed (Multimedia Appendix 2). The control group will participate in a general education and wellness program designed to promote overall well-being and maintain a basic level of activity. This program, matched in duration to the experimental group, will include regular counseling sessions covering topics such as nutrition, stress management, sleep quality, and relapse prevention. In addition, participants will be encouraged to engage in low-impact physical activities, such as short walks and gentle mobility exercises. For the experimental group, the supervised exercise program aims to improve pain, physical function, and quality of life through a variety of carefully selected exercises tailored to each participant's needs. These include stretching exercises, such as pectoral stretches for chest mobility and shoulder and arm stretch to enhance the range of motion and relieve tension. Strength training exercises using resistance bands or light weights will focus on improving upper limb and core strength to enhance posture and stability. Aerobic activities like walking or stationary cycling will be incorporated to boost cardiovascular endurance and mobility. Flexibility exercises, including range-of-motion activities, will help maintain and improve overall flexibility, while balance and coordination exercises will enhance stability and prevent falls. Muscle endurance will also be developed through lightweight or resistance band exercises. The program's design emphasizes a personalized approach, guided by physiotherapists or exercise specialists, to ensure safety and maximize benefits for patients with cancer.

Textbox 1. Strength exercises included in the training plan.

Session 1

- Squats
- Biceps curl
- Superman in quadruped
- Dumbbell chest press in horizontal plane
- Shoulder rotators with elastic band
- Dumbbell rowing

Session 2

- Proprioceptive shoulder exercises with ball on wall
- Static stride
- Upper limb flexion with ball on wall
- Isometric abduction with ball (elbow 90º)
- Prone spine extension
- Quadruped hip abduction

Session 3

- Dumbbell triceps extension
- Quadruped gluteal kick
- Triceps kick with dumbbell
- Lateral shoulder raises with dumbbells
- Dead weight with dumbbells
- Rowing with elastic band

Data Management and Analysis

Once all the measurements included in the measuring instruments section have been taken, they will be recorded and analyzed using SPSS (version 28.0; IBM Corp) [52].

The quantitative data of the sample will be described by number, mean, and SD.

A result is understood to be significant when $P \leq .05$. In statistics, significance or internal consistency indicates that there is congruence between the different results obtained [53].

For the statistical analysis of the results of this test, 2 tests will be performed as follows.

- Repeated measures ANOVA: This analysis allows us to evaluate whether the differences between the results of the same test in a participant are statistically significant. If so, it also determines what percentage of the effect is attributable to the intervention and not to other factors [53]. Two ANOVA analyses will be performed: one comparing the preintervention assessment with the postintervention assessment, and the other comparing the postintervention with the assessment 12 weeks later. This test will check if there is a significant improvement in the different measures of pain, physical function, and quality of life. Finally, the paired comparison table will tell us in which measurement periods the differences are found [53].
- ANOVA of differences: In this case, the differences between the results of the intervention group and the control group will be compared [53]. With the results obtained from this statistical analysis, it will be possible to verify whether the differences between groups in terms of pain, physical function, and quality of life are significant between the participants receiving the intervention and those belonging to the control group.
- MANOVA: To assess the overall effect of the intervention and determine whether the hypotheses can be accepted or refuted, the following hypotheses will be tested [53].

These statistical analyses described the significance between the test results of the same individual and the significance between the different results of both groups of the test that will be tested.

Results

Recruitment and data collection will begin in the third quarter of 2024. Data analysis will be conducted between the first and second quarters of 2025. No results are available at the time of this intervention protocol.

Discussion

Principal Findings

This randomized clinical trial is intended to test the efficacy of an exercise program applied to patients with cancer.

Most of the patients present a deterioration of their quality of life and physical function after suffering breast cancer, physical exercise can be a great ally to counteract these negative effects [23-30]. Therefore, the results obtained in the intervention group are expected to be significantly better than those of the control group. It is likely that there will be benefits to the intervention in some aspects and not in all the variables measured in the study. In addition, the benefits provided are expected to be maintained in the long term, hence the reassessment 12 weeks after the end of the intervention.

A compelling finding emerges from the systematic review by Montaño-Rojas et al [48], which demonstrates significant muscle strengthening benefits, even with low-intensity and short-duration exercise programs. Participants in these programs showed notable improvements in muscle strength compared to those who did not engage in physical activity. This aligns with the meta-analysis by Shen et al [54], which reported improvements in pain and joint amplitude of the upper limb following physical exercise after radiotherapy in breast cancer. These findings complement international guidelines, such as those from the Clinical Oncology Society of Australia (COSA), which recommend at least 150 minutes of moderate aerobic exercise and 2 resistance training sessions per week, tailored to the individual's health and treatment phase. Like the protocol in this study, COSA highlights the benefits of exercise in reducing fatigue, improving musculoskeletal health, and enhancing quality of life [30]. However, COSA also emphasizes the routine integration of exercise into oncology care, a practice that remains inconsistently implemented across European health care systems. This comparison underscores the universal importance of exercise in patients with cancer and highlights the need for tailored adaptations to local health care systems and cultural contexts to maximize accessibility and impact [29].

In line with the aforementioned, Zengin Alpozgen et al [55] obtained positive results in their clinical trials for pain relief. In contrast, the results of Loudon et al [56] are not significant in terms of pain reduction. This difference may be due to the fact that the first two use exercises that involve greater resistance and dosage; in contrast, the latter performs an intervention of a single session per week based exclusively on yoga exercises.

On the one hand, Aydin et al [57] in their clinical trial, show that physical exercise not only has a positive influence on the physical condition of the participants but is also strongly related to the improvement of mental health. In her study with 48 participants, she used the EORTC-QLQ-C30 and WHO Quality of Life–Brief Version scales to measure the quality of life of the sample. On the other hand, Koevoets et al [58] used the EORTC-QLQ-C30 scale to measure the impact of exercise on cognitive function in patients with breast cancer after chemotherapy. Reporting positive results in the participants of the intervention group. On the contrary, Bruce et al [59] in a clinical trial with 392 participants, found no significant differences in the improvement of mental health in participants who had performed physical exercise and those who had followed the usual recommendations. These differences may be due to the sample size as the latter study presents a significantly larger sample than the previous ones. They may also be due to the dosage and type of exercises proposed in the intervention; since Aydin et al [57] and Koevoets et al [58] perform aerobic and general strength exercises of all muscle groups, while Bruce et al [59] only perform a shoulder strengthening program in flexion, abduction, and external rotation.

Regarding when to start the exercise program, authors such as Carayol et al [60] recommend starting a supervised exercise program during chemotherapy or radiotherapy treatment, combined with an adequate diet to improve health status and the consequences of these treatments.

Vincent et al [61] compared in a randomized clinical trial the results obtained in a group that started the intervention with exercise during chemotherapy and in another group that started it after the end of chemotherapy, not observing significant differences between the two and highlighting the importance of performing them either during or after.

From another point of view, not only is the impact of physical exercise after breast cancer being investigated but there is already research that is beginning to show positive results in the prevention of breast cancer through exercise in populations with risk factors. An example of this is the studies by Coletta et al [62] and Khosravi et al [63] where they performed interventions with physical exercise in postmenopausal participants and with various other risk factors to see the impact of this training with leptin and myokine levels. Prevention of both first-time disease onset and recurrence, aided by physical exercise could be a future line of research that will gain more momentum.

The strengths of this study are randomization, as well as the use of previously validated assessment tools, some of them specific to breast cancer, such as the EORTC QLQ-BR23. The variables analyzed range from pain to physical function and quality of life. In addition, it is based on a protocol of resistance exercises, which, according to previously cited research, provides better benefits.

The main limitation of this study is that the intervention will be carried out through patients recruited from a single referral hospital, although a large sample is achieved, it would be interesting for future studies to have a variety of more heterogeneous participants and better generalize the results. In addition to making longer-term measurements to see how the possible improvements acquired are maintained. Furthermore, the study's results may be influenced by factors like hormonal variables, age, and treatment responses. Hormonal changes, such as menopause, can affect treatment effectiveness and side effects. Additionally, younger patients may experience different side effects or treatment responses due to metabolism, health, and comorbid conditions.

Conclusions

Oncology research is advancing at a very fast pace. Therefore, addressing the side effects of the disease is a great success for these patients, who today have a high survival rate. Therapeutic exercise is a great ally in improving strength, pain, and joint mobility after breast cancer, as well as positively influencing the improvement of quality of life.

Acknowledgments

This study received grants aimed at supporting recognized research groups from public universities of Castilla y León starting in 2024 (BU043G24). All authors have approved the final version of the manuscript and agree to be accountable for all aspects of the work. Generative artificial intelligence and artificial intelligence–assisted technologies were not used in the writing process. The study has been conducted with resources available to the authors and their affiliated institutions.

Data Availability

The data that will support the findings of this study will be derived from patient medical record data. The datasets generated during and/or analyzed during this study are available from the corresponding author on reasonable request.

Authors' Contributions

JGM was responsible for conceptualization, formal analysis, investigation, methodology, software, visualization, and drafting as well as reviewing and editing the manuscript. OSV contributed to conceptualization, data curation, formal analysis, investigation, methodology, project administration, resource management, supervision, validation, visualization, and both drafting and revising the manuscript. MSV took charge of the methodology and the preparation and review of the manuscript. JHOH played a role in conceptualization, data curation, formal analysis, investigation, methodology, project administration, supervision, validation, visualization, and manuscript preparation, including drafting and revisions. All authors reviewed and approved the final manuscript and took full accountability for all aspects of the work.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Informant consent.
[DOCX File , 25 KB - resprot_v14i1e63891_app1.docx]

Multimedia Appendix 2
Exercises session.
[DOCX File , 706 KB - resprot_v14i1e63891_app2.docx]

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Abbreviations

COSA: Clinical Oncology Society of Australia
EORTC: European Organization for Research and Treatment of Cancer
MR: maximum repetition
WHO: World Health Organization

Edited by A Schwartz; submitted 05.07.24; peer-reviewed by C Fox-Harding; comments to author 27.08.24; revised version received 30.09.24; accepted 10.01.25; published 12.03.25.

Please cite as:
García-Molina J, Saiz-Vázquez O, Santamaría-Vázquez M, Ortiz-Huerta JH
Efficacy of a Supervised Exercise Program on Pain, Physical Function, and Quality of Life in Patients With Breast Cancer: Protocol for a Randomized Clinical Trial
JMIR Res Protoc 2025;14:e63891
URL: https://www.researchprotocols.org/2025/1/e63891
doi:10.2196/63891
PMID:

Protocol

Demonstrating Tactical Combat Casualty Care in Simulated Environments to Enable Passive, Autonomous Documentation: Protocol for a Prospective Simulation-Based Study

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Abstract

Background: The Telemedicine & Advanced Technology Research Center (TATRC) commenced a new research portfolio specifically addressing Autonomous Casualty Care (AC2) in 2023. The first project within this portfolio addresses the current and historical challenges of capturing tactical combat casualty care (TCCC) data in operational settings.

Objective: The initial autonomous casualty care effort, the Passive Data Collection using Autonomous Documentation research project, conducts systematic, simulated patient and casualty care scenarios, leveraging suites of passive sensor inputs to populate a data repository that will automate future combat care.

Methods: To obtain the required datasets, TATRC will engage care provider participants who provided consent in one of 6 randomized simulated TCCC scenarios leveraging an institutional review board–approved office protocol (#M-11057). These simulations will leverage mannikins (low and high fidelity) and live simulated patients (eg, human actors who provided consent). All consenting participants (eg, both the care providers and live simulated patients) will be equipped with suites of sensors that will passively collect data on care delivery actions and patient physiology. Simulated data is being collected at Fort Detrick, Maryland; Fort Sam Houston, Texas; Fort Indiantown Gap, Pennsylvania; Fort Liberty, North Carolina; and a commercial site in Greenville, North Carolina.

Results: Across all research locations, TATRC will collect and annotate approximately 2500 simulation procedures tasks by March 2025. These study data will generate the first machine learning and artificial intelligence algorithms to populate Department of Defense (DD) Form 1380 fields accurately and reliably. Additional data collected past March 2025 will be used to continue to refine and mature the algorithm.

Conclusions: The military health care system (MHS) lacks real-world datasets for TCCC care at the point of injury. Developing a data repository of simulated TCCC data is required as an essential step toward automating TCCC care. If TATRC's research efforts result in the ability to automate care delivery documentation, this will alleviate the cognitive burden of TCCC care providers in austere, chaotic environments. By generating a TCCC data repository through this Autonomous Documentation research project, TATRC will have opportunities to leverage this research data to create machine learning and artificial intelligence models to advance passive, automated medical documentation across the health care continuum.

International Registered Report Identifier (IRRID): DERR1-10.2196/67673

(JMIR Res Protoc 2025;14:e67673) doi:10.2196/67673

KEYWORDS

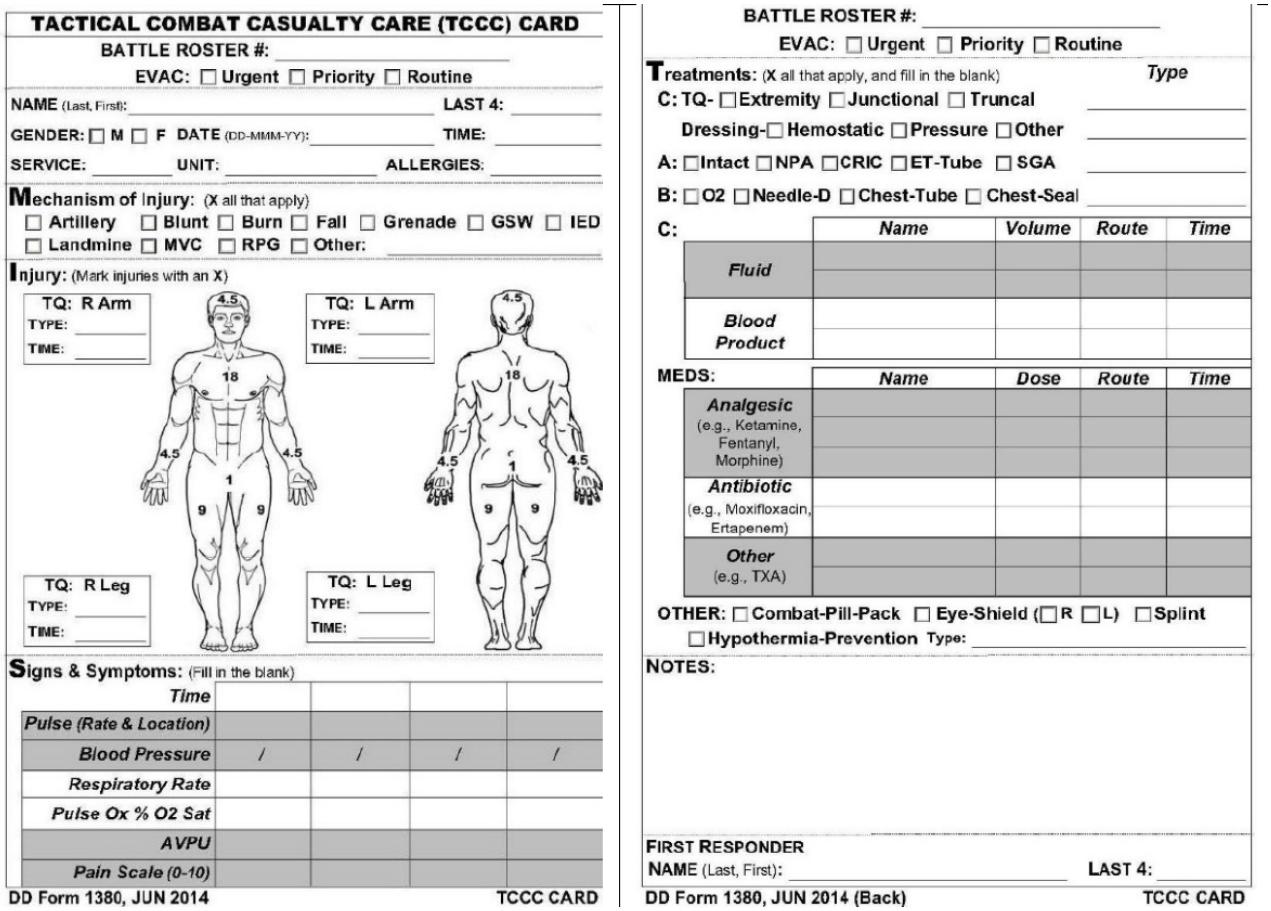
tactical combat casualty care; TCCC, automation; medical documentation; DD form 1380; combat casualty care; artificial intelligence; AI; machine learning; ML; point of injury; POI; simulation; military health; passive data collection; sensors; algorithms; medical record

Introduction

The military health care system (MHS) is a Joint Service health care system that operates under the Defense Health Agency (DHA) [1]. Within this health care system, there is a diversified set of health care data ranging from routine preventative services for service members (SMs) and their families to battlefield casualty statuses. Due to the nature of its complexity, the MHS thrives in stable connected environments and languishes in operational settings where network communications are compromised or insecure. Thus, when our SMs are located in various tactical environments in multidomain operations, the MHS lacks a robust, accurate, and reliable methodology to collect, store, and track health data, often referred to as tactical combat casualty care (TCCC) data.

Historically, TCCC data has been manually collected using the DD Form 1380, also known as the TCCC card (Figure 1). The TCCC card is intended to be filled out by combat medics at point-of-injury (POI) and Role 1 and attached to the casualty's uniform.

Figure 1. DD Form 1380, the TCCC card.



The intent is for this DD Form 1380 to travel with the casualty until they reach their final treatment destination where its contents will be populated into the electronic medical record in the MHS. Current assumptions, which constrain the success of the manual TCCC data capture process, include the following: (1) the DD Form 1380 will be present at the time of the SM's final treatment destination, (2) the DD Form 1380 will be undamaged and legible to transcribe into the medical record, and (3) there will be abundant resources to transcribe all DD Form 1380 data entries or fields into that record.

Due to the chaotic nature of conflict environments, most of the DD Form 1380s are either incorrectly or inadequately completed. Capturing the medical care provided in these austere venues is secondary to saving lives; however, the need for timely, accurate medical documentation remains for acute care and long-term care management [2-4]. In the near term, this data generates valuable information for higher echelons of care, medical resupply, and logistics systems, and command situational awareness. The long-term benefit is the ability to provide a basis for evaluating quality of care and benchmarking key metrics for quality improvement efforts and to leverage machine learning (ML) and artificial intelligence (AI) to enhance future care delivery in the tactical environment, as well as to inform clinical decision support systems and algorithms deployed in these settings [5].

In May of 2023, the telemedicine and advanced Technology Research Center (TATRC) commenced a new Autonomous Casualty Care (AC2) research portfolio with the initial objective of creating an innovative, trustworthy, reliable solution to enhance TCCC and improve medical documentation in the MHS. TATRC intends to develop a passive (ie, with minimal human effort and distraction), autonomous documentation (AutoDoc) solution of medical care in operational environments comprising a system of sensor suites that passively collect accurate and reliable data about casualty status, care provider actions, and real-time resource usage.

The goal will be for the sensor suites to passively and autonomously document data for a digital DD Form 1380. To accomplish this, TATRC will (1) identify which commercial off-the-shelf (COTS) sensors are most suitable to collect TCCC data elements required to populate the DD Form 1380; (2) conduct human subjects research using participants who perform TCCC skills in controlled, simulated environments; and (3) annotate all sensor suite data collected to build a TCCC dataset for current and future ML and AI algorithms to leverage.

Methods

Overview

Since the AC2 mission realignment in May 2023, TATRC has worked in partnership with the United States Army Medical Research and Development Command (USAMRDC) Institutional Review Board Office (IRBO) to ensure optimal human participant protections can be achieved within the scope of our research study. The novelty of developing a study design that leverages sensor suites and simulated data across multiple locations and includes iterative improvements in the technology configuration features due to the agile development process is groundbreaking for the organization. TATRC received its initial human subjects research protocol approval (#M-11057) from the USAMRDC IRBO in February 2024 to conduct this research and will continue to amend the protocol as new collaborators onboard and new methodologies are adapted, as required. Study personnel will follow the protocol requirements including consenting mandates as directed by the IRBO.

Passive data collection using AutoDoc is a research, development, test, and evaluation (RDT and E) project that will be conducted in three separate stages: (1) selection and procurement of sensor suite components, (2) data collection via live human actor simulations, and (3) data annotation.

Sensor Suites

Individual COTS sensors were bundled into synchronized technology suites designed to capture both patient physiological data and care provider interventions. These passive sensor suites generate data that can be used to generate an electronic DD Form 1380. The categories of sensors used in this research project are listed in Table 1. The COTS sensors selected for the research project's suite were based on technology maturity level, National Defense Authorization Act compliance, suitability for the operational environment (eg, durability and ruggedization), and ability to extract data from the sensors (eg, nonproprietary data formats). Before leveraging the passive sensor suites in the AC2 research project, the technologies were systematically evaluated through a series of assessments. The sensor suites are worn by consented participants (eg, both the care providers and live simulated patients) in the simulated TCCC scenarios for data collection.

Table 1. Categories of commercial off-the-shelf sensors integrated into sensor suites.

Sensor category	Sensor type
Primary care providers	
Audio	Microphone clipped to a collar, lapel, or helmet
Identification readers	Near field Communication cards attached to items in the care provider's bag
Inertial measurement unit	Wrist-worn inertial measurement units to track hand movements
Mounted video	Traditional video and infrared video
Simulated Patients	
Vital signs monitor	Velcro blood pressure cuff and skin safe adhesive electrocardiogram electrodes leads, adhesive vitals monitoring patch (blood pressure, heart rate, respiration rate, temperature, and SpO_2[a]), and finger pulse oximeter

[a]SpO_2: oxygen saturation.

Data Collection

Live, controlled, simulated scenarios will be used for all passive sensor suite data collection activities. The purpose of conducting live simulation events is to observe participants performing TCCC-related activities. These structured data collection events allow the research team to obtain relevant data for future algorithm development. The purpose of the data collection events is research-specific, and not to educate, assess, or help caregivers self-identify knowledge gaps.

TATRC has identified Department of Defense (DoD) affiliated collaborators to generate the volume of data needed to train the ML and AI. TATRC personnel are currently collecting data at 5 different locations at Fort Detrick, Maryland; Fort Sam Houston, Texas; Fort Indiantown Gap, Pennsylvania; Fort Liberty, North Carolina; and a commercial site in Greenville, North Carolina.

Settings

Live simulation data collection events are conducted at the 5 approved research locations. At each location, a series of physical spaces are dedicated to simulating the prehospital roles of care: POI (casualty collection point or equivalent), Role 1 (battalion aid station or equivalent), Evacuation to Role 2, and Role 2 (Forward Surgical Team or equivalent). In addition, the equipment and medical supplies that are available at each prehospital venue are accessible to the research participants. Data collection locations can create immersive virtual environments, sounds, or other environmental characteristics (smoke, smells, etc) to create a realistic combat environment. In addition, an audiovisual system (AVS) is leveraged to record and archive activities conducted during the data collection events. When data are collected in a formal laboratory venue, the AVS is fixed, but in other locations, a portable AVS is leveraged (Figure 2).

Figure 2. Staged simulation scenario of primary care provider triaging simulated patient (Mannikin).

Study Participants

Participants will be split into two groups: (1) care provider and embedded participant or (2) simulated patient, based on inclusion criteria. The research team is using video, audio, and kinematic recording equipment to collect first-person data from care providers and embedded participants during the TCCC scenarios. The first-person sensors will record casualty injury patterns, care and tasks provided by the care providers, equipment and supplies used, and other environmental factors. In addition, vital signs monitors, such as finger pulse oximeters, blood pressure cuffs, adhesive electrocardiography patches, and so on, will be placed on the simulated patient participants to record physiological data.

Inclusion Criteria

Care provider and embedded participants specific inclusion criteria. This research population group must be a certified provider, as defined below, to participate, ensuring that the simulated data collected reflects data that would be collected by a care provider in a real battle space (Textbox 1). Care provider participants will be split into 2 separate roles during a scenario:

1. Primary care provider (PCP): The PCP is the person providing care to the patient in the scenario and will be required to wear the system of sensors during the simulation.
2. Embedded participant (EP): The EP assists the PCP throughout the scenario by updating vitals, holding items, injecting added pressure onto the PCP, prompting the next steps, and so on.

Textbox 1. Inclusion criteria and exclusion criteria by participant role.

Inclusion criteria

- Primary care provider or embedded participant
- Are between the ages of 18 and 65 years
- Must have one or more of the following:
  - Active tactical combat casualty care certifications for All Service Members, the Tier 1 course
  - Working knowledge of combat casualty care skills through medically related training (eg, combat medic or equivalent training)
  - Deployment with medical experience in the last 36 months
- There are no preexisting conditions that would negatively impact their ability to provide care for a 20-minute simulated trauma care scenario or work outside for prolonged periods of time (eg, extreme allergies or extreme reactions to sun exposure, etc)
- Simulated Patient
- Age 18 years or older
- Must have the ability to act injured and unconscious for the duration of a 20-minute patient care scenario. The range of injury acting will vary from a state of unconsciousness (ie, lying still) to yelling and writhing in pain

Exclusion criteria

- All participants
- Younger than 18 years
- Currently pregnant
- History of abnormal heart rate (eg, arrhythmias)
- Internal electric medical devices (eg, pacemakers)
- Uncontrolled high blood pressure disorders
- Uncontrolled breathing disorders
- Severe allergies
- Epilepsy
- Primary care provider or embedded participant
- Younger than 18 years or older than 65 years
- Do not hold an active certification for tactical combat casualty care Tier 1
- Simulated Patient
- Younger than 18 years
- Unable to meet the physical requirements of acting as an injured or unconscious patient, such as an inability to act in a predetermined way for up to 20 consecutive minutes or having an adverse response to prolonged time outdoors

Exclusion Criteria

For generalized and participant-specific exclusion criteria, please see Textbox 1.

Procedures

After recruitment, enrollment, and consent, each participant will be placed into one of 6 simulated scenarios that were scripted for this project. Participants will be paired based on similar levels of expertise described in Bloom's Taxonomy and then randomized into provider type groups [6].

A total of 6 combat casualty care scenarios were designed and written by TATRC's combat medic subject matter experts. The injury patterns were developed using common battlefield mechanisms of injury and real-world scenarios. The majority of the TCCC tasks in the scenario correspond to an Individual Critical Task List item for the 68W Combat Medical Specialist, with only a few exceptions. The severity of the casualties differs to capture all triage categories and levels of difficulty. Baseline simulations were developed for each scenario by selecting the appropriate patient mannikin, applying relevant moulage (medical makeup), and by selecting the applicable scene location for POI care. The six scenarios are as follows:

> *26-year-old male infantryman injured by small arms fire during dismounted patrol. Patient is unresponsive and has a massive hemorrhage from the face or neck and left inguinal area. Enemy threat has been eliminated, and combat lifesaver (CLS) has been attempting to control bleeding for several minutes unsuccessfully.*
>
> *29-year-old male SM involved in improvised explosive device (IED) explosion. Patient alert to verbal stimuli,*

and complains of 10/10 pain all over. Obvious right leg below knee amputation. Bleeding from right chest and forehead.

23-year-old male SM injured by small arms fire during key leader engagement. Patient suffered multiple gunshot wounds to the left shoulder, left arm, and left leg. Patient presents with moderate bleeding but alert.

25-year-old male platoon leader injured by mounted IED explosion. Patient has shrapnel and burns to the left arm, leg, and torso with minimal bleeding. Patient is alert and complaining of 10/10 pain. Enemy threat in the area has been eliminated and CLS has been attempting to control bleeding for several minutes unsuccessfully.

35-year-old male platoon sergeant injured by mortar strike. Patient is alert and has right arm amputation below elbow and shrapnel wounds to the right side with moderate bleeding. Patient is alert and complaining of 10/10 pain.

31-year-old male involved in an IED explosion. Patient alert to verbal stimuli with complaints of 10/10 pain on left side of body. Patient has burns to neck and face with stridor. Left side "peppered" with minor shrapnel injuries. Patient is found extricated from vehicle and burning process has been stopped. Scene is absent of enemy activity and no percutaneous transluminal angioplasty treatment has been provided.

Before the simulation commences, the PCP is trained on how to use the sensor suite and if using a simulated patient, the appropriate moulage is applied. The participants are then taken to one of two locations, depending on their assigned scenario: (1) indoor laboratory or training facility: fully controlled environment; and (2) outdoor training facility: partially controlled environment, used for scenes with potential for care under fire.

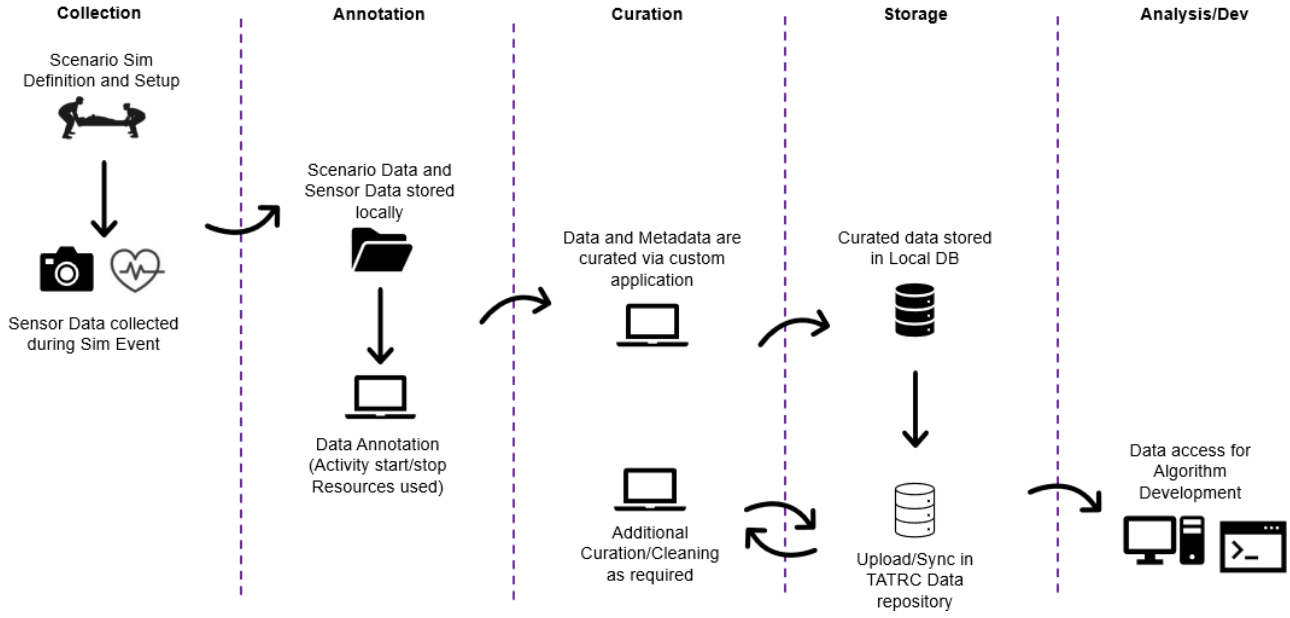
After arriving at their assigned location, each participant is given a scenario brief. The scenario brief contains information on simulation tasks, conditions, and standards, and allows time for the participants to prep their equipment and supplies or ask any last-minute questions.

The data collected from each scripted scenario will differ based on each PCP. Each caregiver will manage the problem set differently based on their personal experiences and knowledge base resulting in individualized outcomes (Figure 3). Only one PCP will manage the simulated patient. The generalized process of how each scripted scenario occurs is as follows:

1. The simulated patient, PCP, and EP are all present at their assigned location.
2. The PCP is trained on the sensor suite technology while the simulated patient is reviewing the script and having moulage applied.
3. The simulated patient, PCP, and EP are given a scenario brief.
4. The start cue is given, and the scenario commences.
5. The simulated patient begins to act out their injuries.
6. The PCP begins performing care to treat the simulated patient, while the EP is standing by. The EP only intervenes if the PCP requests their assistance (eg, to hold equipment or to provide updated patient information), to troubleshoot equipment, or to prompt the PCP.
7. After a determined amount of time, the PCP is notified that evac has arrived.
8. The scenario ends.

From the beginning of the scenario brief to after action reporting, each participant will be engaged in the study for a maximum of 2.5 hours, where 50 minutes is the maximum amount of time a participant can participate in a simulation run.

Figure 3. Autonomous documentation flow diagram from simulation data collection to algorithm development. TATRC: Telemedicine & Advanced Technology Research Center.



Data Annotation

Following the simulation, all simulated TCCC data collected on the sensor suites will be uploaded into TATRC's secure, PIA-approved data repository. The data are considered "unlabeled" and will require annotation with "labels" for future use in algorithm development.

Unlabeled sensor data must be annotated with labels defining a specific action necessary for algorithm development or "training." In this case, the object is to build algorithms that, based on sensor data collected in each scenario (input), infer a specific treatment or procedure was performed by providers (output). For example, if a combat medic is placing a tourniquet, then the algorithm must be able to correctly label this specific act using sensor-generated data including start and stop times. Task start and stop times are recorded relative to the simulation start time. The annotation process can be summarized as follows: annotations are applied to each simulation, and 2 annotators review the video and audio resulting from the simulation.

Individually, the annotators record start and stop times for standardized TCCC tasks of interest. Start and stop time identification is guided by pre-established start and stop time markers specific to each task. Examples of the annotations and descriptions of the time points can be visualized in Table 2 below.

1. Comparison and review: task periods (bounded by start and stop times) are compared between the 2 annotators. Any task with less than 80% overlapping between the annotators must be discussed and reannotated by each annotator. If an 80% overlap is still not achieved, another annotator will annotate and review the data. This process will continue until >80% overlap is achieved.
2. Label combination: the final bounds for each task are defined as the outermost stop and start times between the 2 annotators (ie, the union of A and B). The original start and stop times each annotator records, will also be maintained for transparency.

All annotations will be stored in a spreadsheet linked to simulation metadata via a unique simulation ID. The goal of this project is to develop a cloud-based dataset that will enable ongoing and future ML and AI algorithm development for automatic, passive documentation of DD Form 1380 data fields.

Table 2. Examples of annotations and descriptions of time points.

Task	Start time (s)	Stop time (s)	Duration (s)
Start of scenario	0	76	76
Tourniquet application	85	142	57
Chest seal application	167	253	86
Nasopharyngeal airway	195	214	19
Treat a casualty for a cold injury	270	346	76
Uses sensor	355	465	110
Documentation	404	579	175
Administer medication	542	579	37
Chest needle decompression	583	612	29
Initiate an intravenous	652	717	65
Uses sensor	681	708	27
Uses sensor	715	738	23
Initiate an intravenous	739	848	109
Administer medication	854	917	63
Administer fluids through an infusion	884	980	96
Documentation	923	954	31
Administer tranexamic acid	956	1048	92
Uses sensor	1010	1050	40
Documentation	1053	1116	63
Bag-valve-mask assisted ventilation	1125	1294	169
Chest needle decompression	1143	1164	21
Documentation	1209	1294	85
End of scenario	1293	1303	10

Ethical Considerations

Ethics Review Approvals or Exemption

This protocol was reviewed and approved by the USAMRDC IRBO, which included human subjects' ethics review. The approved protocol (#M-11057) was classified a minimal risk to human participants and undergoes annual continuing reviews by IRBO to ensure the safety and ethical considerations of research on all human participants in our research.

Informed Consent

Within 48 hours before the simulation scenarios are conducted, one of the research team members will provide the individual with a mailed hard copy or emailed electronic copy of the consent to review and contact them over either a secure telecommunication software or face-to-face, whichever is most convenient for the potential study participant. In either form of meeting, the ombudsperson is also present to explain that participation is voluntary and that the information provided about the research is consistent with the institutional review board (IRB)–approved materials. If over telecommunication software, the research staff member ensures the participant is in a private space and can adequately hear all explanations. If the consent process is in-person, the process takes place in a private area. The trained research effort staff members are completely trained on providing all necessary information to the potential participants and go through the consent form with them. This consent form explains the activities, potential risks, and data collection that the Principal Investigator would like to conduct. The consent form highlights that the data collected in this effort contains footage of the participant's faces or participants' voices. As the research team member reviews the consent form with the potential participants, they encourage the participants to ask questions about the data collection specifics.

After the review is complete, the participants are told they may review the consent information up until the day data are collected as the consent form describes and their decision to participate or does not negatively or positively affect their job. The potential participant also is given an opportunity to speak with the ombudsperson alone to discuss any concerns of participation they may have. If the potential participant agrees to participate, she is asked to sign the consent form. Participants will also be asked to sign an optional image release form for use in presentation, promotional, and marketing materials. The participants either sign in person or sign a virtual copy of the consent form and send this back to the research staff member, via methods such as DocuSign or in person. After signing, a copy of the signed consent form is provided to the study participant. The original consent forms are printed and stored in study files in a locked filing cabinet in the TATRC research office. Before leaving the consenting meeting, the volunteers will be reminded that they can reach out to the ombudsperson at any time if they have concerns about participating in this research effort.

Privacy and Confidentiality

Care providers and simulated patient participants are assigned a participant ID to be associated with collected demographics, video, and physiological signal recordings. All data are stored in DoD- and HIPAA (Health Insurance Portability and Accountability Act)-compliant safety and security compliant e-storage facilities. All hard copy documents including completed consent forms are stored in locked filing cabinets at TATRC.

The research team collects all video and physiological signal recordings. Following data collection sessions, all recordings are checked within 1-7 days and before media is removed to ensure no nonconsented individual's identifiable information was not recorded. If any inadvertent recordings were made, the PI or a study team member deletes these segments of recordings. All recordings are stored securely in a DoD-approved, TATRC maintained server or repository including a NAS at Fort Detrick, Maryland. The procedure for consent occurs prior to participants engaging in simulation scenarios. If a person does not consent to data collection, they will not participate in research activities.

One of the main aspects of the data that is collected is that the faces and physiological signatures of the simulated patients are included in the footage of the data. This is needed to be able to accurately train the algorithms and technology that is developing from this effort. This is made abundantly clear to the participants in the consenting process. If they do not consent to their faces being included in this data, they are not allowed to move forward with participating in the collection. Photo Release Waivers for image use in nonresearch activities accompany the consent forms at the start of participation but are entirely optional for participation in the study.

Compensation Details

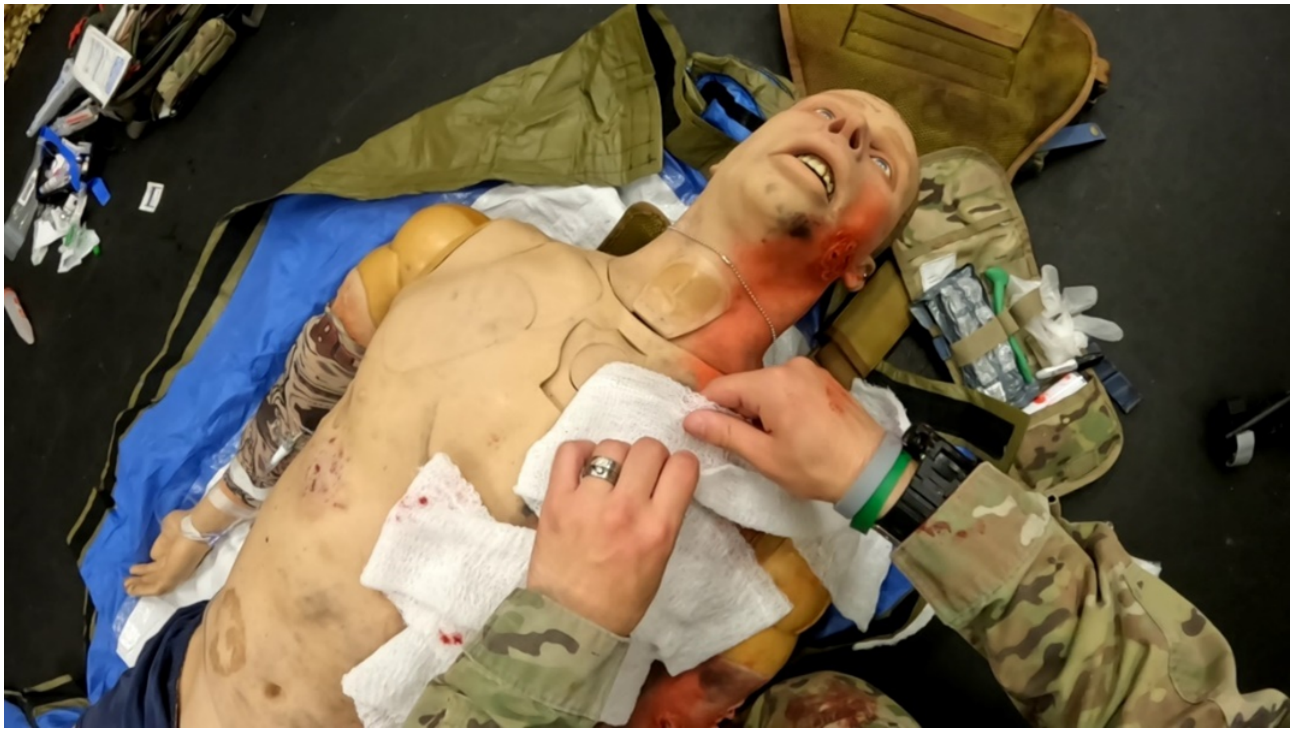
Military volunteers who meet the eligibility requirements and consent to participate in the study have the opportunity to participate in volunteer hours as a participation incentive. After completion of their participation in the study, the participant may request a letter of participation from the research team. The eligibility for volunteer hours toward service recognition will be determined by the units or offices who grant the volunteer hours. The research team will provide the letter of participation in an electronic format to the participant's email address. This process will be mirrored at all data collection locations. There are no monetary incentives or compensation for this research effort for volunteers.

Results

TATRC is on track to collect and annotate approximately 2500 simulation procedures (or tasks) by March 2025. In addition to the data recorded at each TATRC-hosted simulation event, TATRC intends to continue to expand its data repository by acquiring data from similar recorded simulated events at other military and civilian organizations and creating or obtaining augmented or synthetic TCCC data through synthetic modeling environments (ie, digital twin systems). Synthetic modeling environments can generate novel TCCC data to increase the variety and complexity of the datasets. To furthermore diversify the datasets, TATRC plans to collect simulation data from non–TATRC sponsored events (ie, research conferences, operational exercises, etc). Combining both physical and augmented simulation data, TATRC's aspirational goal is to

accumulate approximately 100,000 TCCC simulated procedure or task recordings to populate and generate DD Form 1380 elements by the end of September 2025 (Figure 4). As the annotated simulation procedures are aggregated into TATRC's data repository, contracted extramural partners will commence algorithm and software development to support TATRC's goal if automating combat casualty care scene interpretation and patient encounter documentation to significantly reduce manual data entry and enhance the capabilities of combat medics. By September 2025, the extramural algorithm partners intend to complete the machine perception algorithms and associated software to leverage data collected by the AutoDoc suite of sensors to auto-populate all DD Form 1380 elements into a digital XML or JSON format.

Figure 4. Primary care provider camera view while performing TCCC procedures on simulated patient (Mannikin). TCCC: tactical combat casualty care.



Discussion

TATRC's AC2 mission focuses on addressing and improving the current reality for combat medics:

> *A distracted, stressed combat medic managing their way through a chaotic battlefield with multiple casualties surrounds them, with only a bag full of supplies, including one permanent marker and several DD Form 1380 cards.*

There are minimal improvements in how the Joint Forces have documented health data beyond our borders, specifically in operational settings in times of conflict, despite the large advancements in data science and technology in the last decade. TATRC's goal is to replace the current, paper-based process, with modern, passive data collection and automated documentation. The aim is not only to create a more reliable, accurate method for collecting casualty care data but to alleviate the care provider's cognitive burden in the battle space of this strenuous additional duty.

The methodology for collecting TCCC data may raise questions on why our research team is not leveraging existing or available datasets from historical conflicts. The simple answer is that they do not exist. During the Afghanistan and Iraq conflicts, there were approximately 30,000 documented casualties but only 10% of those casualties had any documentation of prehospital care, and 1% or less had sufficient information to inform care at the next echelon [7]. Similarly, an unpublished 15-month review by the Joint Trauma System (JTS) found that from 172 submitted DD 1380 Forms from the field, more than 50% of them did not meet the criteria for completeness as measured by a quality checklist developed by the JTS. Furthermore, there is a lack of data granularity necessary in medical documentation from the POI based on an analysis of the JTS DOD Trauma Registry database in 2011 by Therien et al [8]. How, when, and where this data was stored remains unknown. These previous publications have illustrated the extreme, nearly impossible, expectation of documenting TCCC while in the battle space. Limiting TCCC data collection to just 1 form and expecting this 1 form to travel with the casualty from the POI to their final treatment destination, without being damaged or lost, is the reason why only less than 1% of DD Form 1380 during the Afghanistan and Iraq conflicts were sufficient to inform the next echelon of care. The result is that there are no existing combat casualty care datasets within the MHS.

TATRC's solution to this data limitation is using scripted, simulated TCCC scenarios to capture the data. TATRC has partnered with other DoD entities to provide an environment emulating specific battlefield conditions generating realistic TCCC data outcomes. Together, TATRC and partners, are testing and refining the sensor suites while simultaneously diversifying the TCCC dataset and generating the volume of

data needed to create trustworthy solutions for care providers across the echelons of care. Although the AutoDoc project primarily focuses on building DD 1380 Forms, the data obtained across all research locations could be used to create an abundance of tools and capabilities, such as algorithms to automate personal health information documentation into an existing electronic health record (eg, MHS). The possibilities to use this data to benefit the warfighter are limitless as long as you can find a way. TATRC is devoted to having this data serve as a foundation for future research, development, test, and evaluation projects across the DoD to improve our understanding of TCCC and allow organizations across the DoD to build upon our work and create innovative tools to automate future healthcare and improve the current standard of care.

Acknowledgments

The authors would like to acknowledge the contributions of COL Jeremy Pamplin and COL Sharon Rosser for their leadership and encouragement during the initiation and execution of our new research journey.

In addition, the authors would like to acknowledge the contributions of the TATRC staff members in the development of this research protocol, including Carl Ducummon, SSG Lam Bui, Jonathan Chambers, Evan Feuer, Nathan Fisher, Sharon Garlena, Wesley Huff, Courtney Kentrus, Benjamin Knisely, Zack Lattimore, Jaeyeon Lee, Carl Manemeit, Moriah Newman, Keo Pich, Matt Quinn, Mark Spears, Jesse Steffens, Ann Trout, SPC Dustin Turner, and Kerri Virtz.

Finally, the authors would like to thank the United States Army Research Institute of Environmental Medicine for assurance and adverse effect reporting.

The funding for this project (#CO23004) is under the Joint Program Committee-6 Combat Casualty Care Research Program. The funder did not influence the design of the study or strategies related to its collection, analysis, or interpretation of data.

Federal Disclaimer

The views expressed are those of the authors and do not reflect the official policy of the Department of the Army, the Department of Defense, the Defense Health Agency, or the US Federal Government.

There was no usage of generative AI tools throughout the entire manuscript ideation, planning, outlining, drafting, and submission process.

Data Availability

The data obtained in this study contains PII. According to our IRB protocol, in order to protect the confidentiality of our participants, the Headquarters, Medical Research and Development Command institutional review board (IRB) requires any institution to execute the proper agreements between HQ MRDC IRB and their respective local IRB.

Authors' Contributions

JL, TRN, and HP drafted the original manuscript. JL, EQ, JG, and ESB designed this research. JL, TRN, HP, OB, CY, JG, CD, CY, and TH edited the manuscript. All authors read and approved the final manuscript.

Conflicts of Interest

None declared.

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Abbreviations

ACC: autonomous casualty care
AI: artificial intelligence
AutoDoc: autonomous documentation
AVS: audiovisual system
COTS: commercial off-the-shelf
DoD: Department of Defense
EP: embedded participant
HIPAA: Health Insurance Portability and Accountability Act
IED: improvised explosive device
IRB: institutional review board
IRBO: Institutional Review Board Office
JTS: Joint Trauma System
MHS: military health care system
ML: machine learning
PCP: primary care provider
POI: point of injury
SM: service member
TATRC: Telemedicine & Advanced Technology Research Center
TCCC: tactical combat casualty care
USAMRDC: United States Army Medical Research and Development Command

Edited by T Leung; submitted 18.10.24; peer-reviewed by WT Davis, P Kwon; comments to author 27.11.24; revised version received 27.11.24; accepted 12.12.24; published 17.03.25.

Please cite as:
Little JR, Rivera-Nichols T, Pavliscsak HH, Badawi O, Gaudaen JC, Yeoman CR, Hall TS, Quist ET, Stoor-Burning EL
Demonstrating Tactical Combat Casualty Care in Simulated Environments to Enable Passive, Autonomous Documentation: Protocol for a Prospective Simulation-Based Study
JMIR Res Protoc 2025;14:e67673
URL: https://www.researchprotocols.org/2025/1/e67673
doi:10.2196/67673
PMID:

Protocol

Evaluation of a Smartphone-Based Weight Loss Intervention with Telephone Support for Merchant Women With Obesity in Côte d'Ivoire: Protocol for a Randomized Controlled Trial

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Abstract

Background: The obesity rate among women in Côte d'Ivoire is rising, particularly in urban areas. Merchantry is the leading occupation for women in the country, and merchant women face a high risk of obesity owing to their sedentary lifestyle. A previous survey indicated that the obesity rate among merchant women was 30%, double the national average. Furthermore, 82.2% of merchant women with obesity were unaware of their condition, and 40.1% expressed no interest in losing weight. While most weight loss programs target individuals ready to lose weight, community interventions should also address those with minimal readiness. Additionally, low-cost weight-loss interventions that do not require health professionals are needed in countries with limited medical resources. Smartphones could offer a cost-effective solution as they enable self-monitoring and remote communication.

Objective: This study will evaluate a low-cost smartphone-based intervention that targets individuals who are not ready to lose weight without the involvement of health professionals.

Methods: The intervention will run for 6 months, and its efficacy will be assessed in an unblinded, parallel-group, randomized controlled trial with 108 participants per group. All direct interventions for participants in this study will be carried out by staff without medical qualifications. The intervention group will receive weighing scales and be encouraged to record their weight with a smartphone app. Health education will be provided via weekly group messages and monthly phone calls. The evaluation will be conducted face-to-face. The primary outcome will be the weight change, and the secondary outcome will be differences in body fat percentage, abdominal circumference, and stage of behavioral change in weight loss behaviors from baseline to 3, 6, and 12 months.

Results: In accordance with this protocol, the recruitment of participants started on August 26, 2024. A total of 216 participants were allocated, with 108 in the intervention group and 108 in the control group. The baseline survey began on November 15, 2024, and is currently ongoing as of the end of November 2024.

Conclusions: This study will be the first in sub-Saharan African countries to implement a smartphone app-based weight loss program in sub-Saharan Africa that does not require direct intervention by health care professionals but specifically targets communities. Furthermore, if the effectiveness of this program is confirmed, it has the potential to serve as a low-cost sustainable weight loss model at the policy level.

International Registered Report Identifier (IRRID): DERR1-10.2196/69264

(JMIR Res Protoc 2025;14:e69264) doi:10.2196/69264

KEYWORDS

West Africa; sub-Saharan Africa; obesity; noncommunicable diseases; mHealth; mobile health; eHealth; randomized controlled trial; Côte d'Ivoire; weight loss program

Introduction

Background

Obesity caused an estimated 5 million deaths associated with noncommunicable diseases (NCDs) such as cardiovascular diseases, diabetes, cancers, and chronic respiratory diseases [1]. Additionally, its high prevalence in people 18 years and older is a critical issue, at 17.9% for women and 13.6% for men in 2022. In Africa, the obesity rate was 17% in women and 6.8% in men in 2022 [2]. This difference is particularly significant, making obesity among women an urgent issue. The percentage of women with obesity in Côte d'Ivoire has doubled compared to 20 years ago (7.3% in 2002 and 15.7% in 2022) [2].

The characteristics of the occupational style of African market traders indicate that these traders are at high risk of obesity due to long sedentary hours and easy access to food [3-5]. In Abidjan, the largest city in Côte d'Ivoire, 64.3% of working women are merchants [6], and merchant is a common occupation among women from lower- and middle-income groups. A survey of medical facilities in Abidjan also showed that merchantry was the most common occupation among patients with overweight and obesity [7]. Furthermore, our all-inclusive market survey showed that the obesity rate among merchant women is 30% [8], double the national average of 15.3%. This indicates an urgent need to address obesity among individuals in the merchant community.

Obesity is a substantial cause of NCDs such as heart disease and type 2 diabetes [9,10], and weight loss can reduce the risk of NCDs. However, in Côte d'Ivoire, there is no community-targeted weight loss program. In general, weight loss programs often target those who wish to lose weight. However, in African countries such as Côte d'Ivoire, where being plump is a symbol of wealth and power, many individuals with obesity have no desire to lose weight. Notably, 82.2% of merchant women with obesity who work at the targeted market were unaware that they had obesity, and 40.1% did not wish to lose weight (38.6% wished to maintain their current weight and 1.5% wished to gain weight) [8]. Thus, in an environment such as that in Côte d'Ivoire, developing measures to address obesity in communities that include those with minimal readiness for weight loss is necessary.

To increase the willingness of individuals with obesity to undergo weight loss, we must educate them on their condition and reasons to lose weight. Weighing is key to this; however, in our study, 53.3% of merchant women with obesity did not weigh themselves once a year, and 95.5% of them did not own a scale. Regular weighing is effective for weight loss even without interventions such as weight loss programs [11] and is one of the most cost-effective and easiest weight loss methods to implement. In this study, we aim to increase the awareness of one's own weight through regular weighing, promote awareness of health risks, and increase readiness for weight loss.

Noninvasive exercise and diet are the cornerstones of behavioral therapy as a treatment method for obesity [12]; overweight and obesity management guidelines [13] that include behavior change programs have been established in the United States. However, these are primarily conducted by primary care physicians in medical institutions and require advanced medical personnel and resources such as frequent counseling and elaborate individualized behavioral strategy planning. Therefore, implementing these behavior change programs as is in resource-limited countries such as Côte d'Ivoire is challenging [14,15].

Mobile health is cost-effective and impactful in supporting diet and exercise regimens [16-20]. Self-monitoring using smartphones is more effective than other methods of weight management [20]. Enhanced social support through online social networking services (SNSs) can also be effective. For example, Facebook groups have shown weight loss benefits [21]. In Côte d'Ivoire, WhatsApp is a popular private communication tool; however, studies on implementing behavior change using WhatsApp are limited [22]. Most studies that use smartphone apps and SNSs have been conducted in high-income countries. Such studies are limited in sub-Saharan Africa because sociocultural backgrounds and the use of smartphones and SNSs are different.

The prevalence of smartphones in sub-Saharan Africa was 45% in 2019 and is expected to steadily increase [23]. In our previous study, 77% of female traders in the target markets used smartphones [8], suggesting that interventions using smartphones are feasible. Smartphone use is important in areas requiring low-cost interventions.

Community-based weight loss interventions in sub-Saharan Africa include a group session intervention in South Africa [24] and a program initiated in Burkina Faso that includes multiple in-person dietary counseling sessions with experts [25]. These include multiple in-person sessions with health professionals, counseling, and health education.

Considering their feasibility in areas where medical resources are scarce, smartphone use that allows for remote intervention and methods that require less intervention by health care workers are required.

In this study, we aim to examine the effectiveness of a low-cost versatile weight loss intervention that can be implemented without intervention by health professionals in a community that comprises those with minimal readiness for weight loss. Specifically, this study will examine the effectiveness of a weight loss intervention that incorporates weight measurement promotion, the use of a smartphone app, and communication with non–health professionals among female merchants with

obesity in Côte d'Ivoire. This will be an unblinded, parallel-group, randomized controlled trial.

This paper outlines the study protocol of a randomized controlled trial, describing the intervention and examining its effectiveness.

Hypothesis

This study hypothesizes that the intervention group will achieve a weight loss of at least 2% [13] from baseline to 6 months, significantly differing from the control group. We will consider 2% weight loss as a clinically meaningful value; since the average weight of women with obesity in the target market is 85.6 kg [8], the equivalent of 2% is –1.7 kg. Based on the results of previous studies [19], this goal was deemed feasible.

Methods

Research Design

This study will focus on market A in Abidjan, Côte d'Ivoire. The effectiveness of the weight loss intervention will be tested in a parallel-group (1:1) randomized controlled trial among Merchant women with obesity within this market. As standard treatment, the control group will be weighed and provided with their BMI based on physical measurements, whereas the intervention group will receive a scale and the weight loss intervention using a smartphone app, and the differences will be compared. The study will be unblinded, and the effectiveness of the program will be evaluated after 6 months. In addition, a follow-up evaluation will be conducted 12 months later to assess sustained changes after the intervention is complete. We followed the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) 2013 statement and CONSORT-eHEALTH (Consolidated Standards of Reporting Trials of Electronic and Mobile Health Applications and Online Telehealth) checklist (V 1.6.1).

Eligibility Criteria

The target population will be female merchants between 18 and 65 years of age working in market A with a BMI ≥30 who own a smartphone for personal use and who can use WhatsApp. The exclusion criteria included those who are pregnant or lactating, those who are found pregnant during the intervention period, those for whom weight loss is contraindicated (due to a cancer diagnosis, eating disorders, poorly controlled hypertension, diabetes, etc), and those using physician-prescribed weight loss medication. If they have medical records, we will review them for the eligibility assessment. If they do not, we will ask about their conditions in detail and make a judgment.

Recruitment

Four interviewers and supporters will visit the target market, approach potential participants, and screen them to see if they satisfy the inclusion criteria by asking a few questions and taking physical measurements (weight and height measurements). If the participants were eligible, we explained the purpose of the study, the intervention and procedures, and the eligibility and exclusion criteria in detail and returned at least half a day later to obtain their signatures on a consent form. We also explained that the participants would be randomly assigned to either the intervention or control group and would not be able to self-select. We explained that all participants would be weighed regularly at the beginning of the intervention as well as 3, 6, and 12 months later, and that their height would be measured at the beginning of the study so that their BMI would be known each time. We further explained that the control group will have access to free scales placed at several locations in market A 12 months after the end of the entire study, which they can use at their leisure. We also informed them that smartphone apps and other devices would be introduced to them at the end of the study.

Participants could withdraw from the study at any time before data collection at 6 months by submitting a consent withdrawal form to a member of the research team.

Intervention

The weight loss intervention implemented in this study will target communities, including those who have no desire to lose weight, and will be low-cost without direct intervention by health professionals. The basic framework will be based on the American Heart Association (AHA)/American College of Cardiology (ACC)/The Obesity Society (TOS) guidelines for the management of overweight and obesity in adults [13] and the Burkina Faso program [25], which is implemented in the sociocultural context of West Africa. However, since both of these programs include direct intervention by health professionals, which differs from the purpose of this study, the content of the intervention is adapted to the situation in Abidjan in this study (Table 1). The weight loss intervention will be conducted for 6 months. The intervention will be based on self-weighing [11], which has been shown to be beneficial for weight loss, and will include the use of a low-cost personalized support smartphone app [16]. In addition, direct contact with the intervention group will be conducted by Ivorian non–medical professional supporters who were selected based on their research experience within Côte d'Ivoire and have received training for this study.

The intervention consisted of the following three components: (1) promoting weight measurement and encouraging self-monitoring through a smartphone app; (2) health education using a messaging app; and (3) in-person or telephone health education based on the stage of behavior change [26]. Lose it! (FitNow, Inc.) is a weight management app that will be used for weight self-monitoring [27], which has been used in weight loss programs in previous studies [20,28] and is available for free. WhatsApp, which is widely used in Côte d'Ivoire [29], can send and receive images, videos, audio, and text [30], and can deliver a variety of health education messages at low cost [31,32]. In addition, a step-counting app, such as Google Fit (Google Inc) for Android users and Health Care (Apple Inc) for iPhone users, can be installed for weight change and step-count monitoring. These apps will be installed on the smartphones of the intervention group, and participants will receive an orientation on their use. Additionally, they will be able to contact their supporters via WhatsApp to inquire about the use of Lose It! and another app at any time.

Health education should include recommendations for and emphasize the importance of a healthy diet, exercise, and weight

measurement. Diet and exercise content should be in line with the "Diet and Exercise" described in the "Obesity" chapter of the Côte d'Ivoire National Disease-Specific Cookbook Guidelines [33]. In-person or telephonic health education will be conducted once a month and tailored to the stages of behavioral change [26] (precontemplation, contemplation, preparation, action, and maintenance) of the target population. Interventions corresponding to the change process [34-36] of each stage are provided. The intervention stimulates interest in weight loss during the precontemplation stage, motivates implementation during the contemplation stage, supports implementation during the preparation stage, supports continuation during the action stage, and supports maintenance during the maintenance stage to maintain confidence in behavior. The intervention and evaluation schedules are shown in Table 2.

To maintain consistency among supporters in the intervention, a manual was developed on how to send health education material via WhatsApp. A manual for telephone interviews was developed, and supporters will conduct telephone interviews according to the manual and provide a report on the content of the interviews. Supporters will be trained on the content of the intervention and the survey to ensure the quality of the intervention and the survey.

No interventions are administered in the control group. For the control group, height and weight are measured at baseline and at data collection at 3, 6, and 12 months, and BMI is calculated and reported on the spot by the supporter. This allows participants in the control group to know their weight and BMI regularly. In addition, after the 12-month survey is completed, scales will be installed in the target markets free of charge so that participants can continue to measure their weights. In addition, we will introduce the app to those who wish to use it.

Table 1. Adaptations of the weight loss program following the American Heart Association (AHA)/American College of Cardiology (ACC)/The Obesity Society (TOS) guidelines for the management of overweight and obesity in adults.

Variable	AHA/ACC/TOS guidelines [13]	Intervention adapted to this study	Reason for adaptation
Participants and setting	Individual with obesity who contacted with general practitioner or another medical organization	Community recruitment	Many individuals with obesity are unaware of their obesity risk and do not feel the need to lose weight, making them less likely to visit a health care facility voluntarily.
Intervention method and frequency	In-person, high-intensity (≥14 sessions in 6 months) sessions and counseling for feedback (face-to-face or telephonic)	6 phone calls and 3 face-to-face health education sessions (focused on behavior change stages, not full medical counseling)	For nonmedical interventions, feasibility was considered.
Intervention duration	6 months	6 months	No change
Interventionist	Health professionals (registered dietitians, psychologists, exercise specialists, health counselors, or professionals in training) who adhered to formal protocols in weight management	Trained non–medical professionals over 3 days, covering coaching, intervention methods by behavior change stage, and diet/exercise per Côte d'Ivoire obesity guidelines	Côte d'Ivoire's limited medical personnel and resources were taken into consideration.
Weight loss goal	Loss of 5%-10% of baseline weight within 6 months	Loss of 2% of baseline weight within 6 months	It is a clinically meaningful minimum value and is feasible according to previous studies [8,19].
Physical activity	Advice by health professionals; increased aerobic physical activity (such as brisk walking) for ≥150 min	Recommend increasing the number of steps in one's daily routine and establish a step count goal	With limited facilities and resources for fitness programs, the plan recommends daily walking and using a smartphone app for exercise.
Dietary intervention	Advice by health professionals; daily energy deficit of 500 kcal typically achieved with dietary intake of 1200-1500 kcal/d for women	Advice from trained non–health professionals based on the National Recipe Guidelines: offer recommended local dishes and cooking tips	The method is feasible for non–health professionals, using guidelines adapted to local eating habits without calorie calculations, which are difficult for participants and interventionists.

Table 2. Enrollment, intervention, and data collection timeline.

	–2 months	–1	0[a]	1	2	3	4	5	6	12
Enrollment										
Eligibility assessment	✓									
Informed consent	✓									
Allocation		✓								
Intervention										
Distribution of scales			✓	✓						
App installation and orientation			✓	✓						
Health education via message app (1 time/wk)				✓	✓	✓	✓	✓	✓	
In face-to-face health education (at the time of survey)			✓			✓			✓	
Health education by phone				✓	✓		✓	✓		
Data collection for intervention group										
Collect data at time of call (weight, stage of behavior change)				✓	✓		✓	✓		
Data collection for intervention group and control group										
Weight, body fat percentage, and abdominal circumference measurements	✓		✓			✓			✓	✓
Height measurement	✓									
Structured interview	✓		✓			✓			✓	✓

[a]The intervention lasted from months 0 to 6.

Outcome

The primary end point of the study is to compare weight changes from baseline to the end of the intervention (6 months later) between the intervention and control groups.

Secondary end points include the differences in body fat percentage, abdominal circumference, stage of behavioral change in weight loss behaviors such as diet and exercise, percentage of individuals with correct weight perception, degree of body pain (with visual analog scale [VAS]), and self-rated health at the end of the intervention (6 months later) compared to baseline. Simultaneously, the intervention group will be evaluated in terms of the frequency of inputs to the self-monitoring apps, degree of participation in WhatsApp groups, average number of steps taken, and degree of weight loss during the intervention period.

To evaluate the interim process of the intervention, the intervention and control groups will be compared and analyzed in the same manner as described above, 3 months after the start of the intervention. In addition, the intervention group will be evaluated for weight change at 1, 2, 4, and 5 months and for changes in the behavioral change stage of weight loss behaviors such as diet and exercise.

As a follow-up evaluation after the intervention, both groups will be evaluated at 12 months (6 months after the end of the intervention) in the same way.

Sample Size Calculation

For the sample size calculation, we relied on a meta-analysis [19] of a smartphone app–based weight loss intervention. We applied –1.5 (95% CI –2.09 to –1.09) kg as the clinically meaningful difference between the 6-month smartphone-only intervention without face-to-face motivational interviewing and the control group, as indicated in the meta-analysis. However, the meta-analysis did not provide SD values, so we used the SD (–1.8, SD 3.7) [37] value of the smartphone self-monitoring–only intervention results as a reference and set the expected value at –1.5 (SD 3.7) kg. Furthermore, the α error was set at 5% (95% CI=1.96), power (1 – β error) at 80% (0.842), and the dropout rate at 10%. Based on the above values and after consulting a statistical expert, the sample size was calculated to be 108 individuals for each group (N=216 in total).

Assignment, Allocation Concealment, and Blinding

The random assignment will be performed using the permuted block method. Stratification will be conducted based on BMI (threshold: 32 kg/m^2) and age (threshold: 45 years), which represent the median values reported in a previous study. The four resulting strata will be as follows: (1) BMI ≥32 and age ≥45 years, (2) BMI ≥32 and age <45 years, (3) BMI <32 and age ≥45 years, and (4) BMI <32 and age <45 years.

The list of potential participants recruited was sent to study member allocator 1 in Japan. Allocator 1 prepares a provisional ID list that does not contain attributes other than BMI and age to ensure concealment and sends it to allocator 2. Allocator 2 creates an allocation table with an allocation ratio of 1:1 and BMI and age as adjustment factors using software for randomized controlled trial–stratified substitution blocks and allocates the provisional IDs to each stratum in descending order of provisional ID numbers, from top to bottom.

This study will be conducted in an unblinded manner. This is because the intervention group will be given a scale and an app to be installed; therefore, blinding of the participants will not be possible. In addition, the content of the questions asked during each evaluation differs between the intervention and control groups, making blinding difficult for supporters and research team members.

Data Collection Methods

Data will be obtained from supporters visiting the market to conduct face-to-face structured interviews (Multimedia Appendix 1) and anthropometric measurements. Body measurements will be taken at the time of recruitment to measure height and weight, and BMI will be calculated immediately. Subsequent data collection will include weight measurements, body fat percentage, and abdominal circumference. Height will be measured using a hardware SHUREMAN Lock Convex measuring tape (Kenoh Co, Ltd, Japan, model LC-5525) with a locking function, and an InBody (InBody Japan Inc, model H20N) will be used as the body composition scale. Structured interviews will be conducted using a questionnaire asking about sociodemographics, weight perception, behavioral change stages related to weight loss, behaviors related to weight management, body pain level (using the VAS scale), and the use of smartphone apps for weight management.

In addition, the intervention group will be asked about the weight and behavioral change stages of exercise and diet during the monthly telephone intervention.

Statistical Methods

The primary outcome will be evaluated by comparing the difference in weight change between the intervention and control groups 6 months after the intervention ended. In addition, the effectiveness of the weight loss intervention will be estimated using a linear regression model with weight change at 6 months as the dependent variable and the affiliation group, stratification variables, and other sociodemographic attributes as covariates.

Among the secondary outcomes, weight, body fat percentage, abdominal circumference, and degree of body pain (VAS scale) will be measured and compared in the same way as the primary outcome at all evaluation periods (3, 6, and 12 months). Other secondary outcomes will be compared to differences in rates at baseline and 3, 6, and 12 months. These analyses will follow the intention-to-treat principles. Additionally, intention-to-treat and per-protocol analyses will be performed and compared to address cases of protocol noncompliance.

Within the intervention groups, weight loss will be used as the dependent variable, and linear regression model analyses will be performed to estimate the impact of self-monitoring input frequency, WhatsApp group participation, and sociodemographic characteristics as covariates.

Data Management and Monitoring

All data will be collected on paper, entered into an Excel data entry format, and stored as digital data. The reason for this is that the intervention in this study involved self-monitoring of weight by app and encouraging behavioral change, so no significant safety issues are foreseen [38,39].

The research team will create a participant management sheet and continuously monitor the participants' health and weight loss status during the supporters' calls to identify any problems. During the study period, supporters will hold web-based meetings with the research team 1-6 times a month to share the participants' situation, which will facilitate the detection of unexpected adverse events.

Ethical Considerations

This protocol (version 6) and all related materials for this study were reviewed and approved by the Ethics Committee for Research on Life Sciences and Medicine Involving Human Subjects of Yokohama City University, Japan (approval General 2024-020) and by the National Ethics Committee in Health and Life Sciences of Côte d'Ivoire (RefNo 218-23/MSHPCMU/CNESVS-km). In the event of a protocol change, the ethics committee and UMIN Clinical Trials Registry will be notified.

After receiving a full explanation face-to-face, the participant will be asked to sign an informed consent form. At the same time, the participant will be informed that she can withdraw her consent (Multimedia Appendix 2). The collected digital data will be password-protected, and the paper-based data will be stored in a locked cabinet. Additionally, the data for this research will only be accessible to the research team members who have been instructed to maintain strict confidentiality. The results of this research will be published in a peer-reviewed international scientific journal.

The study was registered in the UMIN Clinical Trials Registry (ID 000055142) (Multimedia Appendix 3).

Results

In accordance with this protocol, the recruitment of participants started on August 26, 2024; by September 8, 2024, a total of 231 people were recruited. After reconfirming eligibility, one participant was excluded, and from 230 people, 108 were allocated to the intervention group and 108 were allocated to the control group. The baseline survey began on November 15, 2024, and is currently ongoing as of the end of November 2024.

Discussion

Expected Findings

The expected outcomes will analyze body weight, body fat percentage, and abdominal circumference. It is anticipated that the intervention group will achieve greater reductions in these three indicators compared to the control group. Additionally, the difference between the intervention and control groups is expected to be greater at 6 months and remain stable at 12 months.

Comparisons With Prior Work

There are fewer community-based weight loss programs in sub-Saharan Africa than those conducted within health care facilities. One such program is that of Herrmann et al [25];

however, it primarily involves interventions led by health care professionals with specialized knowledge and does not use smartphones or web-based media.

In our study, we deliberately chose to use nonmedical staff as direct interventionists to evaluate the feasibility of implementing a weight loss program by those staff in sub-Saharan African countries where human resources in health care are particularly scarce.

Additionally, weight loss programs that use smartphone apps often recruit participants via web-based media, thereby primarily attracting individuals who are already motivated to lose weight [20]. Our study differs from previous research in that it targets communities with cultural norms that view being plump as a virtue, includes individuals who may not be aware of the need to lose weight, and recruits participants through face-to-face interactions.

To our knowledge, this is the first study to implement a smartphone app–based weight loss program in sub-Saharan Africa that does not require direct intervention by health care professionals and targets specific communities.

Study Significance and Feasibility

The findings of this study will provide information on the effectiveness and feasibility of a smartphone app–based weight loss program for communities in sub-Saharan Africa. Additionally, it will offer evidence on the extent to which interventions led by nonmedical individuals can be effective.

In Côte d'Ivoire and neighboring countries, the most common occupation among women is merchant [40-43]. If the feasibility of using smartphone apps within this community is demonstrated, it could pave the way for applying it to other health programs. Furthermore, if the effectiveness of this program is confirmed, it has the potential to serve as a low-cost, sustainable weight loss model at the policy level.

Limitations

First, the intervention cannot be blinded to the participants because those in the intervention group will receive a weighing scale. It is also difficult to make the supporters blinded because the questionnaires are different between the two groups. Second, it is not possible to perfectly prevent the participants from exchanging information with each other. However, we will try to understand the status of communications between the two groups by including a related question in the questionnaire. Third, the target population of the study may not represent all female merchants in Côte d'Ivoire as we only included those who have smartphones. However, as the smartphone ownership rate among female merchants in the market in the previous study was 77% [8], we judged this to be feasible.

Acknowledgments

This work was supported by grant 23K16403 from the Japan Society for the Promotion of Science KAKENHI (Grants-in-Aid for Scientific Research of Japan).

Data Availability

The datasets generated or analyzed during this study will be available from the corresponding author upon reasonable request.

Authors' Contributions

All authors made substantial contributions to the study concept, data analysis, and interpretation. RU drafted the manuscript, and MA, SK, SW, BTJS, KK, and YK critically revised it for important intellectual content. All authors have approved the final version of the manuscript for publication and agreed to be accountable for all aspects of this work.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Survey form (baseline, 3, 6, and 12 months later).
[PDF File (Adobe PDF File), 4621 KB - resprot_v14i1e69264_app1.pdf]

Multimedia Appendix 2
Consent form and related documents.
[PDF File (Adobe PDF File), 556 KB - resprot_v14i1e69264_app2.pdf]

Multimedia Appendix 3
Table of WHO Trial Registration Data Set.
[PDF File (Adobe PDF File), 116 KB - resprot_v14i1e69264_app3.pdf]

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Abbreviations

ACC: American College of Cardiology
AHA: American Heart Association
CONSORT-EHEALTH: Consolidated Standards of Reporting Trials of Electronic and Mobile Health Applications and Online Telehealth
NCD: noncommunicable disease
SNS: social networking service
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials

TOS: The Obesity Society
VAS: visual analog scale

Edited by A Schwartz; submitted 26.11.24; peer-reviewed by H Abe; comments to author 06.02.25; revised version received 19.02.25; accepted 24.02.25; published 18.03.25.

Please cite as:
Usui R, Aomori M, Kanamori S, Watabe S, Sehi BTJ, Kawano K, Kanoya Y
Evaluation of a Smartphone-Based Weight Loss Intervention with Telephone Support for Merchant Women With Obesity in Côte d'Ivoire: Protocol for a Randomized Controlled Trial
JMIR Res Protoc 2025;14:e69264
URL: https://www.researchprotocols.org/2025/1/e69264
doi:10.2196/69264
PMID:

Protocol

Predicting Therapy Outcomes in Patients With Stress-Related Disorders: Protocol for a Predictive Modeling Study

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Abstract

Background: While cognitive behavioral therapy has shown efficacy in treating stress-related disorders, such as adjustment disorder and exhaustion disorder, knowledge about factors contributing to treatment response is limited. Improved identification of such factors could enhance assessment procedures and treatment strategies. In addition, evaluating how traditional prediction methods and machine learning can complement each other may help bridge gaps in understanding and predicting treatment response.

Objective: This study aims to (1) evaluate putative predictors of treatment response in patients with stress-related disorders using traditional prediction methods and (2) model treatment outcomes using a machine learning approach. This design combines the interpretability of traditional methods with the ability of machine learning to identify complex patterns.

Methods: We will analyze data from a randomized controlled trial comparing 2 internet-delivered treatments, cognitive behavioral therapy versus an active control treatment, for patients diagnosed with adjustment disorder or exhaustion disorder (N=300). Prediction models will be based on pooled data from both treatment arms due to the limited sample size and lack of knowledge on predictors of treatment effects. Putative predictors include sociodemographic and clinical information, clinician-assessed data, self-rated symptoms, and cognitive test scores. The primary outcome of interest is responder status on the Perceived Stress Scale-10, evaluated based on the reliable change index posttreatment. For the traditional approach, univariate logistic regressions will be conducted for each predictor, followed by an ablation study for significant predictors. For the machine learning approach, 4 classifiers (logistic regression with elastic net, random forest, support vector machine, and AdaBoost) will be trained and evaluated. The dataset will be split into training (70%) and testing (30%) sets. Hyperparameter tuning will be conducted using 5-fold cross-validation with randomized search. Model performance will be assessed using balanced accuracy, precision, recall, and area under the curve.

Results: All data were collected between April 2021 and September 2022. We hypothesize that key predictors will include younger age, education level, baseline symptom severity, treatment credibility, and history of sickness absence. We anticipate that the machine learning models will outperform a dummy model predicting the majority class and achieve a balanced accuracy of ≥67%, thus indicating clinical usefulness.

Conclusions: This study will contribute to the limited research on predictors of treatment outcome in stress-related disorders. The findings could support the development of more personalized and effective treatments for individuals diagnosed with adjustment disorder or exhaustion disorder, potentially improving clinical practice and patient outcomes. If successful, this dual approach may encourage future studies with larger datasets and the implementation of machine learning models in clinical settings, ultimately enhancing precision in mental health care.

International Registered Report Identifier (IRRID): DERR1-10.2196/65790

(JMIR Res Protoc 2025;14:e65790) doi:10.2196/65790

KEYWORDS

adjustment disorder; cognitive behavioral therapy; exhaustion disorder; machine learning; predictive modeling; psychological stress; therapy outcome

Introduction

Background

Mental disorders have a negative effect on quality of life, often precipitating personal suffering and work disability [1]. Around 23% of all who receive a psychiatric diagnosis in Swedish primary care receive a stress-related diagnosis [2], and these account for most psychiatric long-term sickness absences [3]. In Sweden, disorders believed to stem from persistent or overwhelming subtraumatic life events are often categorized using the diagnostic labels adjustment disorder (AD) or exhaustion disorder (ED). Even though ED is only recognized as a medical diagnosis in the Swedish version of the *International Classification of Diseases, Tenth Revision*, the clinical picture of ED is similar to the internationally acknowledged burnout construct [4], a condition that is often associated with significant suffering and work disability [5].

According to diagnostic definitions of AD and ED, these conditions develop in the context of one or several subtraumatic life events (stressors), resulting in mixed symptoms of anxiety, depressed mood, disturbed sleep, fatigue, and impaired memory and concentration. They share symptomatology with other mental disorders, and their diagnostic validity is debated [6,7]. Despite evidence indicating the efficacy of cognitive behavioral therapy (CBT) [8-10] and problem-solving interventions [11] on symptoms of stress, many studies have suffered from significant attrition, and knowledge regarding the factors that contribute to treatment response is still limited [8,12]. Improved identification of such factors could facilitate development of improved assessment procedures and adaptive treatment strategies that might improve outcomes [13].

Research on predictors of psychiatric treatment outcomes is limited [14,15] but demographic factors (eg, age and education level) [16,17], clinical characteristics (eg, use of medication and symptom severity) [17-19], treatment-related factors (eg, treatment credibility and adherence) [16,18] and cognitive functioning [20] have been associated with treatment outcomes.

When it comes to studies investigating predictors of treatment for stress-related disorders, Kocalevent et al [15] found that symptoms of anxiety but not perceived stress, depressive symptoms, or demographic variables predicted self-rated mental health following treatment for patients diagnosed with AD. In a study investigating burnout, Pallich et al [21] identified emotional competence, but not demographic characteristics, as a predictor of treatment response. However, both of these studies suffer from limited generalizability due to their inadequate description of the treatment offered, the fact that the interventions were conducted in an inpatient setting, and the lack of control groups. In ED patients, one study identified several predictors of treatment outcome following multimodal rehabilitation, including younger age, baseline symptom severity (insomnia, anxiety, and depression), perfectionism, physical activity level, treatment credibility, and a history of sickness absence due to ED [22]. However, the effects of demographics and pretreatment symptoms were so small that they offered limited clinical utility. In sum, at the current stage of research, it is a challenge for clinicians to determine who will benefit from treatment, underscoring the imperative for more sophisticated predictive studies.

Traditionally, prediction in psychiatry has relied on interpretable linear or logistic regression models. The aim has been to identify variables explaining a statistically significant portion of the variance in outcome, under the premise that such variables should inform researchers and clinicians. For example, the presence of previous sickness absence and earlier unsuccessful treatment attempts might lead a psychologist to conclude that a patient requires additional support, possibly extending the treatment duration. Although this approach of identifying predictors has offered some clinical utility, it often falls short in practice; the predictive power of specific variables in isolation is typically inadequate to inform assessment, treatment selection, and adaptations of interventions. Given the inherent complexity of mental disorders, the likelihood of pinpointing strong predictors with clinical utility is small, thus limiting the practical value of this approach [23,24].

Machine learning (ML) represents a promising methodological shift in psychiatric prediction modeling, transitioning from the identification of statistically significant predictors to an emphasis on quantifiable model performance, characterized by ensemble methods and adaptability to new datasets. This approach often sacrifices explainability in favor of enhanced predictive performance but offers unique value in handling the complex, nonlinear, high-dimensional data characteristic of mental disorders [25]. With this approach, a model generates a prediction (eg, remission, yes or no) intended to be actionable for a clinician. For example, patients predicted to have low probability of treatment success could be offered additional psychological support or an alternative intervention, thus increasing the likelihood of remission [26,27].

Forsell et al [28] have proposed a balanced accuracy (BACC) threshold of 67% as a benchmark for clinical utility in psychiatric applications, offering a tangible goal for ML implementation. However, the efficacy of ML in this domain remains an ongoing area of inquiry, and its capacity to surpass conventional methods in clinical usefulness is yet to be established [29].

Given the high prevalence and substantial societal costs associated with stress-related disorders, it is imperative to critically evaluate both the applicability and the limitations of ML within this specific context. Such an assessment will not only contribute to the broader understanding of the role of ML in precision psychiatry but also inform the development of more effective diagnostic and treatment strategies for stress-related disorders.

Objective of the Study

The overall objective of this study is to predict treatment outcomes in patients with stress-related disorders. Due to limitations in existing methods for prediction analyses, this study aims to first evaluate putative predictors using a traditional prediction paradigm, and second to model treatment outcomes using an ML approach. Our primary outcome of interest is responder status after treatment on the Perceived Stress Scale-10 (PSS-10), evaluated using the reliable change index (RCI; further described in the Planned Statistical Analysis and Data Cleaning and Preparation sections). On the basis of earlier research on predictors of treatment outcome, we hypothesize that key predictors will include younger age, education level, baseline symptom severity, treatment credibility, and history of sickness absence. Furthermore, we anticipate that the ML models will outperform a dummy model predicting the majority class and achieve a BACC of ≥67%, thus being indicated clinically useful [28].

Methods

Study Design

We will use collected data from a randomized controlled trial (RCT; N=300) of internet-delivered CBT for patients diagnosed with AD or ED compared to an active, internet-delivered control condition consisting of general health-promoting advice. A priori power analysis conducted for the main outcome in the RCT indicated that 300 study participants would be needed for a 90% power to detect a between-group effect size of Cohen *d*=0.4 with a significance level of .05 and an expected attrition rate of 10%. Due to the limited sample size and general lack of knowledge on predictors of treatment effect, prediction models in this study will be based on pooled data from both treatment arms. The study design is prospective, and predictors will include sociodemographic and clinical information, clinician-assessed data, self-rated symptoms, and results from cognitive test scores. The results will be reported in line with the TRIPOD+AI (Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis+Artificial Intelligence) statement [30].

Ethical Considerations

The study was approved by the Swedish Ethical Review Authority (registration 2020–03198; 2023–06857-02) and was preregistered on ClinicalTrials.gov (NCT04797273). All participants provided written informed consent before inclusion, and their data are pseudonymized and securely stored on an encrypted server. Participants received no monetary compensation but accessed study interventions free of charge. No identifying information of participants will be included in the manuscript or supplementary materials.

Procedure

Participants

In total, 300 nationally recruited individuals were diagnosed with a primary diagnosis of AD (n=142, 47.3%) or ED (n=158, 52.7%) and were included in the RCT. Participant recruitment was carried out through social media, newspaper advertisements, and information provided to health care clinics. Participants self-referred to the study web page, where they signed digital informed consent and completed a screening battery consisting of sociodemographic and clinical background questions as well as self-report symptom questionnaires. Participants were subsequently clinically assessed by a psychologist using a structured diagnostic interview, including Mini International Neuropsychiatric Interview [31], self-rated ED [32], and the Adjustment Disorder New Module-8 (ADNM-8) [33]. For inclusion, participants needed to (1) fulfill the criteria for a primary diagnosis of AD or ED, (2) be aged between 18 and 65 years, (3) have regular access to a computer with internet access, and (4) be able to read and write in the Swedish language. Exclusion criteria included (1) drug use or addiction during the past 6 months, (2) current or past psychosis or bipolar disorder, (3) current risk of suicide, (4) changed psychopharmacological treatment in the past month, (5) other ongoing psychological treatment, and (6) previous experience of CBT for AD or ED in the past year.

Treatment

Patients were randomized to one out of two 12-week internet-delivered treatments (CBT and general health-promoting advice). They both consisted of web-based text-based modules with related exercises and assignments. Patients were guided sequentially through the modules by a therapist via a secure web-based platform. The therapists' primary role was to provide feedback on exercises, support in problem-solving, and to give emotional and technical support via weekly asynchronous text messages. Therapists were licensed clinical psychologists or clinical psychology students in their final year of training. Because this study will not evaluate the individual treatments, they will not be further described here. A full description of the treatments is described in the study by Sennerstam et al [34].

Outcomes

The primary outcome in this study and the original RCT is PSS-10 [35]. The PSS-10 is a self-report questionnaire developed to evaluate an individual's perception of life as unpredictable, uncontrollable, and overwhelming. Responses are recorded on an ordinal scale ranging from 0 n*ever* to 4 *very often*, reflecting the individual's feelings and thoughts over the

past month. It contains statements, such as '*In the last month, how often have you been upset because of something that happened unexpectedly?*' and sum scores range from 0 to 40. The PSS is the most commonly used outcome measure of stress-management interventions globally [8,36,37]. For this study, a Swedish version of the PSS-10 was used. The PSS-10 has been found to exhibit high internal consistency (Cronbach α=0.84) and adequate construct validity [38]. The PSS-10 was administered digitally through the web-based study platform before randomization to treatment, every 3 weeks during the treatment phase, and at treatment completion (12 weeks). During treatment, the instructions for the PSS-10 were modified to have patients consider the last week instead of the last month. For this study, the sum score of the PSS-10 will be dichotomized into responder or nonresponder after treatment based on the RCI criteria [39] to differentiate between statistically significant change and those attributable to measurement error or natural variability. The PSS-10 baseline and 3-week measurement will also be used as predictors.

Putative Predictors

Overview

Predictors were gathered through self-report measures that were administered in the web-based study platform, clinical assessment conducted before inclusion to the study, and remote cognitive testing. Table 1 presents all predictors included in the study.

Table 1. Putative predictors of treatment outcome in stress-related disorders

Predictor	Construct measured	Type	Clinician-rated	Scoring range
Sociodemographics				
Age (y)	—[a]	Interval		18-65
Sex	—	Categorical		Male or female
Relationship status	—	Categorical		3 categories
Number of children	—	Interval		0-∞
Educational attainment	—	Ordinal		9 categories
Employment status	—	Categorical		8 categories
Employment type	—	Categorical		11 categories
Self-rated computer skills	—	Ordinal		5 categories
Self-rated reading skills	—	Ordinal		5 categories
Swedish native speaker	—	Categorical		Yes or no
Clinical characteristics				
Number of medications	Medication	Interval	✓	0-4
Antidepressants	Medication	Categorical	✓	Yes or no
Sleep medication	Medication	Categorical	✓	Yes or no
Pain medication	Medication	Categorical	✓	Yes or no
Anxiolytics	Medication	Categorical	✓	Yes or no
Diagnosis	Primary diagnosis	Categorical	✓	2 categories
Secondary diagnosis	Secondary diagnosis	Interval	✓	0-4
Depression	Secondary diagnosis	Categorical	✓	Yes or no
Anxiety disorder	Secondary diagnosis	Categorical	✓	Yes or no
Insomnia	Secondary diagnosis	Categorical	✓	Yes or no
Other disorders	Secondary diagnosis	Categorical	✓	Yes or no
S-ED[b]	Exhaustion disorder	Ordinal	✓	3 categories
ADNM-8[c] criteria	Adjustment disorder	Categorical	✓	Yes or no
ADNM-8 number of stressors	Adjustment disorder	Interval	✓	0-11
ADNM-8 stressors	Adjustment disorder	Categorical	✓	16 categories
Duration of current episode	—	Interval	✓	0-∞
Age of first episode (y)	—	Interval	✓	0-65
Sick-leave status	Sickness absence	Interval		0%-100% 5 steps
Sick-leave duration	Sickness absence	Ordinal		5 categories
Self-rated symptoms				
AUDIT[d]	Alcohol consumption	Interval		0-40
GAD-7[e]	Anxiety symptoms	Interval		0-21
SMBQ[f] cognitive weariness	Burnout	Continuous		0-7
SMBQ exhaustion	Burnout	Continuous		0-7
SMBQ listlessness	Burnout	Continuous		0-7
MADRS-S[g]	Depression	Interval		0-54
KEDS[h]	Exhaustion disorder	Interval		0-54
WHODAS[i] 2.0	Functional disability	Continuous		0%-100%

Predictor	Construct measured	Type	Clinician-rated	Scoring range
EQ-5D-5L	Quality of Life	Interval		5-25
BBQ[j]	Quality of life	Interval		0-96
ISI[k]	Insomnia severity	Interval		0-28
SRH-5[l]	Self-rated health	Interval		0-5
PSS-10[m]	Perceived stress	Interval		0-40
PHQ-15[n]	Somatoform symptoms	Interval		0-30
6-QEMP[o]	Subjective memory impairment	Interval		0-30
3-week measurement				
SMBQ cognitive weariness	Burnout	Continuous		0-7
SMBQ exhaustion	Burnout	Continuous		0-7
SMBQ listlessness	Burnout	Continuous		0-7
ISI	Insomnia severity	Interval		0-28
PSS-10	Perceived stress	Interval		0-40
Treatment-related predictors				
Clinician treatment expectancy	—	Interval	✓	0-10
Treatment credibility scale	—	Interval		0-10
Cognitive functioning				
SDMT[p]	Attention and processing speed	Interval		0-∞
FAS[q]	Executive functions	Interval		0-∞
Stroop index	Executive functions	Continuous		0-∞
Stroop inhibition	Executive functions	Continuous		0-∞
CERAD[r] learning	Memory	Interval		0-30
CERAD recognition	Memory	Interval		0-10
Corsi forward	Memory	Interval		0-9

[a]Not applicable.
[b]S-ED: self-rated exhaustion disorder.
[c]ADNM-8: The Adjustment Disorder New Module-8.
[d]AUDIT: Alcohol Use Disorder Identification Test.
[e]GAD-7: General Anxiety Disorder-7.
[f]SMBQ: Shirom-Melamed Burnout Questionnaire.
[g]MADRS-S: Montgomery-Åsberg Depression Rating Scale.
[h]KEDS: Karolinska Exhaustion Disorder Scale.
[i]WHODAS: World Health Organization Disability Assessment Schedule.
[j]BBQ: Brunnsviken Brief Quality of Life Scale.
[k]ISI: Insomnia Severity Index.
[l]SRH-5: Self-Rated Health-5.
[m]PSS-10: Perceived Stress Scale-10.
[n]PHQ-15: Patient Health Questionnaire-15.
[o]6-QEMP: 6-item Questionnaire of Everyday Memory Problems.
[p]SDMT: Symbol Digit Modality Test.
[q]FAS: Verbal Fluency Test.
[r]CERAD: Consortium to Establish a Registry for Alzheimer's Disease.

Sociodemographic Variables

Information on age (interval), sex (male, female, other, or prefer not to disclose), relationship status (in relationship, single, or widowed), number of children, educational attainment (in 9 categories between <9 years of school to PhD), employment status (eg, student, unemployed, or full-time work), and employment type (in 11 categories, eg, employed in the private sector, by the municipality, or other) was gathered before the start of treatment using the web-based study platform. Self-rated reading and computer skills were rated separately on a 5-step ordinal scale from *poor* to *very good*. Patients also reported if they were Swedish native speakers.

Clinical Characteristics

During the clinical interview, patients reported their medication regimen, specifying both the number (0-4) and type of medication (antidepressants, anxiolytics, sleep medication, and pain medication and yes or no). Primary diagnosis (AD or ED), and possible secondary psychiatric diagnosis (eg, anxiety or depressive disorder) was assessed by the clinician using Mini International Neuropsychiatric Interview, self-rated ED (ordinal categories ranging from *no* to *yes—to a high degree*) [32], and the ADNM-8 [33]. Using ADNM-8, the patient was asked about which specific stressors had been present in the past 2 years (in 16 options, eg, *too much or too little work* or *financial difficulties*). The clinician assessed the length of the current episode (in months), and the age of the patients first episode (in years). Sick-leave status upon inclusion in the study (0%-100% in 5 steps), length of current sick-leave episode (*0-1 months* to *>12 months* in 5 categories) was self-reported.

Self-Rated Symptoms

Alcohol use was assessed using the Alcohol Use Disorder Identification Test [40,41]. This 10-item screening instrument evaluates alcohol consumption, drinking behavior, and alcohol-related problems over the past year. It contains items, such as *How often do you have six or more drinks on one occasion*? rated on various ordinal scales, typically ranging from 0 to 4.

Symptoms of anxiety were measured using the Generalized Anxiety Disorder-7 scale [42]. This screening tool assesses generalized anxiety symptoms over the past 2 weeks. It comprises 7 items, such as *not being able to stop or control worrying* rated on a 4-point ordinal scale ranging from 0 *not at all* to 3 *nearly every day*.

Symptoms of burnout were measured using the Shirom-Melamed Burnout Questionnaire [43,44]. It aims to measure 3 components of burnout; emotional and physical fatigue, cognitive weariness, and listlessness and contains statements such as *I have difficulty concentrating* rated on a 7-point scale ranging from 1 *never or almost never* to 7 *always or almost always* with some items using reversed scoring.

Symptoms of depression were measured using Montgomery-Åsberg Depression Rating Scale [45]. It is a 9-item questionnaire used to measure different aspects of depression such as concentration difficulties, suicidal thoughts, sadness, and affected appetite with answers rated on a 7-point ordinal scale from 0 to 6.

Symptoms of exhaustion disorder were measured using the 9-item Karolinska Exhaustion Disorder Scale [46]. Measuring different aspects of exhaustion such as fatigue, endurance, and sleep impairment, answers are rated on an ordinal scale from 0 to 6 (eg, ability to concentrate; ranging from 0 “I do not have any difficulty concentrating, and can read, watch TV and converse normally” to 6 “I cannot concentrate on anything at all.”)

Functional disability was measured using The World Health Organization Disability Assessment Schedule (2.0) [47], developed to assess functioning in the last 30 days in 6 different life domains, including cognition, mobility, self-care, relationships, life activities, and societal participation. It contains statements, such as “I have difficulty standing for longer periods such as 30 minutes.” Answers are rated on a 5-point ordinal scale ranging from 0 *never* to 4 *extreme or unable*. A 12-item version was used.

Quality of life was assessed using the EQ-5D-5L [48,49] and the Brunnsviken Brief Quality of Life Scale [50]. The EQ-5D-5L contains 5 dimensions: mobility, self-care, usual activities, pain or discomfort, and anxiety or depression each rated on 5 levels of severity from *no problems* to *extreme problems*. The Brunnsviken Brief Quality of Life Scale is a 12-item questionnaire that assesses 6 life areas (leisure time, view on life, learning, creativity, view of self, and friends and friendship). Ratings range from 0 *strongly disagree*, to 4 *strongly agree*, on statements of the importance and satisfaction of each area.

Insomnia severity was measured using the Insomnia Severity Index [51]. The Insomnia Severity Index is a 7-item questionnaire designed to assess aspects of insomnia, including difficulty falling asleep, difficulty staying asleep, and satisfaction with sleep. Ratings are given using an ordinal scale ranging from 0 to 4.

Self-rated health was assessed using Self-Rated Health 5 asking patients to rate their general health on a scale of 1, *very bad* to 5 *very good* [52].

Somatoform symptoms were assessed using the Patient Health Questionnaire [53]. It consists of 15 questions covering somatic symptoms commonly seen in primary care, such as back pain, headache, and nausea. Answers are rated on a 3-point ordinal scale ranging from *not at all bothered* to *bothered a lot.*

Subjective memory impairment was measured using the 6-item Questionnaire of Everyday Memory Problems (6-QEMP) [54]. A 5-item version has previously been used to assess subjective memory problems in this patient population [55,56]. The present version was adapted by Stigsdotter Neely for use in patients with stress-related disorders with statements, such as “How do you think your memory functions now compared to before your stress-related mental health problems?.” The answers are rated on a 5-point ordinal scale.

Treatment-Related Predictors

Clinician Treatment Expectancy was judged after patient assessment, upon inclusion in the study, by clinicians rating the probability of the patient improving after treatment on a scale of 0 *no improvement* to 10 *full remission*.

The *Treatment Credibility Scale* was administered 3 weeks after the start of treatment [57]. Patients were asked questions about their impression of the treatment and if they thought they would improve. It included statements such as "How logical do you think this treatment is?" and "How confidently would you recommend this treatment to a friend with the same problems as you?" on a scale of 0 *not at all* to 10 *very logical*, *very confidently.*

Cognitive Functioning

Attention and processing speed were measured using the Symbol Digit Modality Test. A test originally developed by Smith [58,59] that measures visual detection, attention, and processing speed. A key with 9 different symbols and matching numbers is shown on the upper part of the display. At the center one of these 9 symbols are shown and the task of the participant is to choose the corresponding number using the key as guidance. The test score is the number of correct entries in 90 seconds. Comparable substitution tasks are considered sensitive to treatment effects for patients with multiple sclerosis [60] and depression [61], and it has been used in patients with stress-related disorders [62].

Executive functioning was measured using the Verbal Fluency Test (FAS) Word Fluency Test and the Stroop test. FAS was first described by Spreen and Benton [63], and it measures spontaneous verbal fluency and selective attention and shifting. The participant is tasked with producing words beginning with a certain alphabet letter (F, A, and S). Names, numbers, or repeated words are not allowed. The test score is the number of correct words beginning with the letter. FAS and similar word fluency tasks have been shown to be impaired in patients with stress-related exhaustion [62].

The Stroop test, originally developed by Stroop [64] and described by Jensen and Rohwer [65], measures executive functioning, inhibition, as well as updating and processing speed [66]. The test has 2 parts, (1) 20 color words are presented (green, yellow, blue, or red) and they are colored congruent to their meaning (eg, the word red colored in red). In the bottom part of the display, the color words are displayed on 4 buttons. The task is to, as quickly and thoroughly as possible, click the correct button. (2) Twenty color words are presented but displayed in an incongruent color (eg, the word red colored in green). The task of the participant is to click the button containing the color of the word as quickly and thoroughly as possible. Test score is calculated as an index (number of correct answers in part 2 divided by average time in seconds from part 2) and for interference (average time in part one–average time in part one). Performance of Stroop in patients with stress-related disorders has been shown to be impaired in 2 studies [62,67], but not in others [68,69].

Memory and learning were assessed using the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) Word List Learning Test and Corsi block-tapping test forward. CERAD was originally developed for use with Alzheimer disease [70] but is similar to other word-list tasks used in this patient population. It measures verbal learning and episodic memory. In the learning part of the test, a word list containing 10 words is presented over 3 trials and the task after every trial is to recall the words from the list. For every presentation the order is mixed. In the delayed recall part of the test (trial 4) that occurs after 5 to 10 minutes, the participant is asked to recall the words. Test score for the learning time is number of correct words in trial 1 to 3, and in the delayed recall part, number of correct words in trial 4. Similar word-list tasks have been used previously to assess memory functioning in patients with stress-related disorders [62,69].

Corsi block-tapping test forward gives information about visual ability of attention, short-term memory and working memory [71]. It contains 2 parts, but in this test battery, only the first part of the test is used. Nine blocks are displayed, and the testing platform starts by lighting up a sequence of blocks. The task is to repeat the sequence of blocks that the platform has displayed. The task starts out easy with only 2 blocks, but the difficulty increases by adding a longer sequence of blocks until the participant enters the incorrect sequence twice at the same number of blocks. The test score is the maximum number of correct repeated blocks. A cross-sectional study comparing patients with stress-related disorders to a healthy normative group found impaired performance on this test [62].

Planned Statistical Analysis

All data will be prepared and analyzed using the latest version of Python [72] and the libraries NumPy [73], Pandas [74], and scikit-learn [75] or equivalent statistical packages. A notebook containing the analysis in documented code will be made available on Open Science Framework [76] for research transparency following the analysis.

Data Cleaning and Preparation

We will transform categorical variables into a format suitable for numerical analysis. For binary categorical variables, we will use label encoding. For multinomial variables, we will apply one-hot encoding. In addition, for ordinal data, which have a natural order, we will transform the categories into integers.

Predictor variables with over 20% missing data will be excluded from the analysis. Categorical variables exhibiting low variance, as determined by predictors with <5% of a certain response will be removed. For instance, by removing the variable "Sleep medication" if it only occurs in 3 out of 300 patients. This approach aims to reduce unnecessary complexity in the predictions and to minimize the risk of overfitting. To control for multicollinearity, variables with a correlation coefficient ≥0.8 will be removed from the traditional prediction analysis but will be retained for the ML model development. Data that are highly skewed will be transformed if deemed appropriate.

Cognitive test results will be manually reviewed before model fitting to validate a proper result. Comments pertaining to technical difficulties and disturbances that may have affected the test result will be assessed by two of the authors and lead to exclusion if so judged. Participants who have noted during

screening that Swedish is not their native language will be excluded from the analysis for CERAD and FAS. We will standardize the raw scores from the cognitive tests using normative regression models with age, education and sex as covariates. This standardization process will convert raw scores into *Z* scores, as previously described by Franke Foyen et al [62] and for a full overview of the multiple linear regression models used and how they were calculated, see the studies by Mindmore [77] and van den Hurk et al [78].

Patients who have missing data for the posttreatment PSS-10, ie, the missing outcome variable for the primary aim, will be replaced by a PSS-10 process measurement at week 10 if available; If not, the patient will be excluded from the analysis. The number of participants excluded from the final models will be described.

To prepare our primary outcome, RCI for the PSS-10 before to after treatment will be computed using the following formula [39]:

Cronbach α=0.83 from normative data will be used [38]. Patients exhibiting an RCI of −1.96 will be classified as responders.

Descriptive Statistics

Descriptive statistics will be used to summarize the sample characteristics and pretreatment variables, including mean or median, SDs and IQR for continuous variables, and proportions for categorical variables.

Predictor Analysis

For the traditional regression analysis, data will be imputed using the KNN imputer. The imputer, a nonparametric imputation method, works by imputing missing values based on the k-nearest neighbors; in this study *k* will be determined by cross-validation. It uses the Euclidean distance metric to find the nearest neighbors and can be used for both numerical and categorical data. Each missing value is imputed using values from its k-nearest neighbors. After imputation, we will run univariate logistic regressions for each predictor listed in Table 1 using RCI as a target variable. Predictors that are statistically significant in the univariate analyses will then be included in an ablation study, a systematic approach to evaluate feature importance. This method involves iteratively removing each significant predictor from a full model, measuring the change in explained variance, and then reinserting it, thereby quantifying each predictor's unique contribution to the model's explanatory power in the context of all other features.

ML Model Development

For an introduction on the technical terms introduced in this section, see the review article by Bzdok and Meyer-Lindenberg [13].

Train Test Split

As the ultimate goal of any model is to predict an outcome in unseen data, the ML models will be developed using a training set, and then evaluated on a test set stratified on main diagnosis (AD or ED) and responder status. In total, 70% of the data will be used for selecting predictor variables and training the models, and 30% for testing the prediction accuracy of the models. The choice of 70 to 30 was due to the limited size of our sample, as fewer observations in the testing data makes it difficult to use uncommon predictors. No external validation set is currently available at the time of writing.

Standardization and Imputation

Standardization and imputation will be applied on the training and test data separately to avoid data leakage. Numerical data will be standardized and all missing data will be imputed using the KNN imputer.

Model Descriptions

We will train and evaluate 4 different ML classifiers, a multiple logistic regression (LogReg) classifier using elastic net, a random forest (RF) classifier, a support vector machine (SVM) classifier, and an AdaBoost classifier. For a review of the models used, see the textbook by Geron [79]. In short, the LogReg classifier works by modeling the probability of a binary outcome based on one or more predictor variables, using the logistic function to ensure the output is between 0 and 1. We will use elastic net regularization to facilitate feature selection and prevent overfitting. Elastic net combines L1 (lasso) and L2 (ridge) penalties, encouraging sparsity and maintaining stability in the model. The RF classifier works by building multiple decision trees on random subsets of data and predictors. Each tree's prediction is based on splits that minimize variance in the target variable, with the final model ensembling these predictions. The SVM classifier works by finding the hyperplane that maximizes the margin between different classes in the feature space. SVM is particularly effective in high-dimensional spaces and when the number of dimensions exceeds the number of samples. AdaBoost, the final classifier, works by combining multiple weak classifiers, typically decision trees, into a single strong classifier. It sequentially fits these weak learners on repeatedly modified versions of the data, focusing more on misclassified instances to improve overall accuracy.

Hyperparameter Tuning

We will conduct 5-fold cross-validation using randomized search for hyperparameter tuning and training evaluation to enhance the external generalizability and robustness of the results. This process involves defining a hyperparameter space, then randomly selecting a predetermined number of samples—in this case, 10—from this space, and conducting 5-fold cross-validation for each selected set of hyperparameters. Fivefold cross-validation is done by partitioning the data into 5 subsets, training the model on 4 subsets, and validating it on the remaining subset. This process is repeated 5 times, with each subset used exactly once as the validation data. The best performing hyperparameters will be chosen for the final models that are trained and then evaluated on the test set.

The hyperparameter ranges for the LogReg will include C values from 0.01 to 100 and l1_ratio values from 0 to 1. For RF, the parameter ranges will include the number of estimators from 5 to 1200, minimum samples required to split a node from 10 to 200, maximum depths from 5 to 750, and a binary indicator for bootstrapping. For SVM, the parameter range for the randomized search will include regularization parameter C values from 0.01 to 1 and for AdaBoost, the parameter ranges for the randomized search will include the number of estimators, ranging from 1 to 1500, and learning rates from 0.001 to 2.5.

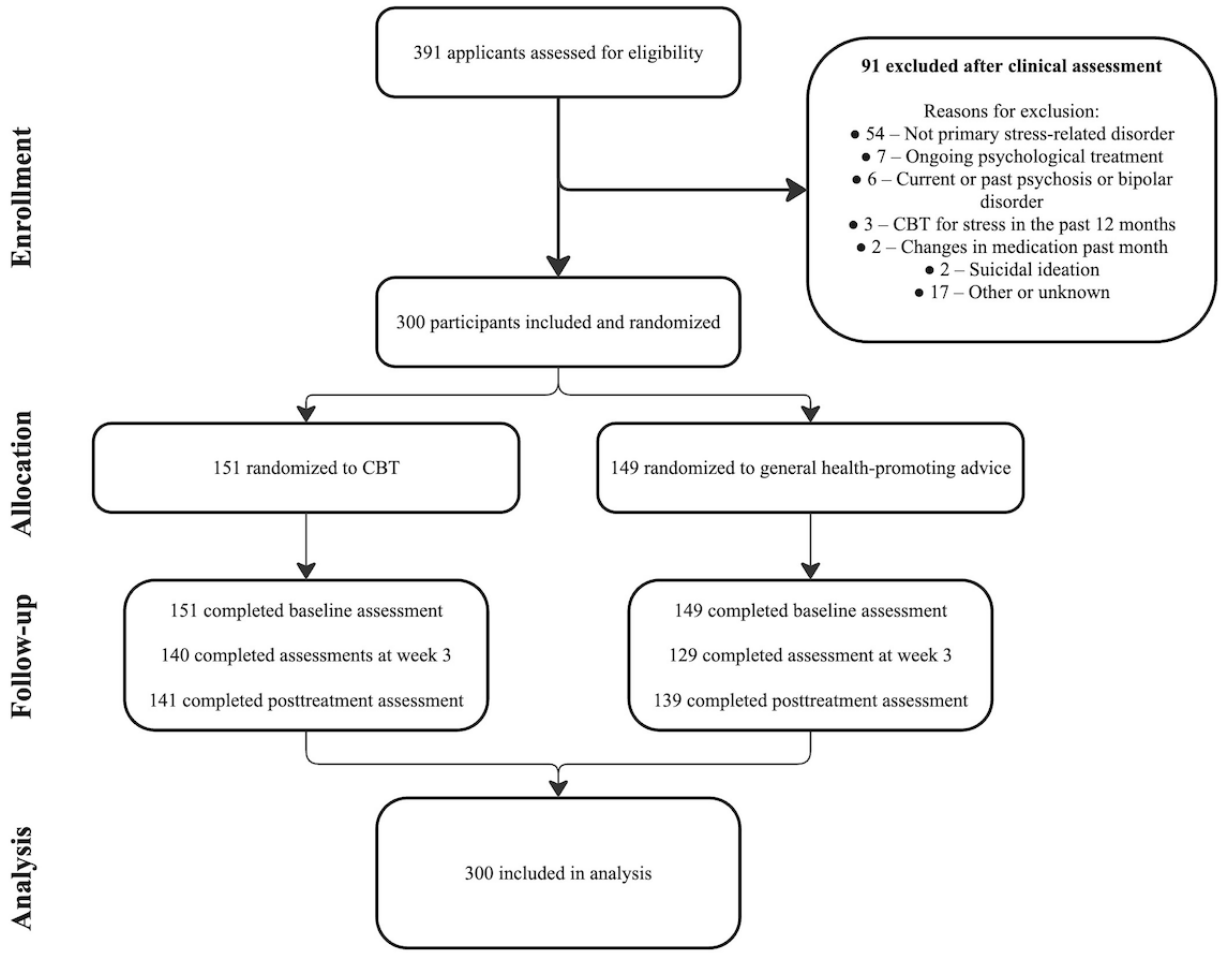
Model Interpretation

The models developed to identify the responder status will be evaluated using BACC, precision and recall, both in the training set obtained through k-fold cross-validation and in the test set. Predictor importance in the RF model will be determined using Scikit-learn's Feature importance function, which quantifies each predictor's contribution to the model's balanced classification accuracy. Area under the curve will be used to assess the models' capability to distinguish between classes accurately. The approach will aim to provide a clear understanding of the models' effectiveness and the role of various predictors. Our primary outcome of interest for comparison will be BACC in each model in the test set with the aim that (1) the model should perform better than a dummy model that simply predicts the most common responder status, and (2) that the model should perform 67% BACC or above to be deemed clinically useful [28]. Furthermore, the models will be statistically compared using bootstrap sampling. Specifically, we will generate 5000 bootstrap samples from the test set, calculating the BACC for each model on each sample. The distributions of these bootstrap BACCs will be compared and we will conclude that there is a statistically significant difference between models if the CIs do not overlap.

Results

This study was funded by ALF medicin (20190148), Region Stockholm (SLSO 2022–1278; SLSO 2022–1276), and Region Stockholm in collaboration with Stockholm university (FoUI-939533). OF is supported by the Swedish innovation agency (No. 2022-00549). All data were collected (N=300) between April 2021 and September 2022. For a participant flow diagram throughout the study, see Figure 1.

Figure 1. CONSORT (Consolidated Standards of Reporting Trials) diagram showing participant flow through enrollment, allocation, follow-up, and analysis. CBT: cognitive behavioral therapy.



A cross-sectional study investigating baseline cognitive functioning as compared with a healthy reference group has been published indicating small-to-moderate objective cognitive impairments [62], raising the question of whether objective cognitive function serves as a predictor of treatment response. In addition, an interim analysis of pre- and postcomparisons was presented at a conference in September 2022. These earlier analyses addressed separate research questions and did not influence the design, methods, or objectives of the current protocol. As of March 2025, data have not been analyzed for this study.

Discussion

Overview

This study will use a high-quality dataset from an RCT to investigate potential treatment predictors using both traditional prediction methods and an ML paradigm. This dual approach will enable the identification of predictors of treatment response in a patient population where prior research is limited. In addition, it will facilitate comparisons between different methodological approaches to prediction research.

Comparison to Prior Work

To the best of our knowledge, this is the first study to apply an ML approach to study predictors of treatment outcome in patients diagnosed with AD or ED. In line with previous traditional prediction research of treatment outcomes in stress-related disorders, we hypothesize that younger age, education level, symptom severity, treatment credibility, and history of sickness absence will predict treatment response [15,22]. Furthermore, we anticipate that the ML models will outperform a dummy model and achieve a BACC of 67% or higher, surpassing the benchmark indicated by Forsell and others [28]. If confirmed, our findings would support the notion that predictive models using sociodemographic, clinical, self-rated, treatment-related, and potentially cognitive variables are valuable when predicting therapy outcomes, as have been suggested in other patient populations [17,18,80]. In subsequent research, these models should be externally validated and tested in implementation trials to assess their utility as decision support tools. Such trials could evaluate whether integrating predictions into treatment planning improves outcomes and supports personalized care.

Strengths and Limitations

The study's strengths include the use of a multimodal dataset from an RCT, including objective cognitive functioning. By comparing traditional prediction methods with advanced ML models and employing techniques, such as cross-validation and hyperparameter tuning, the study has the potential to generate robust and generalizable insights into treatment outcomes, contributing to methodological advancements in prediction research.

A limitation is the modest sample size (N=300) which may increase the risk of overfitting. While smaller sample sizes have been used in previous ML studies [80-82], it is well established that limited sample sizes can hinder generalization [23]. The minimal sample size required for ML prediction in mental health research depends on the explanatory power of the predictors, with some researchers advocating for at least 300 observations [83], while others recommend a larger sample of 500 to 1500 for studies involving predictors with low explanatory power [84]. External validation is widely regarded as the gold standard to ensure model generalizability [85], but such data are not currently available for this study. However, ongoing data collection by the research group may enable external validation in the near future. In the meantime, k-fold cross-validation on the training set and validation on a separate test set will be used to estimate and mitigate overfitting, providing a basis for model evaluation within the study's constraints.

In addition, the recruitment strategy, which relied on social media, newspaper advertisements, and health care clinic referrals, may introduce selection bias and limit the generalizability of the findings. Participants recruited through these channels may not fully represent the broader population of individuals with stress-related disorders, potentially overrepresenting individuals with higher internet access, health literacy, or willingness to participate in internet-delivered interventions. These factors should be considered when interpreting the applicability of the study's results to other settings or populations.

Finally, ML models, such as RF, while effective at handling complex datasets, often prioritize predictive performance at the expense of interpretability. Unlike traditional statistical methods, their inclusion of numerous variables can make it challenging to understand the relationships between predictors and outcomes, limiting their integration into clinical practice where transparency is essential. Efforts to address this, such as using feature importance metrics, will be necessary to bridge this gap moving forward.

Implications for Clinical Practice

The study's findings could significantly impact clinical practice by contributing to the limited research on predictors of treatment outcome for stress-related disorders. Given the current lack of a gold standard treatment for AD and ED, this research is particularly timely and relevant. The investigation into ML models for treatment outcome prediction may encourage future larger-scale studies and, potentially, the implementation of these models in clinical settings as decision support tools. These could help clinicians tailor treatments by integrating complex data, such as patient demographics, symptom severity, and treatment history, to recommend evidence-based options, guiding therapy selection, and monitoring progress in real time. By operationalizing predictive insights, decision support tools could enhance clinical precision, reduce trial-and-error in treatment, and improve patient outcomes for individuals with stress-related disorders.

Acknowledgments

The research team gratefully acknowledges the contributions of all study patients, without whom this work would not have been possible.

Data Availability

The data referenced in this study protocol are not yet available, as the study has not yet been conducted. Once the study is completed, data may be made available on reasonable request, subject to compliance with Swedish law (the Swedish Ethical Review Act: 2003:460). For such requests, please contact the corresponding author.

Conflicts of Interest

LFF was previously employed by the cognitive testing company Mindmore until 2023 and runs a small-scale clinical psychology practice. All other authors declare no other conflicts of interest or financial involvement.

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Abbreviations

AD: adjustment disorder
ADNM-8: Adjustment Disorder New Module-8

BACC: balanced accuracy
CBT: cognitive behavioral therapy
CERAD: Consortium to Establish a Registry for Alzheimer's Disease
ED: exhaustion disorder
FAS: Verbal Fluency Test
ML: machine learning
PSS-10: Perceived Stress Scale-10
RCI: reliable change index
RCT: randomized controlled trial
RF: random forest
SVM: support vector machine
TRIPOD+AI: Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis+Artificial Intelligence

Edited by A Schwartz; submitted 26.08.24; peer-reviewed by RS Gomaa Mahmoud, G Bucur, M Wagner; comments to author 20.12.24; revised version received 22.01.25; accepted 19.02.25; published 25.03.25.

Please cite as:
Franke Föyen L, Sennerstam V, Kontio E, Flygare O, Boman M, Lindsäter E
Predicting Therapy Outcomes in Patients With Stress-Related Disorders: Protocol for a Predictive Modeling Study
JMIR Res Protoc 2025;14:e65790
URL: https://www.researchprotocols.org/2025/1/e65790
doi:10.2196/65790
PMID:

Protocol

Feasibility, Acceptability, and Potential Effects of a Digital Oral Anticancer Agent Intervention: Protocol for a Pilot Randomized Controlled Trial

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Abstract

Background: Individuals taking oral anticancer agents (OAAs) often face important challenges, requiring more timely informational support, ongoing monitoring, and side effect management.

Objective: This study, guided by the Self-Efficacy Theory, aims to assess the feasibility, acceptability, and potential effects of a comprehensive, digital OAA intervention.

Methods: A 2-arm, mixed methods, pilot randomized controlled trial took place at a large university-affiliated cancer center in Montreal, Quebec, Canada. Participants (N=52) completed baseline self-report e-questionnaires and subsequently were randomly assigned to the experimental group (intervention plus usual care, n=26) or control group (usual care only, n=26). The study intervention, designed to increase medication adherence via medication adherence self-efficacy and decreased symptom distress, included (1) OAA informational videos, (2) OAA-related e-handouts and other supportive resources, (3) nurse-led follow-up calls, and (4) e-reminders to take OAAs. The e-questionnaires were completed once a week for the first month and every 2 weeks for the subsequent 4 months, or until OAA treatment was completed. A subset from both groups (n=20) participated in semistructured interviews once they completed the study requirements. Study feasibility is assessed using recruitment, retention, and response rates, as well as intervention uptake. Through e-questionnaires and exit interviews, intervention acceptability is to be assessed prospectively at baseline and retrospectively upon study completion. Potential effects are then assessed via medication adherence self-efficacy, medication adherence self-report, and symptom distress.

Results: Data collection was completed by December 2023 with a final sample size of 41. Results are expected to be published in 2025.

Conclusions: This study relies on a theoretically based, OAA digital intervention with modalities tailored to the needs and preferences of participants. The use of quantitative and qualitative methods enriches our understanding of the potential contributions of the intervention. In addition, following participants over the course of treatment captures potential changes in oral treatment–related processes and outcomes.

Trial Registration: ClinicalTrials.gov NCT04984850; https://www.clinicaltrials.gov/study/nct04984850

International Registered Report Identifier (IRRID): DERR1-10.2196/55475

(JMIR Res Protoc 2025;14:e55475) doi:10.2196/55475

KEYWORDS

oral anticancer agent; supportive intervention; medication adherence; cancer; oncology; feasibility; acceptability; digital health; anticancer; adherence; compliance; RCT; randomized controlled trial; drug; pharmacy; pharmacology; pharmacotherapy; pharmaceutic; pharmaceutical; medication; mobile phone

Introduction

Background

It is estimated that 18.1 million new cancer diagnoses occur globally every year [1,2]. Whereas survival rates vary among cancer diagnoses and countries, mortality rates for the most prevalent cancers in high-income countries continue to decrease [2,3]. Individuals with cancer are living longer and with higher quality of life due to improvements in prevention, detection, and advancements in treatment [4]. More specifically, driven by cost-effectiveness, patient convenience, and the potential for improved patient outcomes, the use of orally administered anticancer drugs continues to grow. It is now estimated that 60% of all new cancer medications currently in development are oral, across all cancer types and stages [5].

Oral anticancer agents (OAAs), having grown in popularity in the past few years, demonstrate equivalent efficacy, safety, and outcomes as intravenous chemotherapy, while being less invasive and easier to administer [6]. As OAAs are taken at home rather than in cancer centers or hospitals, medication management resides with patients- requiring them to be active in their care [7]. For OAAs to be as effective as possible and demonstrate outcomes equivalent to those seen in clinical trials, patients must follow best practices for their treatment, resulting in added responsibilities for medication management [8]. These include attention to treatment adherence, as well as monitoring and management of side effects and adverse events, especially at OAA treatment onset when side effects and toxicity may be high [9,10]. However, the literature to date suggests that patients often report having unmet OAA-related needs, feeling helpless at home, receiving insufficient knowledge and support to manage their treatment, and having suboptimal medication adherence [10-13].

A Canadian survey conducted among individuals treated for cancer in the last 6 months (N=3300), for instance, found that only 62% of individuals on OAAs reported receiving information and guidance on potential side effects and how to manage them, compared to 74% for radiation and 76% for intravenous chemotherapy. In the same sample, only 67% of individuals on OAAs felt their care provider did everything they could to help with side effects, compared to 73% for radiation and 76% for intravenous chemotherapy [14]. Elsewhere, the lack of OAA information and monitoring for side effects were found to be significantly related to fatigue, nausea and vomiting; change of taste; and poorly managed mouth sores [15].

Medication adherence, the extent to which a person's medication-related "behavior corresponds with agreed-upon recommendations from their health care provider" [16], denotes a collaborative relationship between the health care provider and patient where the patient plays an active role in taking their prescribed treatment [17]. Medication adherence is construed as one of the primary determinants of treatment success, as unwanted alterations in dose and timing affect treatment-related outcomes [18,19]. However, medication adherence rates for OAAs vary significantly, with a systematic review across 63 studies reporting adherence rates ranging from 46% to 100% [20]. Lower OAA adherence is found to be related to decreased treatment effectiveness, increased health care utilization, and increased costs due to more physician visits, higher hospitalization rates, longer hospital stays, and in some cases, decreased survival [21-24].

As OAA development and use expands, medication adherence issues related to OAAs are increasingly of interest to multiple stakeholders, including policy makers, insurance companies, drug makers, health care providers, and researchers [25]. A systematic review of factors influencing adherence to oral anticancer drugs identified three potentially modifiable factors that interventions should address: (1) side effects and toxicities, (2) forgetfulness, and (3) the lack of timely information [26]. The American Society of Clinical Oncology and the Oncology Nursing Society jointly released evidence-based guidelines and OAA management standards. These emphasize patient education at OAA initiation and ongoing monitoring throughout treatment to enable early identification of side effects and toxicities, thus preventing complications [27,28]. Consequently, there is a need for more timely and more accessible patient support for individuals taking OAAs [28].

A comprehensive, personalized, digital OAA intervention was developed based on Bandura's [29] "Self-Efficacy Theory." One of the intervention goals is to increase medication adherence by increasing medication adherence self-efficacy (SE) and symptom distress. SE refers to individuals' beliefs in their own ability to successfully perform a specific task related to specific behavior, for instance, remembering to take medication on time to adhere to treatment, or effectively self-managing fatigue experienced from treatment [29,30]. A systematic review of the relationship between SE and medication adherence found a positive link between these two variables in 59 out of the 66 studies reviewed [31]. Behavior is influenced by the interaction between perceived SE and expectations surrounding the outcome of the behavior; thus, medication adherence is affected by a patient's belief in their capacity to consistently remember to take medication and the belief that consistently taking the medication, as prescribed, will be an effective treatment to kill cancer cells in their body. Knowledge and self-management skills of disease care can enhance SE through expectations [32]. In support of this, a standardized patient education and follow-up intervention for oral chemotherapy by Tokdemir and Kav [33] successfully increased medication adherence SE after the intervention (66.39 vs 71.04; $P<.05$). Herein, we tested a broader multimodal intervention that went beyond patient education.

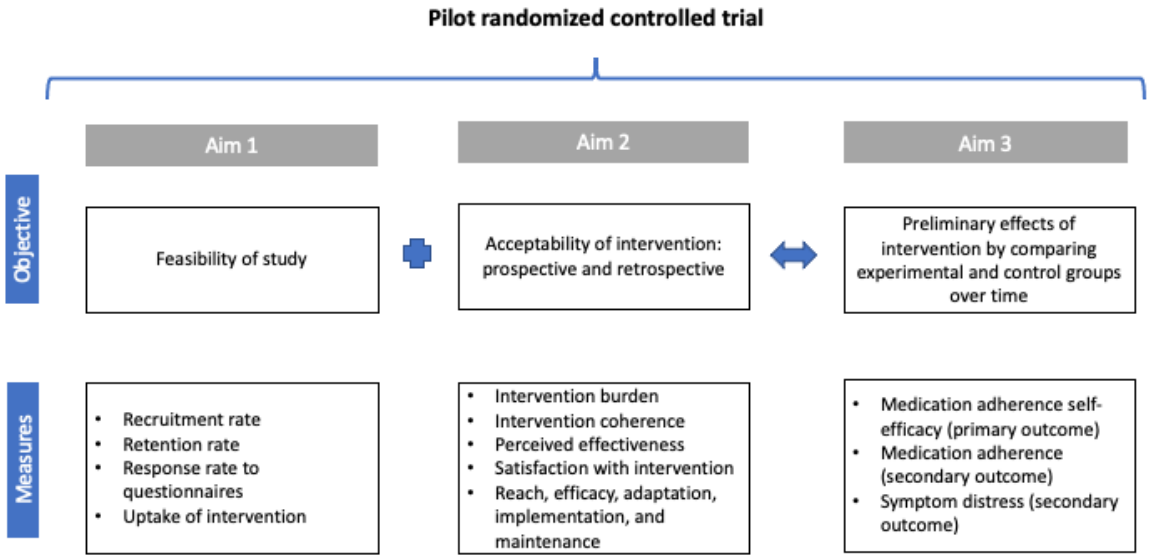
Purpose of Study

The aim of this pilot randomized controlled trial (RCT) was to document the feasibility and acceptability of the experimental

intervention. Pilot studies are critically important as a first step to address practical, logistical, and methodological issues that may arise. In addition, this pilot RCT seeks to determine whether study components can be executed and delivered to participants as planned and the intervention's potential impact on medication adherence SE, adherence, and symptom distress among participants on OAAs.

More specifically, the study's first aim was to establish feasibility, defined as "whether the intervention, study design, and procedures can be successfully executed by the researcher and delivered to the participants as planned" [34]. The constructs of feasibility herein include participant recruitment, retention, self-report questionnaire response, and uptake of the intervention. Predetermined objectives and measures of success for each are reviewed in the *Methods* section while Figure 1 provides an overview.

Figure 1. Study aims, objectives, and measures.



The second aim is to determine the acceptability of the intervention. The definition and measures of acceptability are based upon theoretical framework of acceptability of health care interventions by Sekhon et al [35], which defines acceptability as a multifaceted construct reflecting the appropriateness of the intervention. A key feature of this framework is the distinction between prospective, concurrent, and retrospective acceptability, emphasizing that acceptability can be assessed before, during, and after the intervention as all 3 can have an impact on participant use and access to the intervention. Although Sekhon et al [35] propose 7 concepts of intervention acceptability, only the 3 most relevant are included herein, namely intervention burden, coherence, and perceived effectiveness.

The third aim of the study focuses on documenting the potential effects of the intervention: As stated in the CONSORT (Consolidated Standards of Reporting Trials) on randomized pilot and feasibility trials [36], pilot trials may assess potential effectiveness using surrogate outcomes—substitute measures used as alternatives to clinical outcomes that may be challenging to assess directly [36]. Herein, potential intervention effects are assessed by comparing experimental and control groups over time, from baseline, every 2 weeks (depending on the outcome), and after the intervention. It is hypothesized that over time, compared to the control group, the experimental group will report higher medication adherence SE, higher medication adherence, and lower overall symptom distress.

Methods

Design

A prospective, mixed methods, 2-arm, pilot RCT is being conducted to address the study aims and hypothesis.

Setting

The study takes place at a large academic cancer center in a university-affiliated hospital in Montreal, Quebec, Canada.

Ethical Considerations

The study received approval from the Psychosocial Research Ethics Committee of CIUSSS West-Central Montreal Research Ethics Board (Project 2021-2861). Participants provided written informed consent. A randomly generated unique number (combination of numbers containing no identifiers) was generated and assigned to each participant such that all data collected were deidentified. As a token of appreciation for the time spent completing study e-questionnaires at baseline and follow-ups, participants received a CAD $10 (a currency exchange rate of CAD $1=US $0.69 is applicable) gift card at baseline as well as an additional one for each set of e-questionnaire completed. In sum, each participant could receive a maximum of CAD $120 in gift cards over the 5-month study period. If they withdrew from the study at any time, they receive a minimum of CAD $10 for the baseline e-questionnaire with an additional CAD $10 for each follow-up e-questionnaire completed.

Sample

A sample of 52 participants (26 per arm) was to be recruited and randomly assigned, at any moment from the decision to start OAA therapy to the completion of their first oral medication cycle.

Sample Size

Sample size calculation was undertaken using procedures provided by the software program G*Power 3 [37]. As per our statistical consultant, the calculation was undertaken to determine adequate power in the determination of the potential effects of the intervention (aim 3), in which a repeated-measures ANOVA with a within-between interaction would be the statistical test used. The parameters for the power calculation included an effect size of 0.25 (standard medium effect size for ANOVA) [38], α of .01, and a power of 0.95. The sample size was further increased to account for a 30% attrition rate over the study duration, determined to be appropriate given a review of attrition rates in supportive oncology trials found a mean of 26% (95% CI 23%-28%) across 18 trials (ie, the original sample size was 36, total with added 30%, attrition is 52) [39].

Inclusion Criteria

The inclusion criteria were as follows: being 18 years or older; being seen at the study cancer center; having a diagnosis of cancer at any stage; and being about to start or within the first cycle of oral anticancer treatment (traditional cytotoxic, targeted therapy, or hormonal therapy as adjuvant treatment). Potential participants had to have access to a computer tablet or smartphone device with internet, as well as the ability to communicate, read, and write in English or French.

Exclusion Criteria

The exclusion criteria were as follows: receiving intravenous chemotherapy, immunotherapy, or oral hormonal therapy as long-term maintenance treatment for the prevention of cancer's return or growth of cancer cells after initial treatment, assisting in prolonged remission; any significant physical or cognitive limitations that would prevent the ability to fully participate in the study (as reported by the patient, primary health care provider, or research staff); and being at imminent "end-of-life," defined as a condition in rapid decline whereby active treatment is stopped and considered in the actual process of dying [40]. We also excluded patients who were already participating in an ongoing clinical trial.

OAA Experimental Intervention

All study intervention components were available remotely using a study-specific access code on Belong – Beating Cancer Together [41], a supportive digital platform with a closed community for patients, caregivers, and health care providers at the institution to create networks and connect with other patients [42]. Participants could access the platform on their smartphone or tablet and enter an access code for the study as a closed community in the platform. As opposed to a "one-size-fits-all" approach, the study intervention accords the choice to select the support received. Participants in the experimental group were provided access to all intervention components and chose which specific components to use at any time during study participation. The intervention was developed through rigorous multistakeholder consultation processes, beginning with a comprehensive review of existing OAA-related interventions and evidence by the senior author. Noting no published OAA-specific supportive interventions at the time, the senior author (CGL) secured funding from the Rossy Cancer Network to design and test an OAA intervention, including videos and e-handouts addressing potential side effects and complications related to OAA intake. After meeting with Precare, a company providing educational video resources to patients [43], the first and senior authors gathered initial intervention feedback from oncology nurses, oncologists, researchers, cancer community organizations, patient partners, and informal caregivers or family member representatives. More specifically, these stakeholders provided insights into the content, duration, and overall aspects of the videos and e-handouts, contributing to the refinement of the intervention format and delivery. The final version was thoroughly reviewed by the first and senior author and subsequently integrated into an app [41]. The multimodal OOA intervention components are mentioned in Textbox 1 and Figures 2-4 below.

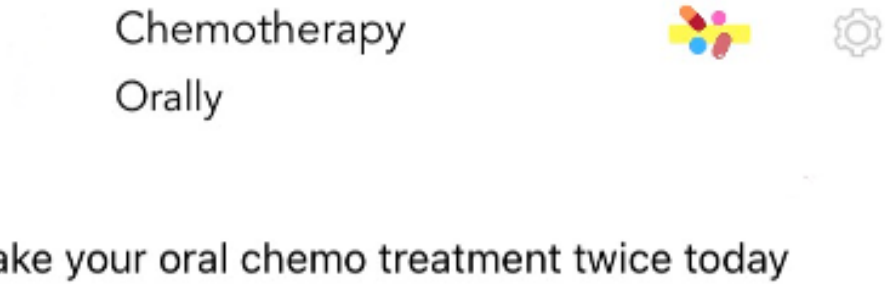
Textbox 1. Multimodal oral anticancer agent intervention components.

1. Oral anticancer agent informational videos
   - Topics: General information, side effects, support, fertility and work, and symptoms
2. Symptom management tip sheets and additional web-based resources
   - Topics: Pain, fatigue, drowsiness, nausea and vomiting, lack of appetite, shortness of breath, depression, anxiety, well-being, insomnia, fear of cancer recurrence, and work
3. Call with a nurse navigator.
   - Support and dispatch
4. Medication reminders
   - Reminder notification pop-ups
5. Any combination of services above

Figure 2. The multimodal OAA intervention contained OAA informational videos on general information (seen here), side effects, support, fertility and work, and symptoms. OAA: oral anticancer agent.

Figure 3. The multimodal OAA intervention contained symptom management tip sheets and additional web-based resources on pain, fatigue (seen here), drowsiness, nausea and vomiting, lack of appetite, shortness of breath, depression, anxiety, well-being, insomnia, fear of cancer recurrence, and work. OAA: oral anticancer agent.

Figure 4. The multimodal OAA intervention contained medication reminders as reminder notification pop-ups. OAA: oral anticancer agent.



OAA Informational Video

In the context of this study, an evidence-based animated video was developed (Figure 2). The content of the video has been reviewed by multiple stakeholders, including health care providers, patients, and caregivers. The video is available to be watched in English or French, with subtitles available in 16 languages. The video contains 4 parts: general information on oral chemotherapy, side effects, support, fertility and work, and symptoms.

Symptom Management Tip Sheets and Additional Web-Based Resources Common Physical and Psychosocial Concerns of Oral Anticancer Therapy

These e-handouts provide knowledge, facts, tips, and additional or telephone resources (Figure 3). The content has been reviewed by multiple stakeholders, including health care providers, patients, and caregivers. The e-handouts are available in French and English on the following 12 topics: pain, fatigue, drowsiness, nausea, lack of appetite, shortness of breath, depression, anxiety, sleep, fear of cancer recurrence, and work. The e-handouts are available for download in PDF format.

Follow-up Calls From Oncology Nurse

Participants in the experimental group can receive a call from the oncology nurse specific to their tumor site. A participant may request a phone call at each follow-up e-questionnaire by selecting “I would like to receive a phone call from a nurse” and identifying the topic they would like to discuss. The study coordinator forwards the participant’s name and contact number to the nurse. The participant’s symptom scores from the e-questionnaire are shared with their nurse at this time. The nurse calls the participants and speaks to them on the topic of their choice, and the interaction is documented in the patient chart as a virtual encounter.

Medication Reminders

Participants can receive daily e-reminder notifications on their smartphones to take their OAA medication (Figure 4). The e-reminders use preconfigured templates tailored to a 21-day cycle (14 days on per 7 days off) or a 28-day cycle (21 days on and 7 days off) that users must select, with options for once or twice daily reminders. Upon the conclusion of each cycle, users receive a notification prompting them to refill their prescription and reload the 21-day or 28-day cycle template.

In sum, the study intervention was designed to increase SE for OAA adherence through direct mastery experiences (self-management and reminders), vicarious experiences (video), verbal persuasion (phone calls), and feedback (self-management and reminders).

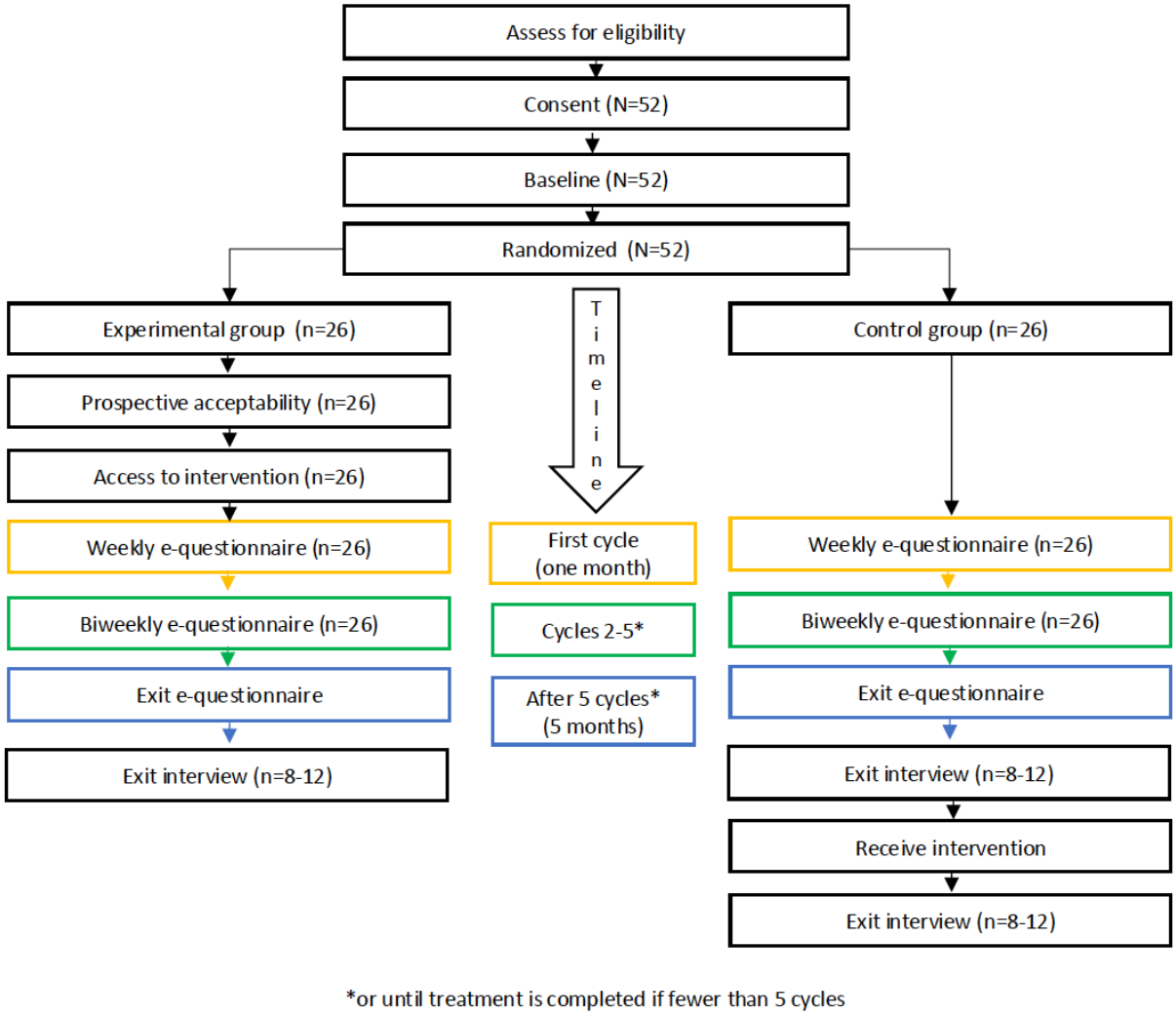
Participants in the control group continued to receive care as usual. This includes follow-up care with their oncologist, contact with their pharmacist and nurse as needed, as well as access to any internal and external supportive services from other health care professionals (eg, psychosocial oncology, social services, physiotherapist, occupational therapist, etc).

Recruitment, Consent, and Randomization

Participant recruitment occurred at the cancer center in two ways. First, a member of the oncology clinical care team (oncologist, radiation oncologist, nurse, or administrative staff) briefly explained the study and asked patients if they were interested in hearing more about the study. If yes, a member of the study team was informed (in-person, email, or telephone) and contacted the patient. Second, a study poster placed at relevant locations within the cancer center contained the contact information (QR code, email, and telephone number) of the study team. The patients then contacted the team directly.

Interested individuals met with a member of the research team in person or communicated over email or telephone. Study details were provided, and eligibility was verified. If still interested and eligible, a secure link to an electronic consent form was emailed, followed immediately by the baseline questionnaire. Participants were randomly assigned to intervention plus usual care (experimental group, n=26) or usual care only (control group, n=26). Once initial consent was given, those in the experimental group reconsented. Participants in the control group were blinded to group assignment (Article 3.7A of Tri-Council Policy Statement 2) [44]. The randomization sequence was determined on R (R Core Team), a software program, using the randomized R package for clinical trials [45]. Diagram of study design, measurement points, and timeline is shown in Figure 5.

Figure 5. Diagram of study design, measurement points, and timeline.



Data Collection

In both groups, follow-up e-questionnaires were completed every week for the first month and 2 weeks for the following 4 months, or until treatment was completed (if less than 5 months). Given the considerable variability in the duration of time patients may remain on OAAs, the study duration of 5 months was established as a long enough period in consultation with medical oncologists and pharmacists and was deemed appropriate for assessing the primary outcomes of feasibility and acceptability. Participants were monitored more closely during the first treatment cycle, as this period is critical for identifying potential toxicities and making necessary dosage adjustments. Furthermore, it is crucial to establish positive medication adherence behaviors early in the treatment process [46]. After 5 months or until OAA treatment was completed (if less than 5 months), participants completed the exit questionnaire, and a subset of participants in the experimental group (n=10) and control group (n=10) who had completed the study were invited to participate in a semistructured interview.

All e-questionnaires were completed on Qualtrics, a secure web-based electronic data capture system licensed through McGill University [47]. A data management plan between the university and the affiliated hospital was established for the study (Multimedia Appendix 1). Details of each measure and timepoint are provided in Table 1.

Baseline questionnaires completed by all participants included sociodemographic and medical characteristics, cancer information-seeking preferences, and OAA knowledge.

Table 1. Study data collection.

Objective and measure	Instrument	Items, n	Time of collection				
			Baseline	Weekly for the first cycle	Every 2 weeks for cycles 2-5	Final questionnaire	Study completion
Baseline information							
Sociodemographics	—[a]	12	✓	—	—	—	—
Medical characteristics	—	7	✓	—	—	—	—
Oral anticancer agent knowledge	—	9	✓	—	—	✓	—
Cancer information-seeking preferences	Cancer information-seeking profiles	1	✓	—	—	✓	—
Feasibility of study							
Recruitment rate	—	—	—	—	—	—	✓
Retention rate	—	—	—	—	—	—	✓
Response to questionnaire	—	—	—	—	—	—	✓
Intervention uptake	—	—	—	—	—	—	✓
Prospective acceptability of intervention							
Intervention burden perceived effectiveness	Acceptability E-scale for web-based patient-reported outcomes in cancer care	3	✓	—	—	—	—
Retrospective acceptability of intervention							
Intervention burden, perceived effectiveness, and intervention coherence	Acceptability E-scale for web-based patient-reported outcomes in cancer care	5	—	—	—	✓	—
Exit interview	—	—	—	—	—	—	✓
Preliminary effects of the intervention							
Medication adherence	Proportion of days covered	Chart review	—	—	—	—	✓
Medication adherence	Medication Adherence Rating Scale (Professor Rob Horne)	5	—	✓	✓	—	—
Medication adherence self-efficacy	Medication Adherence Self-Efficacy Scale	20	✓	✓	✓	—	—
Symptom distress	Edmonton Assessment Scale revised	12	✓	✓	✓	—	—

[a]Not applicable.

Measures

Sociodemographics and Medical Characteristics

At baseline, participants completed a sociodemographic questionnaire identifying their sex, gender, age, marital status, work status, country of birth, languages spoken, education, and income. They were also asked to complete a medical questionnaire identifying their current diagnosis, cancer stage, coverage of their OAA medication, other medications they are taking on a regular basis, and treatment or treatments received.

Cancer Information-Seeking Preferences Scale

This brief, self-report questionnaire based on Self-Evaluation Theory [48] contains 5 statements related to distinct preferences for cancer information. Respondents select the one that best describes how they go about getting information about their cancer: (1) intense—"I seek as much information as possible about my cancer," (2) complementary—"I seek information about my cancer that adds to what I was told," (3) peer-focused—"I seek cancer information from others diagnosed with same cancer," (4) minimal—"I do not seek information about my cancer," and (5) guarded—"Cancer is stressful enough; I only seek information about my cancer that is hopeful."

In a large sample (N=2142), participants treated for cancer within the past 6 months responded to the Cancer Information-Seeking Preferences (CISP) scale and patient satisfaction survey (Ambulatory Oncology Patient Satisfaction Survey). A total of 50.2% (1076/2142) selected complementary, 25.2% (539/2142) selected minimal, 14.4% (309/2142) selected guarded, 6.4% (137/2142) selected peer-focused, and 3.8%

(81/2142) selected intense, with intense seekers reporting lower satisfaction with cancer care [48,49]. The CISP provides context to the participants' preferences and uptake of the intervention.

Knowledge

The 7-item oral chemotherapy knowledge questionnaire was developed by SA and CGL for the purpose of this study. The scale contains 7 true or false items pertaining to OAA knowledge and self-management (eg, "If I forget to take my oral chemo, I should not double the next dose").

The study feasibility (aim 1) will be determined by the recruitment rate, retention rate, response rate to e-questionnaires, and uptake of the intervention (Textbox 2).

To assess the acceptability of the intervention (aim 2), intervention burden, intervention coherence, and perceived effectiveness were assessed prospectively at baseline and retrospectively at exit [35] by participants in the experimental group. They were asked to complete the Acceptability E-scale for web-based, patient-reported outcomes in cancer care by Tariman et al [56], requiring a mean score of 80% or higher as the objective. It evaluates the acceptability and usability of computerized health-related programs in oncology. The scale has a reliability of 0.757. It contains 6 items that are rated from 1 (very difficult) to 5 (easy to understand), with total scores ranging from 6 to 30. Table 2 presents constructs and definitions of acceptability as well as baseline and exit questions. In addition, postintervention acceptability was assessed in exit interviews with a subsample of participants (n=20, 10 per group) using an author-generated semistructured interview guide developed based on relevant questions using questions based on the RE-AIM (Reach, Efficacy, Adoption, Implementation, and Maintenance) framework by Glasgow et al [57] to evaluate health behavior interventions (Multimedia Appendix 2). Questions explored participants' perceptions of OAA information and support, such as "What are your general impressions of the information and support you received during your OAA treatment?" Participant selection for interviews was convenient. Participants were approached in person or over the telephone, and interviews took place in person or over the telephone by the first author, lasting between 30-60 minutes. Only the researchers and participants were present for the interview. After the total number of subsample participants (n=20) had been interviewed, the first author analyzed the interviews to ensure data saturation had been reached. No additional interviews were required.

The potential effects of the intervention (aim 3) will be assessed by comparing experimental and control groups over time, from baseline, every 2 weeks (depending on the outcome), and after the intervention in terms of the following outcomes: medication adherence SE, medication adherence (self-report and pharmacy records), and symptom distress.

Textbox 2. Study feasibility objectives.

Recruitment rate

- Calculated by dividing the total number of participants recruited throughout the study by the number of months recruitment occurred.
- Objective: Based on clinical estimates of eligible individuals, approximately 3 to 4 participants were recruited each month.

Retention rate

- Calculated by comparing the number of participants who complete baseline e-questionnaires to the number of participants who complete study exit e-questionnaires.
- Objective: Of participants who begin the study, ≥45% complete the study, and reasons for dropout are documented if participants wish to share [39,50].

Response rate to study e-questionnaires

- Determined by the number of completed follow-up e-questionnaire assessments for participants who complete the study.
- Objective: Of participants who complete the study, ≥70% complete outcome measures across all time points. This is slightly higher than the 60% minimum required by biomedical journals [51], typical for web-based questionnaires and patient acceptability and satisfaction research [52,53].

Uptake of intervention

- Nature of intervention access (modality, topics, and time points). Uptake of the intervention will be assessed by the number of participants who access the platform, and the number of times each modality was accessed throughout the study duration.
- Objective: Of participants in the experimental group, ≥85% will access at least one intervention modality [54,55].

Table 2. Constructs and definitions of acceptability [35] as well as questions asked at baseline and exit [56].

Construct of acceptability	Definition	Question at baseline	Question at exit
Intervention burden	Perceived amount of effort required to participate in the intervention	• Do you anticipate the amount of time you will spend reading and watching video or videos in this study will be acceptable?	• Was the amount of time you spent reading the information on the e-handouts acceptable? • Was the amount of time you spent watching the video or videos acceptable? • How easy was it for you to access and use the information and support offered in the study? (overall)
Intervention coherence	Extent to which participant understands the intervention and how it works	—[a]	• How understandable was the information in the e-handouts? • How understandable was the information in the videos?
Perceived effectiveness	Extent to which the participants perceive the intervention as likely to achieve its purpose	• How helpful do you anticipate the information and support offered in this study will be in helping you manage your treatment? (treatment management) • How helpful do you anticipate the information and support offered in this study will be in reminding you to take your medication? (reminders)	• How helpful was the information and support offered in this study in helping you manage your treatment? (treatment management) • How helpful was the information and support offered in this study in reminding you to take your medication? (reminders)

[a]Not applicable.

Medication Adherence Self-Efficacy

The Medication Adherence Self-Efficacy Scale (MASES) [58] asks about participants' level of confidence in taking their medication. The original scale contains 25 items, each rated from 1 (not at all sure) to 3 (extremely sure), with a total score calculated by summing the responses. Initially developed within the context of antihypertensive medication, the scale has been modified and adapted into 24-items for oncology oral agents [33]. For this study, 4 items were removed, and 20 items were used. The 4 items removed were not deemed suitable for the study as they pertain to taking the medication for the rest of their life, coming home late from work, being in a public area, and being afraid of becoming dependent on the medication.

Medication Adherence via Proportion of Days Covered

Participants were asked to provide the name and telephone number of their pharmacy, as well as consent for the research team to contact the pharmacy for records to calculate the proportion of days covered (PDC), in order to obtain the average adherence of each participant over 5 cycles of OAAs. PDC is defined as the "sum of the days" supply for all fills of a given drug in a particular time period, divided by the number of days in the time period" [59]. PDC is preferred over the medication possession ratio as the medication possession ratio can overestimate adherence for patients who refill their prescriptions early [59]. PDC will be assessed as the mean PDC for each group.

Medication Adherence via the Medication Adherence Report Scale

The Medication Adherence Report Scale (MARS-5; Professor Rob Horne) [60] is a validated measure of medication adherence, with a Cronbach α of 0.67 [60,61]. It is the shorter version of the MARS-10. MARS-5 contains 5 items, each rated from 1 (always) to 5 (never). Total scores range from 5 to 25. In addition, participants are asked specifics about their OAA regimen such as timing, dose delays, interruptions, and stoppages [62].

Symptom Distress

Physical and psychosocial distress is measured using the Edmonton Symptom Assessment Scale Revised (ESAS-r). The current version, ESAS-r, has been revised to include psychosocial needs; depression, anxiety, and well-being [63,64]. Each item is rated from 0 (none) to 10 (worst possible). The scale has been tested in cancer populations (Cronbach $\alpha = 0.71$).

Data Analysis

Statistical analyses to be performed rely on Microsoft Excel, SPSS (version 25; IBM Corp) [65], and R (R Project for Statistical Computing) software [66]. For PDC, independent sample 1-tailed *t* tests will be performed to calculate the difference between 2 independent means of the experimental and control groups at one time point—study completion. Changes over time in MARS-5, MASES, and ESAS-r will be assessed using repeated-measures ANOVA. Between-group analyses will be conducted to examine how each group changed over time, and within-group analyses will be conducted to examine how participants changed over time.

The relationship between objective (PDC) and subjective (MARS-5) measures of medication adherence will be assessed using Spearman correlation coefficients. Oral chemotherapy knowledge at baseline and study exit will be compared using paired sample 1-tailed *t* tests.

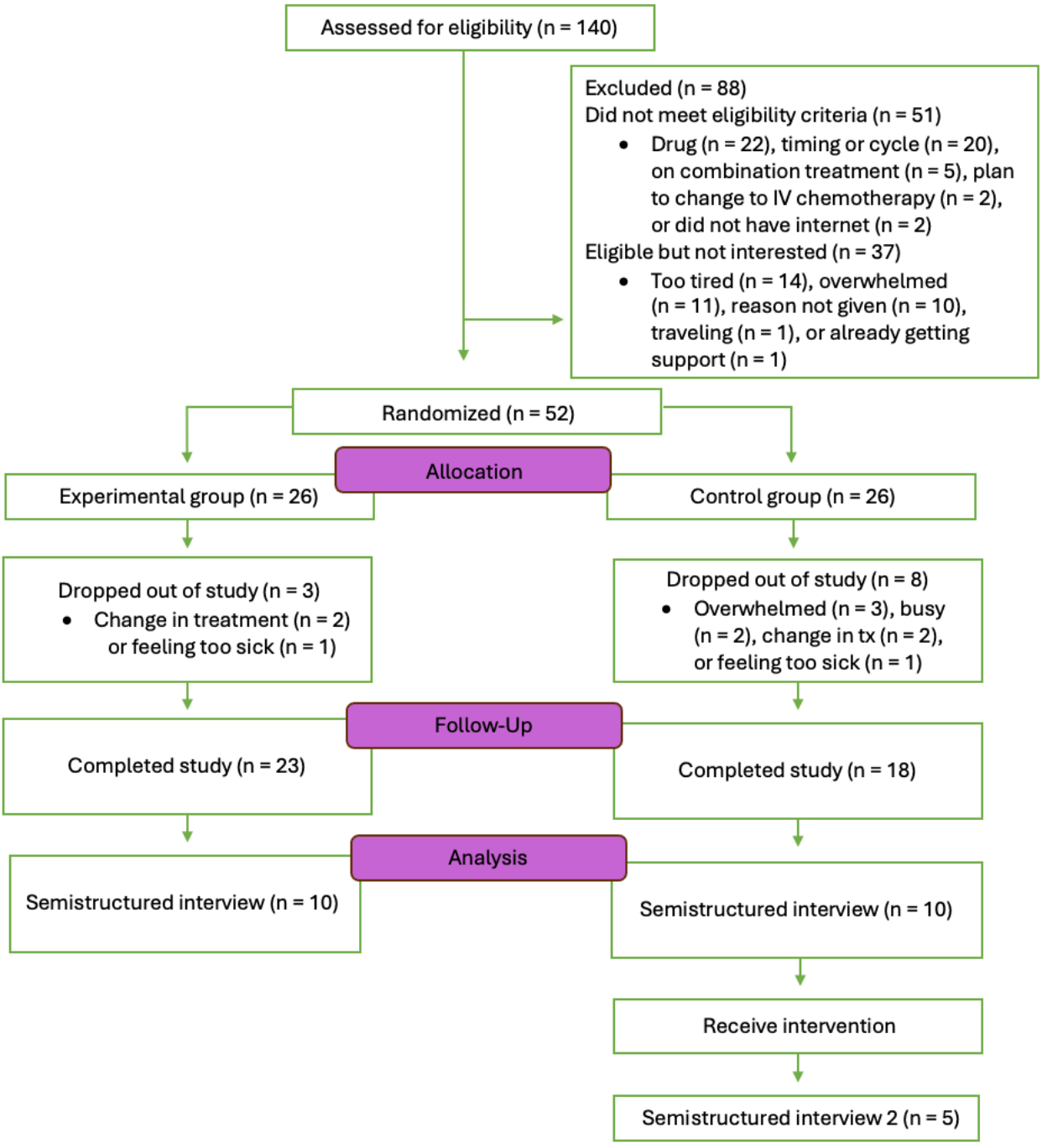
Interviews were conducted individually, audio recorded, and transcribed verbatim by the first author, a doctoral candidate at

the time with experience in qualitative research in oncology working on her dissertation. A reflexive journal was kept to document thoughts and feelings to recognize, acknowledge, and mitigate the influence of her role as a researcher and as someone with lived experience as an informal caretaker for a parent. Interview data were analyzed by the same author using thematic analysis as described by Braun and Clarke [67,68], beginning with several thorough readings of participant verbatim content to familiarize the researcher with the data and the identification of significant statements relating to the phenomenon under investigation [69]. Next, significant statements were placed into initial categories and organized into broader themes and subthemes. Themes and subthemes were reviewed, redefined, renamed, and explored as needed until no new themes emerged from the data.

Results

Data collection was completed as of December 2023 with a final sample of 41 (experimental group, n=23; control group, n=18), considering 11 dropouts after consent. Results are expected to be published in 2025 in a separate manuscript. Figure 6 presents the CONSORT flow chart for the study.

Figure 6. CONSORT (Consolidated Standards of Reporting Trials) flow diagram for the study. IV: intravenous.



Discussion

Principal Findings

Individuals taking OAAs face many challenges, ultimately impacting medication adherence. While studies have begun to test supportive interventions, there remains a lack of theory-based interventions supported by controlled studies that follow explicit reporting guidelines [70]. This pilot RCT sought to inform the study and intervention feasibility and acceptability from the perspective of patients. Given preliminary insights, it is anticipated that feasibility and acceptability objectives will be achieved. As such, the processes of the study and intervention testing will be successful, and the OAA intervention will be well received by participants. Exit interviews further explore OAA-related experiences and distinct narratives of the intervention, which quantitative measures do not capture. Study results will provide preliminary evidence to assess trends using the potential effects of the comprehensive, theory-based intervention when compared to usual care. The use of qualitative interviews will add further insight to study findings, providing context for the significance or nonsignificance of primary and secondary outcomes. As OAA use continues to grow in upcoming years, the study design and reporting of theory-based intervention will contribute much-needed insights toward how patients on these drugs can best be supported.

Of note, the testing of a remote multimodal intervention was particularly timely amid the COVID-19 pandemic, as oncology teams increasingly performed remote consultations, and patients who are immunocompromised were at higher risk for virus-related complications. Social distancing, isolation, and quarantine all further limited the support and resources available to them.

Conclusion

As remote consultations are still used for patients who are immunocompromised in the current period, the proposed intervention is still very relevant. Whether the COVID-19 pandemic may have acted as a confounding factor in this study remains unclear. In addition, since the study took place in a single setting, the next steps should include a multisite investigation to determine whether it is scalable and relevant across settings and geographical regions. The study sample is small, with 41 participants completing the study included in the final analysis for preliminary effects. Whereas the final sample is smaller than anticipated (41 vs 52), reliance on mixed methods provides complementary evidence. Dissemination activities related to the study results and its tested intervention include presentations at tumor boards, scientific publications, conference presentations, and diffusion through professional networks and webinars, as well as patient representative groups.

Acknowledgments

We are most grateful to all patients who participated in this study. We thank the oncologists, nurses, and clinical administrators who assisted in participant recruitment. We are indebted to patient partners, caregivers, and oncology team members who provided valuable feedback on the intervention. We thank Precare for making the educational videos and Belong for its assistance in making the oral anticancer agent intervention available on their app.

We would like to thank the Rossy Cancer Network for providing partial funding for this study (Cancer Care Quality and Innovation Program Research Fund—grant title: “Implementation and testing of a sustainable support program as a complement to an ongoing RCN patient-reported outcome initiative”). CGL’s work is supported by the Christine and Herschel Victor/Hope and Cope Research Chair in Psychosocial Oncology at McGill University. SA’s doctoral work was partially supported by the Maysie MacSporran Graduate Studentship and a studentship from Belong.

Data Availability

The datasets generated during this study will be available from the corresponding author on reasonable request.

Authors' Contributions

SA and CGL are responsible for study and intervention design, operationalization, randomized controlled trial implementation, data analysis, and write-up of the manuscript. CGL wrote the initial study protocol, obtained funding, and supervised the first author during her doctoral studies. CM, WG, and GB provided ongoing feedback on the study protocol and study implementation.

Conflicts of Interest

WG sits on the board of the company that provided the digital patient education but does not receive any monetary benefits.

Multimedia Appendix 1
Study data management plan.
[DOCX File , 58 KB - resprot_v14i1e55475_app1.docx]

Multimedia Appendix 2
Semistructured interview guide.

[DOCX File , 16 KB - resprot_v14i1e55475_app2.docx]

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Abbreviations

CISP: Cancer Information-Seeking Preferences
CONSORT: Consolidated Standards of Reporting Trials
ESAS-r: Edmonton Symptom Assessment Scale revised
MARS: Medication Adherence Report Scale
MASES: Medication Adherence Self-Efficacy Scale

OAA: oral anticancer agent
PDC: proportion of days covered
RE-AIM: Reach, Efficacy, Adoption, Implementation, and Maintenance
RCT: randomized controlled trial
SE: self-efficacy

Edited by A Schwartz; submitted 13.12.23; peer-reviewed by S Green, S Mukherjee, N Li; comments to author 11.05.24; revised version received 22.08.24; accepted 17.01.25; published 26.03.25.

Please cite as:
Ahmed S, Maheu C, Gotlieb W, Batist G, Loiselle CG
Feasibility, Acceptability, and Potential Effects of a Digital Oral Anticancer Agent Intervention: Protocol for a Pilot Randomized Controlled Trial
JMIR Res Protoc 2025;14:e55475
URL: https://www.researchprotocols.org/2025/1/e55475
doi:10.2196/55475
PMID:

Protocol

Treatment of Substance Use Disorders With a Mobile Phone App Within Rural Collaborative Care Management (Senyo Health): Protocol for a Mixed Methods Randomized Controlled Trial

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Abstract

Background: COVID-19 worsened an already existing problem in substance use disorder (SUD) treatment. However, it helped transform the use of telehealth, which particularly benefits rural America. The lack of specialty addiction treatment in rural areas places the onus on primary care providers. Screening, brief intervention, and referral to treatment (SBIRT) is an evidenced-based strategy commonly used in primary care settings to target SUD outcomes and related behaviors. The integration of telehealth tools within the SBIRT pathway may better sustain the program in primary care. Building on Mayo Clinic's experience with collaborative care management (CoCM) for mental health treatment, we built a digitally native, integrated, behavioral health CoCM platform using a novel mobile app and web-based provider platform called Senyo Health.

Objective: This protocol describes a novel use of the SBIRT pathway using Senyo Health to complement existing CoCM integration within primary care to deliver SUD treatment to rural patients lacking other access. We hypothesize that this approach will improve SUD-related outcomes within rural primary care clinics.

Methods: Senyo Health is a digital tool to facilitate the use of SBIRT in primary care. It contains a web-based platform for clinician and staff use and a patient-facing mobile phone app. The app includes 16 learning modules along with data collection tools and a chat function for communicating directly with a licensed drug counselor. Beta-testing is currently underway to examine opportunities to improve Senyo Health prior to the start of the trial. We describe the development of Senyo Health and its therapeutic content and data collection instruments. We also describe our evaluation strategy including our measurement plan to assess implementation through a process guided by Consolidated Framework for Implementation Research methods and effectiveness through a waitlist control trial. A randomized controlled trial will occur where 30 participants are randomly assigned to immediately start the Senyo intervention compared to a waitlist control group of 30 participants who will start the active intervention after a 12-week delay.

Results: The Senyo Health app was launched in May 2023, and the most recent update was in August 2024. Our funding period began in September 2023 and will conclude in July 2027. This protocol defines a novel implementation strategy for leveraging a digitally native, clinical platform that enables the delivery of CoCM to target an SUD-specific patient population. Our trial will begin in June 2025.

Conclusions: We present a theory of change and study design to assess the impact of a novel and patient-centered mobile app to support the SBIRT approach to SUD in primary care settings.

Trial Registration: ClinicalTrials.gov NCT06743282; http://clinicaltrials.gov/ct2/show/NCT06743282
International Registered Report Identifier (IRRID): PRR1-10.2196/65693

(JMIR Res Protoc 2025;14:e65693) doi:10.2196/65693

KEYWORDS

substance-related disorders; mobile apps; primary care; clinical trial; substance use disorder; SUD; addiction treatment; telemedicine; telepsychiatry; care management; community-based care; behavioral health program

Introduction

Limited access to substance use disorder (SUD) treatment was a problem long before COVID-19. Approximately 22 million American people needed SUD treatment in 2019, but only 13% received any intervention [1]. The COVID-19 pandemic coincided with an increase in SUD prevalence, as treatment programs were restricted or closed [2]. The National Institutes of Health described the compounding effects of the concurrent opioid epidemic and COVID-19 pandemic as a national emergency [3]. In response, the White House Office of National Drug Control Policy recommended increased funding for telehealth services and mobile phone apps.

Telehealth use has increased dramatically since the COVID-19 pandemic onset [4]. While numerous patients may benefit from its flexibility, rural patients and stigmatized populations, such as individuals with addiction, may be particularly aided [5]. Before COVID-19, rural patients already had fewer health care providers and mental health service offerings [6]. The pandemic was associated with an increased incidence of SUD in rural areas, where isolation, stress, and boredom exacerbate risks to psychological health [7]. The shortage of SUD providers impairs individuals from receiving specialty treatment and places increased pressure on primary care providers [8]. The incorporation of telehealth helps bridge this gap. We recently published a review showing that the synchronous delivery of care through video visits for SUD treatment has robust safety and efficacy evidence [2].

Screening, brief intervention, and referral to treatment (SBIRT) is the most common strategy to address problematic substance use in primary care. However, there have been significant barriers to translating it into treatment. Data combined from the 2015 to 2019 National Survey on Drug Use and Health found that only 69.9% of adults with alcohol use disorder were screened for alcohol use, with this leading to approximately 5% to 6% of adults who might benefit from treatment being referred to and eventually receiving treatment [9]. Known barriers to SBIRT use are limited clinician time, competing clinical priorities, providers' belief that the intervention will be ineffective, lack of training and experience with delivering the intervention, and the need for integration with the addiction care delivery model [10]. These factors can be addressed with adequate preimplementation support and training [11].

Collaborative care management (CoCM) is a system-based approach that integrates behavioral health care managers into primary care clinics with the support of psychiatrists to assist primary care providers in managing mental health disorders. This improves treatment access and outcomes while decreasing the need for independent psychiatric services [12]. Current evidence supports case management services delivered by various backgrounds (nursing, welfare or social workers, and mental health therapists) to strengthen service connections [13,14]. CoCM has demonstrated effectiveness in improving SUD treatment access, increasing resource efficiency, and reducing substance use [15-17]. However, addressing SUDs within CoCM poses several challenges, including organizational process and infrastructure capacity development for CoCM implementation, training behavioral health care managers, accessing specialty addiction consultation, a national shortage of SUD providers, and overcoming staff stigma [18]. CoCM also relies on symptom monitoring tools [12], and when used within addiction treatment, these must comply with federal and state confidentiality and consent regulations.

Digital CoCM adapts the traditional CoCM framework to a digital format, leveraging telemedicine platforms to overcome geographical and logistical barriers to care. Unlike traditional CoCM, which relies on in-person care teams embedded in clinics, digital CoCM uses digital tools to facilitate integration and communication between primary care providers, care managers, and consulting psychiatrists. Digital platforms allow for the integration of structured workflows, enabling asynchronous communication between providers and giving real-time updates on patient progress. This approach enhances flexibility while maintaining the core components of CoCM: care coordination, systematic case review, measurement-based care, and patient-centered outcomes [19].

Compared to stand-alone telehealth services or other SUD-focused apps, digital CoCM emphasizes integration across the care team rather than focusing solely on the patient-provider dyad. While telehealth visits allow for synchronous patient-provider interactions, they may lack systematic tracking of patient progress, team-based coordination, or integration of psychiatric consultation. SUD-focused apps typically provide self-management tools, such as cognitive behavioral therapy (CBT) modules or contingency management (CM), but they often operate outside the clinical care team and do not facilitate collaborative decision-making between primary care providers and care managers [20]. Digital CoCM bridges this gap by embedding app-based tools within a team-based care model, ensuring that technology supports both patient engagement and provider collaboration. Digitally delivered interventions can positively augment the patient-provider experience by incorporating new ways to interact [21,22], enabling the easy monitoring of clinically relevant measures of substance use and mental health symptoms, and supporting evidence-based practices. However, to our knowledge, no digital telemedicine platform has been tested to facilitate integrated SUD CoCM

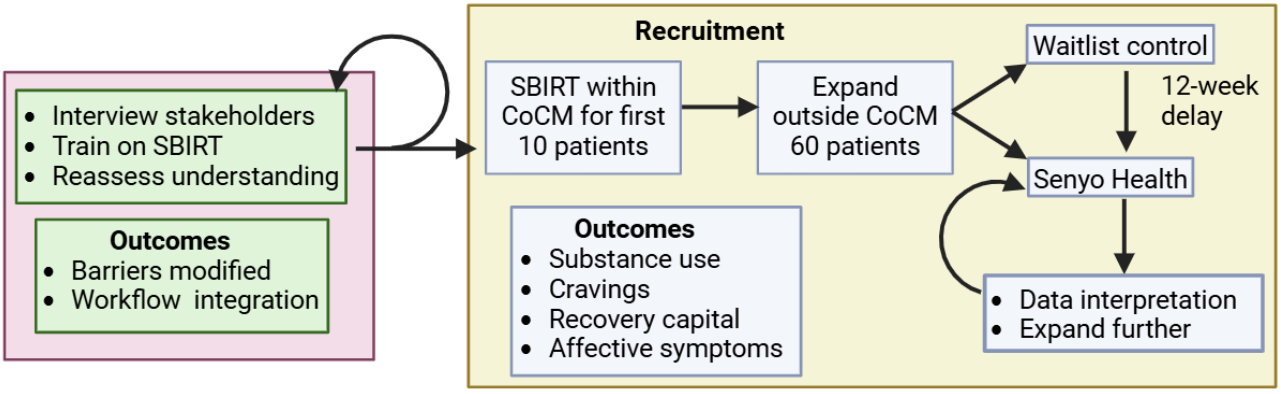
within primary care. This study aims to evaluate the implementation and clinical effectiveness of Senyo Health, a digitally native, addiction treatment and CoCM platform designed to address barriers to SUD treatment in rural primary care settings. Specifically, we aim to identify facilitators and barriers to implementation; improve the integration of SUD treatment into primary care workflows; and assess the platform's impact on substance use outcomes, treatment retention, and recovery trajectory. We hypothesize that this intervention will reduce the frequency and intensity of substance use, promote addiction recovery, and be well received by primary care staff. This protocol details the iterative design, development, pilot-testing, and randomized controlled trial study stages.

Methods

Study Design

This is a mixed methods study. The first stage is focused on implementing SBIRT into primary care and identifying barriers. During this stage, we will use Consolidated Framework for Implementation Research (CFIR) [23]. The CFIR's core domains include intervention characteristics, which focus on the attributes of the intervention itself, such as its complexity and adaptability. The outer and inner settings examine the external and internal contexts, including factors like patient needs, organizational culture, and readiness for implementation. Finally, the characteristics of individuals and the process domains address the roles of individuals involved and the steps taken to implement the intervention, such as planning and engaging stakeholders. The second stage is a waitlist randomized controlled trial studying the effectiveness of the Senyo Health platform in decreasing substance use over a 12-week period (Figure 1). The intervention will have 4 core components that will be iteratively improved based on stakeholder feedback. First, each patient will receive digitally native CoCM for SUD with weekly web-based check-ins with licensed alcohol and drug counselors (LADCs), who will be the main point of contact for patients enrolled in the study. Consistent with CoCM, standardized symptom monitoring and monthly reviews of all clinical cases will occur with the LADC and the overseeing psychiatrist. Second, the patient will be offered, initiated, or continued on medications to manage psychiatric and addiction diagnoses and symptoms. Third, the patients will use a digital clinical platform to complete a set of CBT and behavioral activation–based psychotherapeutic modules. Fourth, patients will use a digital CM platform through an app on their phones.

Figure 1. Study flow diagram. The study is an exploratory, sequential, mixed methods design. The initial study phase is qualitative (left, pink square) with a focus on interviewing clinical stakeholders (physicians, nursing, and medical support staff), training on SBIRT, and reassessing their understanding and experience to iteratively improve the process. The second study phase is quantitative (right, yellow rectangle) with outcomes noted. The first 10 patients will be recruited from ongoing CoCM for mental health services after screening positive on validated alcohol and drug use measures. We then will recruit an additional 60 patients, who will participate in a randomized controlled trial of a 12-week intervention with Senyo Health (active phase) or to a 12-week waitlist control group who will subsequently receive the active intervention. These results and feedback will be used to iteratively improve the intervention after study completion. CoCM: collaborative care management; SBIRT: screening, brief intervention, and referral to treatment.



Ethical Considerations

This study was reviewed and approved by the Mayo Clinic Institutional Review Board (IRB) for human research (#24-007758) in accordance with institutional policies and federal regulations governing human participant research. The IRB determined that this study requires full board review, and no exemption or waiver was granted. Informed consent will be obtained directly from all participants prior to study enrollment, and participants will have the ability to opt out at any time without consequence. This study does not involve secondary data analysis requiring additional consent considerations. No identifiable patient information will be reported, ensuring participant confidentiality and data security. Data collected by the app system are securely transferred using industry-standard encryption to the "Backend Services" (ie, Mayo Clinic servers behind Health Insurance Portability and Accountability Act [HIPAA]–compliant firewall). This cloud-based infrastructure serves and communicates with the patient-facing app. The Backend Services contain all data and analytics specific to the app clients (participants, researchers, and providers). No protected health information is contained in the app itself. All data used by the app follow internationally recognized security standards, including the National Institute of Standards and Technology SP800-53 and HIPAA. All patient information is automatically encrypted when entered in the system, allowing for secure data transfer from the participant device to the provider interface and storage. The treatment phase of this project uses the CM method. Participants earn points for completing treatment tools within the Senyo app. They turn in those points for rewards of specified dollar amounts. These dollar amounts are loaded on a reloadable cash card (ClinCard).

The app will notify study staff of the dollar amount, which will be loaded onto the card and documented in the research participant remuneration application system. The amount of points a participant can earn is approximately 1400 (converts to US $350), but this amount will vary depending on participation and points received. In the follow-up and waitlist phase, participants will receive US $25 for each visit where they complete interviews and questionnaires. Those assigned to the waitlist phase will have an additional 12 weeks of participation than those assigned to the intervention phase. Remuneration will not be provided during time on the waitlist.

Senyo Health Intervention

Overview

Senyo Health has several core features that enable it to deliver digital CoCM for SUD treatment. Senyo offers several well-studied, app-based components to users, including asynchronous CBT modules, CM, behavioral activation, and an interface to interact with the program LADC. We chose these features as our initial intervention based on our research that showed CBT and CM had significant effect sizes for improving substance use-related outcomes, with CM having a large effect [20]. A group of licensed drug counselors meeting an hour a week over the course of several months with a senior patient education specialist employed by Mayo Clinic took individual paper copies of patient education content that presented CBT-based concepts and combined them with CBT content found in National Institutes of Health CBT Content built for "Project MATCH" [24]. This process resulted in the production of 16 modules.

Traditional care coordinator and patient coordination visits involve a comprehensive assessment of the patient's physical, mental, and social health needs. It includes collaborative care planning with input from various health care providers, patient education, and regular follow-up. These visits are typically done in person or over the phone. To add digital care coordination, we incorporated the ability to communicate directly with a LADC care coordinator through the app. Furthermore, the Senyo platform enhances care coordination by providing the care coordinator with a desktop portal directly linked to the patient's mobile phone app. The care coordinators have immediate access to the patient's progress through an interface that showed the patient's use of the mobile phone app features, survey results, and activities. The platform also allows the care coordinator to do video-based conversations that more closely mimic in-person care coordination visits.

The app was designed to be simple and user-friendly. When first using the app, initial prompts are designed for the user to create personalization and review security or privacy settings. Figure 2 displays the patient's to-do list, a behavioral activation goal (walking), and the points received for completing that goal. Figure 3 displays the chat feature, which is a communication portal with the LADC. Modules and surveys can be assigned in response to current symptoms in real time.

Figure 2. Screenshots from Senyo Health app that the individual using the app sees. Panel (A) shows the initial personalization. Panel (B) shows the current "To-do List" and also displays the chat icon at the bottom of the panel. Panel (C) shows a behavioral activation task, and panel (D) showcases the points awarded for completing this task.

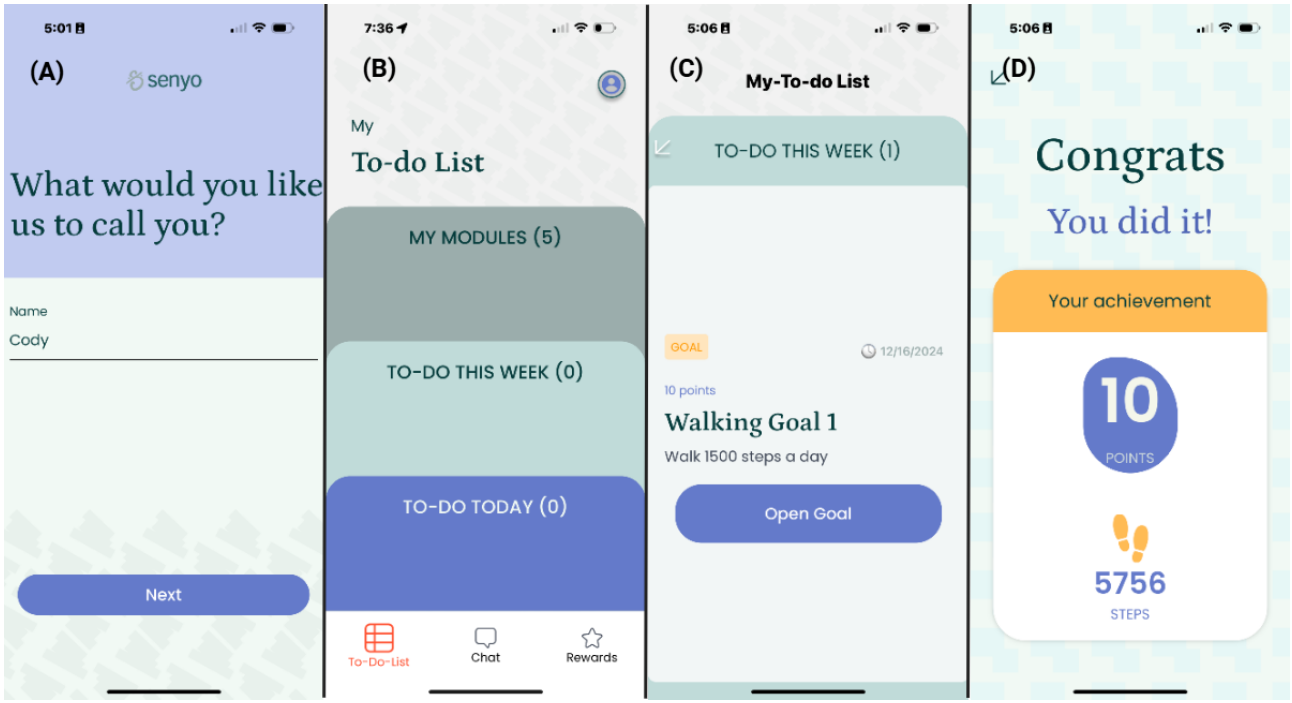
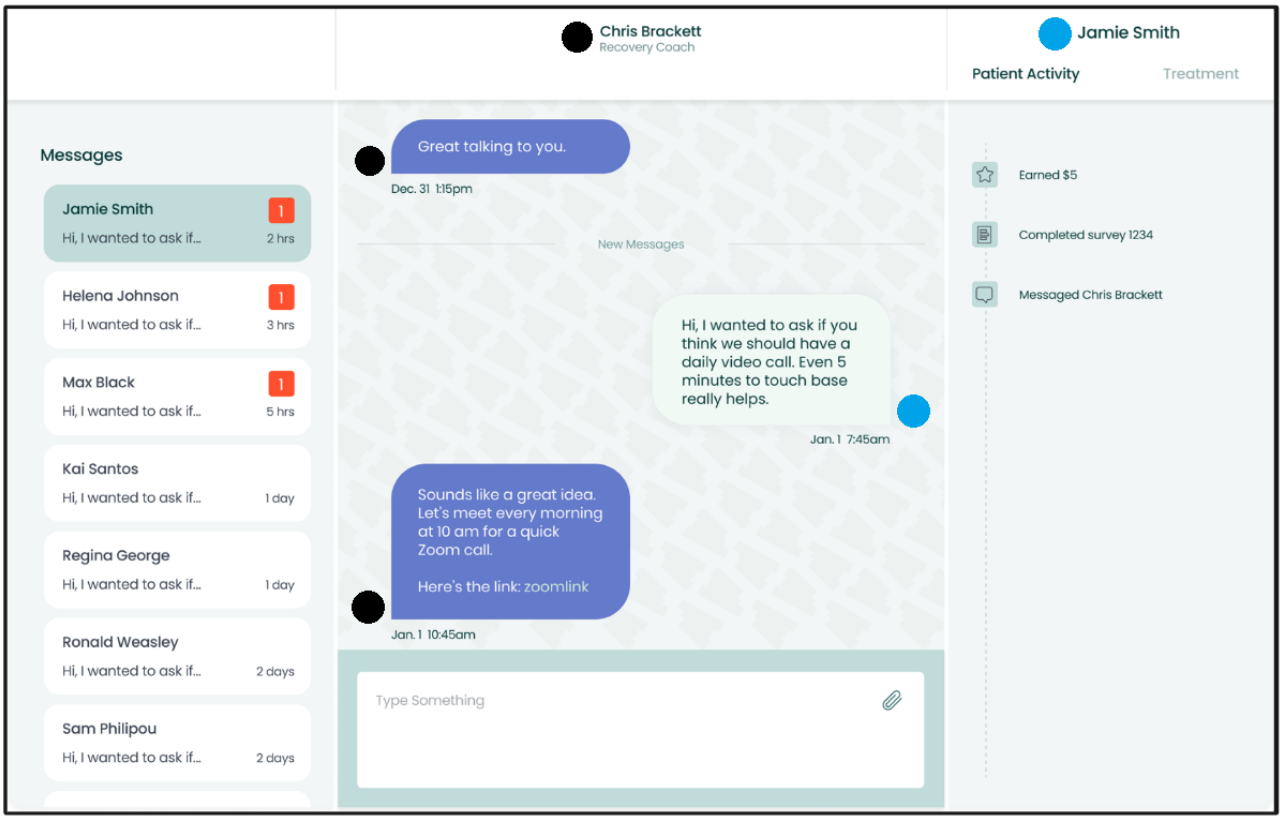


Figure 3. Senyo Health chat feature being displayed from the perspective of the recovery coach. The left is conversations with multiple patients. Once selected, the full conversation appears in the center of the screen, with the recovery coach able to text back and forth. Surveys, modules, and activation tasks can also be assigned to the participant through the chat.



CBT Modules

Apps allow for the asynchronous delivery of therapeutic content that participants can use at any time. Current research supports delivering asynchronous content through "modules" or "activities." Psychotherapeutic modules within apps contain brief text-based content, videos, and related questions that patients can experience independently whenever convenient. CBT is the most researched content type for asynchronous modules [15,25,26]. "Activities" within apps are usually actions that the patient performs, such as filling out a survey, doing a mindfulness exercise, or being physically active [27]. Senyo Health currently contains 16 modules with content based on Mayo Clinic patient education pamphlets. Topics include "addictive thought patterns," "living with emotions in recovery," "self-esteem and relationships," "my recovery building blocks," "self-care in recovery," "cravings," and "relapse prevention."

CM Component

CM is a behavioral therapeutic intervention where monetary or prize-based rewards are "contingent" on objective evidence of drug abstinence and abstinence-promoting behaviors, such as attending mutual support meetings and counseling sessions [28]. Therefore, CM does not deliver education or concepts for individuals to learn; instead, it is a strategy to encourage positive behaviors. CM has decades of research representing hundreds of controlled trials demonstrating its safety and efficacy in assisting in-person SUD treatment [28,29]. It is arguably one of the most effective therapeutic strategies available to date but can be challenging to implement within conventional in-person treatment programs [30]. "ReSET" and "ReSET-O" are Food and Drug Administration–approved products that are available for prospective patients through a prescription that use CM to encourage the completion of in-app modules [25,26]. Digitally delivered CM through an app appears to improve engagement at a similar level to CM delivered in person [31].

The incorporation of CM-based token economy architecture into a CoCM platform makes Senyo Health unique [32]. The app awards points for completing surveys, modules, and activities. The points per action are customizable through the research interface, allowing for the adjustment of relative incentives associated with each task. Participants can use points to purchase rewards through a reloadable card (ClinCard). The purchased rewards will be tracked and documented in the research participant remuneration application. For this study, the point value is US $0.25 per point. One point is earned for each page of a module, minute of a video, and question in a survey.

Activity or Goals

Senyo Health was built to work with Apple and Google health kit wearable platforms to gather data from wearable device sensors. If a device is detected and the patient authorizes this, the wearable device sensor will track activity, heart rate, and oxygen saturation. These data will be used to encourage physical activity by connecting sensor data to CM rewards. These data will only be collected from participants who already have and wear a personal device; the study will not provide such device to participants.

LADC to Patient User Interface

The LADC will use the provider portal to communicate through the app with their patients. Social rewards through apps, such as support from a clinician or peer via messaging or telephone, produce significantly greater user engagement than fully automated apps [32]. Typically, this support aims to maintain patient adherence with the app, monitor user progress through periodic symptom assessments, assist the patient in understanding therapeutic concepts or skills training, and triage patients who do not respond to app-based interventions [33].

Study Sample and Recruitment

Overview

The implementation phase will start with a pilot within a rural primary care site in the upper Midwest region of the United States that is familiar with the CoCM model for mental health treatment. After following the implementation strategy below at the initial location, we will expand to 2 additional primary care sites—1 for a rural service population and 1 for a nonrural service population. This staged rollout will allow for iterative improvements for the subsequent sites based on knowledge gained from the first site.

Provider Engagement and Implementation

Preimplementation

Clinic engagement efforts will start by recruiting a primary care champion at the primary care site. Other primary care clinic key stakeholders (physicians, nursing, CoCM staff, and medical support and administrative staff) will be included as appropriate. Focus groups and interviews with providers and staff engaged in the SBIRT workflow will assess attitudes and perceived barriers toward SBIRT, the use of medications for addiction treatment (buprenorphine, acamprosate, etc), and the use of digital delivery of SUD treatment within CoCM. Focus groups will be interviewed using a semistructured interview based on the CFIR interview guide. Please see Multimedia Appendix 1 for details.

Implementation: Training, Supervision, and Refinement

Research team members with experience treating SUD in primary care clinics will provide education to providers at the participating site. We will be scheduled as part of a regularly recurring staff education curriculum to provide didactic base education on the project (specifically the screening metrics, conducting a brief intervention, and how to refer to this study). The LADC will support voluntary follow-up training on brief interventions, motivational interviewing, and the referral process. Primary care champions at each participating site will encourage other site providers to attend training and initiate medications for addiction treatment for patients with confirmed moderate and severe SUD diagnoses. These champions will also liaise with the LADC.

Throughout the implementation approach described, we will gather feedback from the primary care team on SBIRT, the Senyo Health platform, the CoCM team, and LADC to evaluate the processes. Primary care providers, nurses, key administrators, and clinic staff from each of the sites will be identified for interviews. Feedback on these components will be used to iterate and refine our strategy.

SBIRT Protocol

Screening

Universal patient screening with the Drug Abuse Screening Test (DAST) [34] and the Alcohol Use Disorders Identification Test-Consumption (AUDIT-C) [35] is an eventual goal. These instruments help determine the need for treatment referral using the SBIRT care pathway. The AUDIT-C is already frequently implemented across primary care; however, the DAST is not. Screening frequency will be explored in the feasibility stages based on feedback from clinic staff and leadership. While the US Preventive Services Task Force recommends all adults are screened for substance use, this may not be feasible in all clinic workflows. Stakeholder feedback will monitor excessive screening burden, and process iteration will attempt to minimize unnecessary rescreening to optimize overall results.

Brief Intervention

The brief intervention stage is where the SBIRT pathway often stalls out. Implementation of a brief intervention will be collaborative and iterative with the initial pilot site. FRAMES [36], which consists of feedback, responsibility, advice, menu for change, empathy, and enhancing self-efficacy, will be the primary component of this intervention. If granted permission by the patient in the screening stage, a LADC will provide a brief intervention to the patient (ie, personalized feedback, education, and motivational interviewing). The primary care provider is at liberty to provide some initial counseling to the patient, but the full FRAMES-based structure of the brief intervention is deferred to the LADC. In this modification of the traditional SBIRT framework, the goal is to minimize the additional clinical burden on the primary care providers and emphasize the value of the CoCM program in augmenting the capabilities and capacities of the primary care team. The primary goal of the brief intervention as conducted by the LADC is to facilitate patient enrollment in CoCM or referral to a higher level of care if needed.

Referral

Patients will be informed about local treatment options for treatment as usual and about the option to participate in this study by enrolling in the Senyo CoCM program. They will be allowed to choose which option they feel is best for them. Once the process runs smoothly at the pilot site, we will expand to the next selected site.

Treatment

All patients who consent to study participation will receive care through the Senyo Health platform. However, randomization will determine if this is provided immediately or if access is delayed by 12 weeks (ie, waitlist design). These patients will have outcomes closely monitored as described in the Study Procedures section. To ensure all eligible patients receive treatment regardless of trial participation, study coordinators will attempt to follow up with those who chose treatment as usual to monitor if they do ultimately receive treatment.

Study Criteria

The intervention will be piloted to 10 patients who screen positive on the DAST or AUDIT-C and are already participating in CoCM for depression within primary care (no randomization). In addition to screening results, the clinical team will use their clinical judgment to determine eligibility, prioritizing patients for whom a SUD appears to be the primary psychiatric diagnosis rather than a mood or anxiety disorder. Once these patients have been recruited effectively and we have solidified our implementation strategy, we will broaden screening to primary care patients not currently in CoCM at the participating site. An additional 60 patients will be randomly assigned to immediate access to Senyo Health versus the waitlist. The 30 participants randomly assigned to the waitlist arm will be later added to the active arm (Senyo Health platform), for a total of 70 patients receiving active intervention by study conclusion. A computerized random assignment list will be generated by the study statistician for the study coordinator to assign enrollees sequentially, stratified by sex and restricted to every 10 cases, ensuring equal numbers per group. Due to the nature of the intervention and trial design, no one will be blinded. The study will recruit patients from Mayo Clinic primary care clinics at 3 sites after they have agreed to participate, with 2 serving primarily rural patients and 1 serving primarily nonrural patients.

Inclusion criteria are as follows: age 18 years and older; ability to read, write, and understand English; minimum DAST (1+) or AUDIT-C (3+) scores; and access and willingness to use a mobile device for asynchronous (text) and synchronous (video visits) engagement with care. Exclusion criteria are as follows: already participating in or about to initiate treatment in another structured addiction treatment program; diagnosed personality pathology as the primary presenting concern based on clinical judgment, severe cognitive impairment (eg, intellectual disability or dementia), or psychosis; inability to actively participate in and learn from psychotherapeutic interaction based on clinical evaluation and clinical judgment; needing a higher level of mental health care as demonstrated by American Society of Addiction Medicine assessment; and decline to answer suicidality questions.

Study Procedures

Overview

Once primary care patients have selected the study treatment path, the steps outlined below will occur. These include obtaining and signing informed consent, collecting medical and psychiatric history for comorbidities through patient interview, and answering validated questionnaires on mood, anxiety, and their overall strengths and resources to achieve substance use cessation (ie, recovery capital). Recovery capital is a biopsychosocial model of recovery from addiction, which encapsulates the interpersonal strengths and resources an individual can leverage in pursuit of substance use cessation [37]. Next, participants will be randomly assigned to the waitlist or active intervention. Once randomly assigned, participants will complete visits through a clinical treatment phase and a follow-up phase. The waitlist group will serve as a “waitlist” control and be asked to “cross over” and receive the active intervention after 12 weeks on the waitlist.

Study activities are listed in Textbox 1 and detailed in Table 1.

Textbox 1. Study activities.

- Baseline visit
  - Obtain informed consent from the participant.
  - American Society of Addiction Medicine diagnostic interview [38] conducted by a licensed alcohol and drug counselor (LADC).
    - Participants must meet the criteria for outpatient treatment or indicate that outpatient is their preference.
  - Questionnaires: Brief Substance Craving Scale [39]; Brief Assessment of Recovery Capital [40]; self-reported substance use based on the Timeline Followback [41]; and psychiatric comorbidities measured via Generalized Anxiety Disorder-7 [42], Patient Health Questionnaire-9 [43], and Epworth Sleepiness Scale [44].
  - Treatment attendance monitoring questionnaire.
  - Urine drug test—check for certain drugs, including alcohol and illicit substances (ie, cocaine and methamphetamine).
  - Randomization to active intervention versus waitlist arms.
  - Set up active participants in the Senyo Health app.
- 12 weekly visits with LADC and pertinent study staff during the clinical treatment phase.
  - LADC will provide clinical counseling. The total number of counseling visits will be up to the discretion of the LADC, with a target goal of at least 1 hour weekly.
  - Questionnaires: Brief Substance Craving Scale [39], Timeline Followback [41], Generalized Anxiety Disorder-7 [42], Patient Health Questionnaire-9 [43], and Epworth Sleepiness Scale [44].
- Additional items monthly on weeks 4, 8, and 12.
  - Urine drug screen.
  - Brief Assessment of Recovery Capital [40].
- Final visit of active treatment (week 12).
  - Acceptability of Intervention Measure.
  - Intervention Appropriateness Measure.
  - Feasibility of Intervention Measure.
  - System Usability Scale [45].
- The follow-up phase begins immediately after completion of 12 weeks of active treatment. Visits will occur at weeks 4, 8, and 12, and at 1 year.
  - Questionnaires: Brief Substance Craving Scale [39], Timeline Followback [41], Generalized Anxiety Disorder-7 [42], Patient Health Questionnaire-9 [43], Epworth Sleepiness Scale [44], and Brief Assessment of Recovery Capital [40].
  - Urine drug screen.
- Individuals randomly assigned to the waitlist phase will follow the “follow-up phase” schedule during their 12 weeks prior to active intervention.

Table 1. Study activities[a].

Assessment	Baseline	Active treatment phase (week)												Follow-up or waitlist phase (week)											1 year
		1	2	3	4	5	6	7	8	9	10	11	12	1	2	3	4	5	6	7	8	9	10	11	12	
Consent	✓																									
Check-in		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓				✓				✓				✓	✓
TLFB[b]	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓				✓				✓				✓	✓
BSCS[c]	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓				✓				✓				✓	✓
ESS[d]	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓				✓				✓				✓	✓
PHQ-9[e]	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓				✓				✓				✓	✓
GAD-7[f]	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓				✓				✓				✓	✓
TAM[g]	✓				✓				✓				✓				✓				✓				✓	✓
Urine test	✓				✓				✓				✓				✓				✓				✓	✓
BARC[h]	✓				✓				✓				✓				✓				✓				✓	✓
SUS[i]													✓													
AIM[j]													✓													
IAM[k]													✓													
FIM[l]													✓													

[a]Participants will be randomly assigned to immediately start the 12-week study intervention or be put on a waitlist for 12 weeks and then start the study intervention. There will be long-term follow-up at 1 year.

[b]TLFB: Timeline Followback.

[c]BSCS: Brief Substance Craving Scale.

[d]ESS: Epworth Sleepiness Scale.

[e]PHQ-9: Patient Health Questionnaire-9.

[f]GAD-7: Generalized Anxiety Disorder-7.

[g]TAM: treatment attendance monitoring.

[h]BARC: Brief Assessment of Recovery Capital.

[i]SUS: System Usability Scale.

[j]AIM: Acceptability of Intervention Measure.

[k]IAM: Intervention Appropriateness Measure.

[l]FIM: Feasibility of Intervention Measure.

Outcomes

This protocol has 2 phases. For the initial implementation phase, the primary outcome will be a thematic analysis of coded structured interviews of clinic stakeholders, with a focus on whether noted SBIRT barriers were effectively modified during implementation. For the clinical trial phase, the study end point is the week 12 assessment of the primary outcome measure, overall substance use as measured by Timeline Followback. We anticipate that patient involvement in the active phase will lead to a significant reduction in substance use relative to the end of the waitlist period. Secondary outcomes will explore abstinence rates, treatment retention, along with treatment effects on craving, recovery capital, psychiatric well-being (Patient Health Questionnaire-9, Generalized Anxiety Disorder-7, and Epworth Sleepiness Scale), and use of clinical services throughout the intervention and follow-up periods.

Data Analysis

Qualitative interviews will be recorded, transcribed, and coded on a rolling basis using a rapid, template-based approach derived from the interview protocols [46]. Quantitative clinical treatment outcomes will be analyzed by comparing participant data at baseline, weekly during the intervention, and 12 weeks after the treatment (after completion of LADC visits). Our recent meta-analysis indicated that CM delivered through an app had a large effect size for improving substance use–related outcomes relative to control conditions [20]. Using this to inform our power calculation, there is greater than 0.80 power to see a large effect size between active and waitlist groups at the primary study end point. We will use information from this pilot to inform sample size calculations for a larger controlled efficacy trial. Several exploratory end points (eg, anxiety and depression) will be evaluated to contextualize the primary end-point effect. We will use likelihood methods (eg mixed models) that allow

for data that are missing at random, so we will not impute any missing data. Intention-to-treat will be used.

Safety Monitoring

During the study, the LADC will be the first point of contact with the patient. Their app-based communications with the patient will focus on assessing symptoms, addressing clinical concerns, and providing brief encouragement to continue predetermined goals. The LADC will meet with the study psychiatrist and review the history obtained from the patient during their initial evaluation. The LADC will write a formal weekly update note on each patient, and monthly clinical tracking scores will be reviewed and reported to the consulting psychiatrist. Psychiatric recommendations for the management of addiction concerns and related mental health issues (ie, worsening mood or suicidality) will be reported back to the primary care providers, who will ultimately remain responsible for clinical decision-making and the treatment plan that may involve starting medications as a part of their clinical care. This patient review and consultation system will be managed through the provider portal, which will also serve as the patient population registry for quantitative tracking of clinical concerns with specific and quantitative end-point treatment goals.

Once a patient is enrolled in the study, the LADC and study staff will use the American Society of Addiction Medicine criteria to determine ongoing appropriateness for the current level of care [38]. To stay in the study, participants must remain eligible for outpatient SUD care. If the participant's American Society of Addiction Medicine criteria worsens enough that psychiatric recommendation is a higher level of care, they will be referred clinically to residential SUD treatment. The participant's active treatment phase will be stopped and moved into the follow-up phase for the schedule of visit. Adverse events will be reported to the psychiatrist for evaluation and reviewed for reporting requirements to the IRB.

Results

The Senyo Health app was launched in May 2023, and the most recent update was in August 2024. Our funding period began in September 2023 and will conclude in July 2027. This protocol defines a novel implementation strategy for leveraging a digitally native, clinical platform that enables the delivery of CoCM to target an SUD-specific patient population. Our trial will begin in June 2025.

We have not yet started enrollment in the primary study. In December 2024, focus group testing of the mobile app with people who have SUDs and are in treatment was completed. LADCs who reviewed the mobile and desktop apps were also interviewed. Their feedback has been used to improve the interface, design, and fix bugs, preparing for the primary study enrollment.

Discussion

Overview

This protocol builds from the large literature base that has described the positive effects of telehealth both before and after the COVID-19 pandemic [2,47]. Most treatment-seeking individuals report high patient satisfaction with telehealth [47]. Specific to alcohol use, digitally delivered interventions have been shown to significantly decrease heavy and binge drinking for both male and female patients and increase treatment retention at 1 year [48,49]. The use of telehealth among Medicare beneficiaries with an opioid use disorder was significantly associated with greater treatment retention and reduced odds of medically treated overdose [50]. App engagement, however, is typically low for traditional health-related apps. Individuals often use these apps for less than 1 week [31]. User time, effort, and attention can measure user engagement [51,52]. Greater engagement has been correlated with improved abstinence rates among apps incorporating CM and CBT modules [53]. Social rewards through apps, such as support from a health care provider via messaging, also produce significantly greater user engagement than fully automated apps [32]. These are core features of Senyo Health and help differentiate it from other interventions.

Additionally, the use of digital interventions to drive changes in recovery capital is largely unknown. A study of individuals engaging through a recovery-based web page noted that positive digital interactions help bind individuals within groups, supporting the overall recovery process [54]. This is reflecting community involvement and social connectedness, which are important aspects of recovery capital. Little else is known about the use of digital interventions in this space.

It is important to note that app creation is expensive. Additionally, apps are slow to create and typically costly to update. Senyo Health was created with sustainability in mind. It is owned solely by the Mayo Clinic, is fully operational, and is actively in use. New modules can be created within a desktop-based application directly linked to the app that we call the "researcher portal." The researcher portal allows for easy and rapid creation of new content without the need for changes to the app's code or new versions of the app to be pushed to the App Store. This allows for easy iterative improvements to existing content with no development costs. This feature dramatically reduces long-term costs and allows for real-time improvements based on user feedback.

Principal Findings

We will use mixed methods (interviews and questionnaires or scales) to evaluate implementation outcomes. We anticipate the identification of facilitators and barriers for the successful implementation of SBIRT and Senyo Health within a rural primary care workflow. Based on these findings, our hope is that through iterative enhancements, the rollout from site 1 to sites 2 and 3 will be increasingly streamlined.

While engaged in treatment services, substance use–related outcomes typically improve overall. Our proposed program is a combination of multiple evidence-based interventions, and as such, we expect a significant improvement in the active arm versus the waitlist control group. Additionally, we anticipate seeing recovery capital growth as individuals are engaged in treatment. As this growth has been significantly associated with decreased cravings [55] and past 30-day abstinence of alcohol and methamphetamine use [56,57], we hypothesize a significant

correlation between substance use and recovery capital changes. As recovery capital growth for female patients has been reported as suppressed compared to male patients while in treatment [58], we will also explore possible sex differences.

Limitations

As with all pilot trials, there are potential barriers. This intervention relies on wireless internet or cellular data capabilities. Access to these is improving across the United States; however, residents in rural areas, which is our main target population, have disparities in internet access [6,59]. We do not anticipate that this will affect the app, as the media is cached or can be buffered; however, it may negatively impact live counseling sessions. This will need to be monitored and will be individual-specific. The study also relies on the willingness of primary care patients to participate in a novel addiction treatment paradigm. We suspect that the flexibility, convenience, and potential receipt of positive reinforcers through CM will aid in recruitment. Additionally, because patients in primary care often have an unmet need for specialty addiction treatment, we anticipate strong interest and engagement with this intervention. Finally, a lasting intervention will require clinical champions at primary care sites to help foster interest among treatment staff. If clinical providers are not interested, this will hamper dissemination to patients. The initial qualitative aspect of this trial, which focuses on facilitators and barriers, will be pivotal in maximizing the potential long-term success of this intervention.

Conclusions

Addiction is widely prevalent and negatively impacts health from both acute and chronic use. Treatments are available; however, uptake is low, and access is limited. Senyo Health is a digitally native platform that combines multiple evidence-based interventions to address and treat SUDs. Its flexibility is particularly useful for rural populations, who often experience severely limited access to treatment. Senyo Health is freely available for download to be used without CM, LADC, or CoCM components. However, we feel that these aspects are essential for the highest treatment efficacy.

Acknowledgments

Research reported in this publication was supported by the Agency for Healthcare Research and Quality of the National Institutes of Health (award R18HS029774). Additional support was received from the Terrance and Bette Noble Foundation. BL receives financial support for research through the Mayo Clinic's Robert D. and Patricia E. Center for the Science of Health Care Delivery.

Data Availability

The datasets generated or analyzed during this study are not publicly available due to patient confidentiality protections and institutional data-sharing policies but are available from the corresponding author on reasonable request.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Semistructured interview used in the clinical trial.
[PDF File (Adobe PDF File), 241 KB - resprot_v14i1e65693_app1.pdf]

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Abbreviations

AUDIT-C: Alcohol Use Disorders Identification Test-Consumption
CBT: cognitive behavioral therapy
CFIR: Consolidated Framework for Implementation Research
CM: contingency management
CoCM: collaborative care management
DAST: Drug Abuse Screening Test
HIPAA: Health Insurance Portability and Accountability Act
IRB: institutional review board
LADC: licensed alcohol and drug counselor
SBIRT: screening, brief intervention, and referral to treatment
SUD: substance use disorder

Edited by A Schwartz, T Leung; submitted 22.08.24; peer-reviewed by L Tieu; comments to author 12.12.24; revised version received 07.01.25; accepted 25.02.25; published 26.03.25.

Please cite as:
Oesterle TS, Bormann NL, Paul MM, Breitinger SA, Lai B, Smith JL, Stoppel CJ, Arndt S, Williams MD
Treatment of Substance Use Disorders With a Mobile Phone App Within Rural Collaborative Care Management (Senyo Health): Protocol for a Mixed Methods Randomized Controlled Trial
JMIR Res Protoc 2025;14:e65693
URL: https://www.researchprotocols.org/2025/1/e65693
doi:10.2196/65693
PMID:

Protocol

Efficacy of a Web-Based Integrated Growth Mindset Intervention on Reducing Anxiety Among Social Work and Counseling Practicum Trainees: Protocol for a 2-Arm Randomized Controlled Trial

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Abstract

Background: Practicum is indispensable for the development of professional practitioners; yet, trainees may encounter psychological distress, especially anxiety, brought on by new challenges. Research stated that a positive mindset promotes better learning and mental status. Well-designed interventions have been shown to relieve anxiety and help trainees thrive in their practicums and professions. The proposed study adapted an integrated intervention, We-SMILE (Web-Based Single-Session Intervention of Mindset on Intelligence, Failure, and Emotion), for improving prepracticum anxiety and coping. We-SMILE has the potential to be a low-intensity self-help prepracticum intervention to support students in adjusting their mindsets and overcoming the challenges in practicum.

Objective: Using a 2-arm randomized controlled trial, this study aims to examine the efficacy of We-SMILE on reducing anxiety (primary outcome) and enhancing psychological status, psychological well-being, learning orientation, academic self-efficacy, and confidence (secondary outcomes).

Methods: A total of 117 students will be recruited from the social work and counseling programs and randomly assigned to existing prepracticum training (training as usual [TAU]) or that plus the We-SMILE. Participants will be assessed repeatedly at 3 time points: baseline, 2 weeks post intervention, and 8 weeks post intervention. The outcomes will be measured by validated items and scales on anxiety, mindsets, psychological well-being, and the Failure Mindset Scale. Recruitment for the pilot study was initiated in May 2024 during social work and counseling prepracticum briefing sessions. Participants were randomly assigned to the intervention or TAU group. The intention-to-treat (ITT) analysis principle and linear regression–based maximum likelihood multilevel models will be used for data analysis.

Results: This study has received research ethics approval in May 2024. Participant recruitment started at the end of May 2024, and enrollment was ongoing as of when this protocol was submitted. Data collection and analyses are expected to be complete in 2025.

Conclusions: The randomized controlled trial will compare the efficacy of the We-SMILE intervention group and the TAU group. The results of this study will benefit practicum students, fieldwork supervisors, and social work and counseling programs.

Trial Registration: ClinicalTrials.gov NCT06509802; https://tinyurl.com/36vkwd63

International Registered Report Identifier (IRRID): DERR1-10.2196/67234

(JMIR Res Protoc 2025;14:e67234) doi:10.2196/67234

KEYWORDS

implicit theory; growth mindset; social work students; counselling students; practicum; anxiety

Introduction

Prepracticum Anxiety

Practicum is an essential educational component of professional training [1,2], bridging the gap between theory and practice and enhancing the professional capacity and core competence of future practitioners [3,4]. The quality of fieldwork profoundly influences social work trainees' personal, intellectual, and professional development [4], per communication skills, critical reflection, professional growth, creativity, innovation, and self-efficacy [1,5]. Students and alumni frequently highlight their field experiences as pivotal in preparing them for their future roles [1]. Research indicated that continuous improvements in fieldwork training benefit the training of future practitioners, such as integration of resources, collaboration across sectors, and improvements in curriculum design [1,4,5]. Through practice and feedback, trainees gradually evolve from knowledge receivers to social workers and competent practitioners [6]. However, the process can be challenging and sometimes frustrating, with obstacles such as the rigorous training process and mental distress [4].

Research showed that students indeed face various challenges during practicums, which can be categorized into professional and individual levels [7]. At the professional level, anxiety and stress may rise when students experience issues with engagement, poor relationships, etc, related to trainers and supervisors [1,2,8,9] and are often exacerbated by the distinct cultural context and intense competition [6,7]. Moreover, although the programs usually prepare students for their placements, they may overlook the specific complexities of the work environment and the higher expectations of professional skills [4,10]. On the flip side, students probably encounter mental difficulties (eg, anxiety, stress, and compassion fatigue), financial pressures, maladaptive coping, physical problems, etc [7,11-15]. It has been noted that excessive anxiety and negative emotions can interfere with the practicum process [16]. Being adequately prepared to confront the challenges and difficulties in practicum is crucial for the learning outcomes and well-being of social work and counseling trainees.

Different coping mechanisms among students can lead to varied training outcomes. Clinical practicum students with the abilities to both manage their emotions and understand the emotions of the people around them have been shown to achieve better patient outcomes and patient satisfaction [2]. For example, dietitian students who effectively manage stress report the most supported feeling [10]. Conversely, students may doubt their abilities and talents if they find it tough to handle critical feedback and expectations from their supervisors and placement agency staff, besides the discrepancy between their preconceived notions before the practicum and the real situation [4,9]. Thus, fostering a positive attitude toward negative emotions, challenges, and feedback is essential to facilitate better learning outcomes and maintain trainees' mental health.

Existing Interventions and Gaps

The existing intervention approaches have broadly been delivered from 2 perspectives: the external perspective, such as transition support programs and peer group supervision [17-19], and the internal perspective, such as mindfulness training [20]. Transition support programs usually focus on supervisory support, transition-supportive learning activities, professional behavior and practice, and student internship responsibilities [4,18]. These programs are beneficial to students' mental health, specifically lowering anxiety, increasing confidence, improving preparation levels, and enhancing professional knowledge and skills [4,17]. Moreover, researchers examined the efficacy of peer group supervision in a practicum setting for counseling students [19] and found it was helpful to stimulate and bolster participants' professional self-efficacy, self-confidence, and feelings of pleasure and happiness [21]. However, several pertinent studies particularly highlighted mindfulness interventions for social work and counseling practicum trainees [22-24]. Mindfulness as a self-care practice was valuable for managing trainees' anxiety and strengthening self-care [20,25].

There is a notable lack of research evaluating the implementation of stress and anxiety management interventions in practicum settings for social work and counseling trainees. First, many studies usually develop and apply multiple-session interventions and must be led by professionals, expanding the trainers' workload [26]. More importantly, full-time employees and interns generally face different work tasks, challenges, and pressures [27]. However, existing interventions lack clear definitions and distinctions, so more evidence from interns' perspectives is needed. Lastly, the current interventions require more objective and reliable outcome indicators and well-designed randomized controlled trials. Thus, a low-intensity self-help prepracticum intervention to increase the preparation levels of social work and counseling trainees is desired.

Mindset Intervention

Mindset, which refers to implicit theory, means an individual's belief in the changeability of his or her attributes [28]. Individuals with growth mindsets believe that their attributes are changeable. Believing intelligence and emotion are temporary and evolving will prompt one to make efforts at learning and emotion regulation. In contrast, a fixed mindset indicates the belief that one's attributes are immutable [29-31]. The extant literature shows that the fixed mindset is related to more anxiety and stress, while the growth mindset contributes to proactive coping with anxiety and stress and resilience in the face of drawbacks [28,32]. Mindset is found to be a modifiable factor in intervention, which is essential in clinical psychology, therapy, prevention, and early intervention. These days, the growth mindset has been gradually introduced into practice and has yielded positive results [31,33,34].

Nevertheless, little research has been conducted on integrated mindset interventions, and there is very limited evidence for

this initiative. As mindsets can be domain-specific, one may have different mindsets regarding various domains [35]. When one faces a challenge, multiple mindsets may interact and intervene in one's coping behaviors. As for prepracticum trainees, their anxiety is multifaceted. Instilling growth mindsets regarding intelligence, emotion, and failure-is-enhancing mindsets, respectively, is worthwhile in easing anxiety and stress coping [36]. An integrated mindset intervention may be more efficient in reducing anxiety related to practicum, thereby preparing for the challenges that may be encountered.

Integrated Mindset Intervention: We-SMILE

This research has adapted an existing integrated mindset intervention by the principal investigator (PI: SZ), that is, PC-SMILE (Parent-Child Single-Session Mindset Intervention on Intelligence, Failure, and Emotion) for secondary school students [37]. The design is grounded in implicit theory research and supported by emerging evidence of the effect of brief interventions [38-42]. PC-SMILE is a 45-minute intervention that aims to instill growth mindsets of intelligence, failure-is-enhancing, and belief-in-change of emotion using neuroplasticity and real-life examples among students. The efficacy of PC-SMILE is being examined with a 3-arm randomized controlled trial [37].

The current protocol endeavors to modify the child-version of PC-SMILE for practicum trainees in social work and counseling programs, namely, We-SMILE (Web-Based Single-Session Intervention of Mindset on Intelligence, Failure, and Emotion). We-SMILE adheres to the core concepts of PC-SMILE with specific adjustments to practicum trainees' circumstances, that is, intending to introduce growth mindsets about intelligence, failure, and negative emotion to prepracticum students. We-SMILE starts with stories mirroring scenarios from social work and counseling practicum, followed by key principles from implicit theory, learning mechanisms, and emotion regulation, and finally supports these conceptions with solid evidence from research. One highlight of We-SMILE is that it includes a session dedicated to time management, an issue that new practicum students often struggle with. In this section, students are introduced to effective time management tools and ways of enhancing awareness of allocating time without burning out. Then, transferred to self-care methods to manage emotions caused by practicum experiences.

Aims

The protocol aims to assess the efficacy of We-SMILE through a 2-arm randomized controlled trial.

The primary objective is to evaluate the efficacy of We-SMILE in reducing anxiety related to practicum among social work and counseling trainees compared to the training as usual (TAU) group.

The secondary objective is to evaluate the efficacy of We-SMILE on secondary outcomes, including (1) relieving depression, anxiety, and stress; (2) improving psychological well-being; (3) enhancing learning orientation; and (4) increasing academic self-efficacy and confidence related to practicum compared with the TAU group.

Methods

Design of We-SMILE and Implementation Strategies

Patient and public involvement is a key principle we adopted in the intervention design and implementation strategies. The intervention design was coproduced by the research team and student advisory group who have completed at least one practicum training.

The first step is preintervention development. The needs for prepracticum mindset training were identified through interviews with the students who completed their summer practicum in 2023. Second, during intervention development, a student advisory group of 3 social work students was invited to participate in pilot studies and provide suggestions on the initial questionnaires, videos, and the final intervention regarding content consistency, process clarity, ease of understanding, and intervention duration. Third, after the pilot study in May 2024, participants' open-ended feedback will be collected for intervention improvement. We also invited 3 participants to interview for detailed comments. Based on the feedback and comments, further improvements were made. Thematic analysis will be conducted to integrate participants' feedback to identify what they perceive as the most beneficial aspects of the intervention and those most in need of improvement. Coproduction is helpful to ensure the intervention's acceptability, feasibility, relevance, and effectiveness. Fourth, about implementation strategies. The implementation process was co-designed with the fieldwork coordinators. We collected feedback from supervisors and teachers in the social work program. They will help send invitations to upcoming prepracticum social work and counseling students during briefing sessions and share the research link with the students via WhatsApp group once this study begins. Our study adheres to the CONSORT-EHEALTH (Consolidated Standards of Reporting Trials of Electronic and Mobile Health Applications and Online Telehealth) checklist (version 1.6) and follows the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) guidelines (see Multimedia Appendices 1 [43] and 2 for details).

The intervention is a 45-minute web-based course, finally consisting of five elements: (1) an introduction to a proactive mindset, including neuroplasticity, the malleability of intelligence and emotion, and the importance of failure and feedback in the learning process; (2) stories and testimonials during practicum, which emphasize the belief in change; (3) short videos about allegories of developing intelligence, emotion, and failure mindsets; (4) common questions and misconceptions about growth mindsets; and (5) self-persuasive writing exercises in which participants write down their thoughts and suggestions for others about growth mindsets. Figure 1 displays the intervention home page, Figure 2 provides an example of a story emphasizing the positive aspects of failure, and Figure 3 presents the neuroplasticity foundation linked to a growth mindset. Participants in the TAU group will be provided with the We-SMILE after completing the 8-week follow-up.

Figure 1. Home page of We-SMILE. We-SMILE: Web-Based Single-Session Intervention of Mindset on Intelligence, Failure, and Emotion.

Figure 2. A screenshot from one of three short stories about failure. In the screenshot, Red Bean says, “If only I’d eaten the fourth vegetable and meat bao straight away, just one would have filled me up!”.

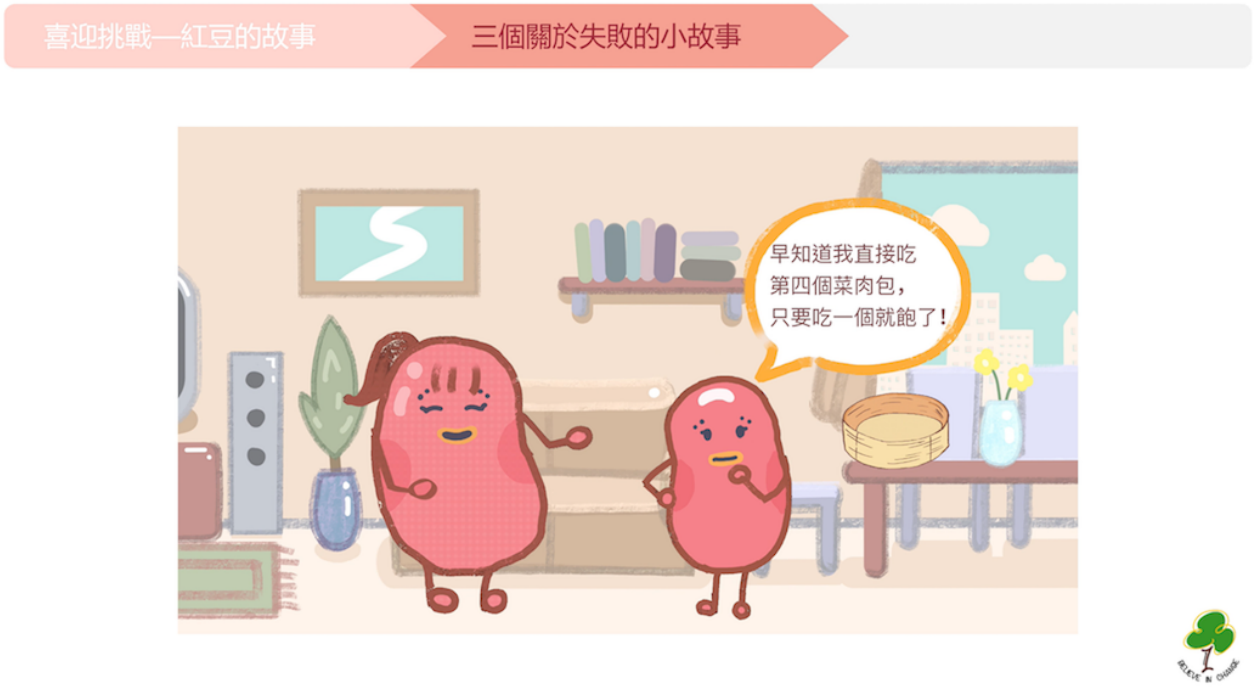
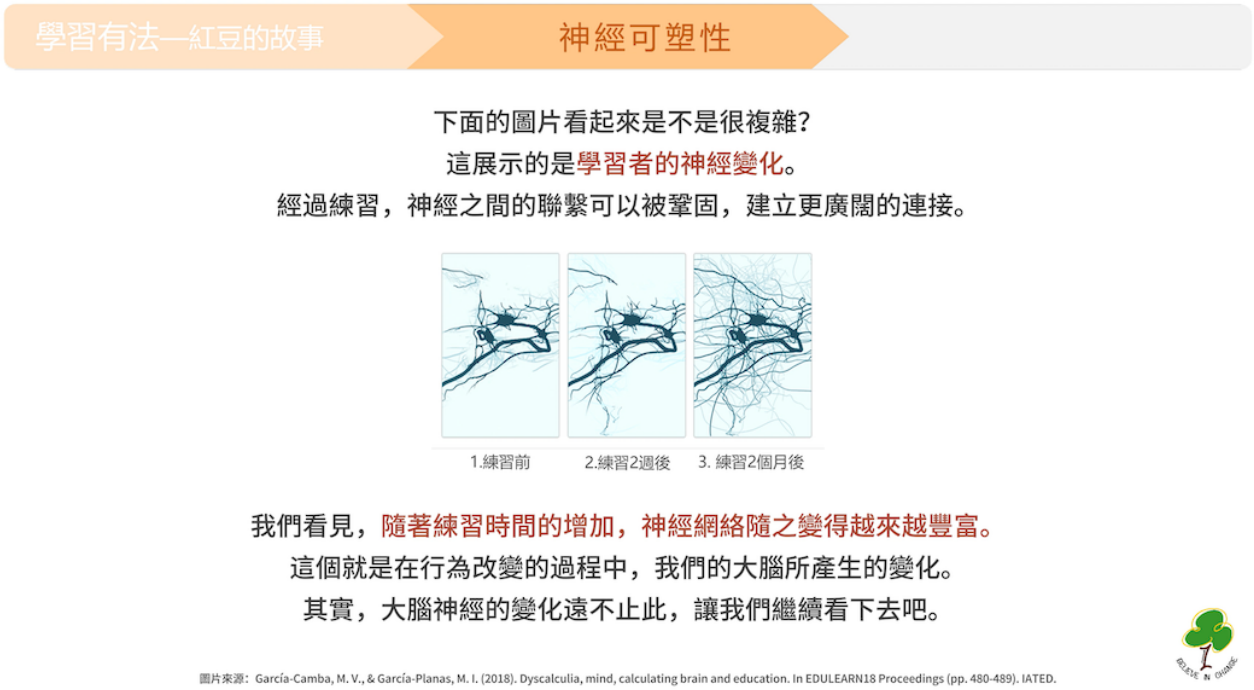


Figure 3. A screenshot demonstrating the neural changes in a learner. The image and text indicate that “Through practice, the connections between neurons can be strengthened, establishing broader connections. We can see that as practice time increases, the neural network becomes progressively more enriched. This is the change that our brains undergo during the process of behavioral change. In fact, the changes in brain neurons go far beyond this. Let's continue to explore.”.



Randomization Process

Randomization will be performed via the randomization module of Qualtrics with a 1:1 allocation, whereby students will be allocated to either the We-SMILE group or the TAU group. Students assigned to the We-SMILE group will receive the intervention link immediately, while participants in the TAU group will be provided with the course 8 weeks later. Both groups will be taught by instructors with equivalent qualifications and expertise in the subject matter to ensure consistency in the teaching quality. Concealment can be ensured as participants complete the survey individually and randomization is set after the baseline assessment. The data will be collected at 3 intervals: baseline, 2 weeks after the intervention, and 8 weeks after the intervention; that is, the research team will send the link of follow-up questionnaires to participants at the corresponding time.

Sample Size and Power Analysis

This study targeted prepracticum social work and counseling students during the period 2024-2025. The sample size is 117, based on the number of trainees. The G*Power is used to determine the target sample size, achieving adequate efficacy to detect mean group differences of small (d=0.2), medium (d=0.5), and large (d=0.8) effect sizes using 2-tailed tests with α=.05. Although previous studies have indicated that the ideal is to detect small effects, the target sample of 117 in this study may reflect the ability to detect moderate to large effects (slightly greater than 0.5) due to limitations on the number of students in the programs [44].

Participant Eligibility

Undergraduate and postgraduate prepracticum students in social work and counseling programs from universities in Hong Kong and Mainland China are eligible. Inclusion criteria are students who (1) are about to start the practicum soon, (2) can read and write Chinese, and (3) consent to participate. Exclusion criteria are students who (1) do not consent to participate, (2) cannot concentrate for at least 45 minutes to complete the intervention and questionnaires, (3) have a disability or serious physical or mental illness resulting in poor condition, and (4) do not participate in the practicum.

Measurements

Figure 4 illustrates the specific research arrangements and measurement schedules.

Figure 4. Study periods, arrangements, and measurement schedules. T: time point; TAU: training as usual.

	Study period						
	Enrollment	**Allocation**	**Postallocation**				**Close-out**
Time point	$-T_1$	0	T_0: week 1	T_1: week 1	T_2: Week 2	T_3: Week 8	T_x
Enrollment							
Eligibility screen	✓						
Informed consent	✓						
Allocation		✓					
Intervention							
Intervention group			◄	►			
TAU group						✓	
Assessments							
Intervention group			✓	✓	✓	✓	
TAU group			✓		✓	✓	
1. Demographics			✓		Student number	Student number	
2. Mindset about intelligence			✓	✓	✓	✓	
3. Mindset about failure			✓	✓	✓	✓	
4. Anxiety related to practicum			✓	✓	✓	✓	
5. Depression, anxiety, and stress			✓		✓	✓	
6. Psychological well-being			✓		✓	✓	
7. Learning and performance orientation			✓		✓	✓	
8. Academic self-efficacy			✓		✓	✓	
9. Confidence related to practicum			✓		✓	✓	
10. Intervention feedback (close-and open-ended)				✓			
11. Motivation				✓			

Demographics

Name, gender, ethnicity, year of birth, year of study, program type, program name, student number, practicum mode, previous social work experience, and other work experience will be collected at baseline. Students' university numbers will be collected again at 2 follow-ups for matching. Collected students' names and university numbers are solely for administrative purposes, such as matching pre- and postintervention data and ensuring accurate contact with participants for compensation after this study.

Fidelity Checking

Mindset about intelligence will be assessed by a 3-item Growth Mindset Scale developed by Dweck et al [45] with high internal reliability across studies, including "you have a certain amount of intelligence, and you can't really do much to change it," "your intelligence is something about you that you can't change very much," and "you can learn new things, but you can't really change your basic intelligence." Each item will be rated from 1=strongly disagree to 6=strongly agree. A higher average score means participants believe less that they can become smarter if they work at it. The reliability was reported in adolescents with Cronbach α of 0.71 [46].

Mindset about failure will be measured by the 6-item Failure Mindset Scale [47,48]. The first 3 items indicate that failure can be a positive motivation (eg, "The effects of failure are positive and should be utilised"), while the last 3 items indicate that failure is a setback (eg, "The effects of failure are negative and should be avoided."). Each item will be rated from 1 (strongly disagree) to 6 (strongly agree). The Cronbach α was 0.76 [48].

Primary Outcome Variable

Anxiety related to practicum will be measured by 4 items proposed by Gelman which parallels with the evaluation often used in social work practice [16], including 1 direct measuring item: "level of anxiety about starting the practicum," and 3 indirect measuring items: "how much your anxiety will interfere with their learning," "how prepared you are for the practicum" and "how excited you are to participate in the practicum" [16,49]. Each statement will be rated on a 10-point Likert scale, ranging from 1=completely not anxious, very small, completely unprepared, and completely unexcited to 10=extremely anxious, very great, perfectly prepared, and extremely excited [16]. The Cronbach α was 0.70 [50].

Secondary Outcome Variables

Depression, anxiety, and stress will be assessed by the simplified 12-item Depression Anxiety Stress Scales (DASS-12) [51,52]. The items of DASS-12 were shortlisted from the DASS-21, such as "I found it hard to wind down" [51,52]. Each item will be rated from 0=never to 4=almost always according to the participant's status over the past week. A higher score indicates a higher level of recognition of one's recent mental distress symptoms. The Cronbach α was 0.90 [52].

Psychological well-being will be measured using the 7-item Short Warwick-Edinburgh Mental Well-Being Scale [53,54]. One example item is "I've been feeling optimistic about the future." Each item is rated from 1 (none of the time) to 5 (all of the time). Higher scores suggest better mental well-being. The Short Warwick-Edinburgh Mental Well-Being Scale was validated in Hong Kong, and the Cronbach α was 0.89 [55].

Learning and performance orientation will be assessed by 11 adapted items from learning orientation and performance orientation scale [56], with 5 items measuring the learning orientation (eg, "I like to learn new knowledge in practicums") and 6 items measuring performance orientation (eg, "I like to seek rewards in short term for my efforts"). Each item will be rated on a 5-point Likert scale from 1=strongly disagree to 5=strongly agree. Reliabilities were reported of Cronbach α with 0.65 and 0.56 [56].

Academic self-efficacy will be measured by 5 adapted items from the Bandura Self-Efficacy Scale [57]. Example items are "I believe that as long as I study diligently, I will be able to master practical skills" and "as long as I am diligent, I can master all of the skills learned during the internship." The items will be scored from 1=strongly disagree to 5=strongly agree and reported a Cronbach α of 0.84 [57].

Confidence related to practicum will be assessed by a 6-item self-developed scale. Items generated from interviews with social work students, such as "I am confident that I can listen to comments from supervisors/colleagues/service users with an open mind" and "I am confident that I can manage my time well and cope with my practicum work and schoolwork at the same time." Each item needs to be rated from 1=strongly disagree to 5=strongly agree. A higher total score represents a higher level of confidence.

Intervention Feedback

Intervention feedback contains both close-ended and open-ended questions. The close-ended intervention feedback will be measured using an adapted 12-item 5-point Likert scale based on the Theoretical Framework of Acceptability scale [36]. The items include affective attitude, burden, perceived effectiveness, opportunity costs, and specific acceptability. A sample item is "does this course affect your daily schedule?" The open-ended question invites participants to share their thoughts about the intervention: "Do you have any other suggestions or feedback about this programme?"

Motivation will be measured using 2 self-designed items: "How much do you want to improve your ability to cope with challenges?" and "how much do you want to use what you have learned in the course to cope with challenges in your current or future practicum?" The items will be measured on a 6-point scale from 1=extremely not willing to 6=extremely willing. Higher scores indicate that participants are more motivated to learn from the intervention, apply it to their practice, and are intrinsically more willing to improve their status.

Pilot Study

The pilot study is initiated at the end of May 2024, before the commencement of the first batch of social work and counseling students' practicum. An overview of the intervention study is incorporated into the prepracticum briefing to attract participants. Upon obtaining consent, program supervisors will distribute the intervention course link to the students. Alongside standardized questionnaires, participants are invited to offer open-ended feedback on the intervention to facilitate future revisions and enhancements after finishing. Examples of feedback we currently received include "The content and duration can be condensed. The principle about red beans' story is something I believe everyone understands. It's better to directly point it out" and "If the voiceover is done by a real person, it would feel more authentic. The sound effects in the stories are very interesting" In the next revised version, the intervention will be shortened and improved with human voice dubbing from a professional actress.

Follow-Up Plan for Distressed Participants

Follow-up plans have been established to support participants who experienced severe distress during the trial. Research staff have been trained to respond to reports of distress from participants. If severe distress is identified, participants will be referred to appropriate resources, including counseling services and crisis hotlines provided by schools, government agencies, and nongovernmental organizations. Additionally, guidance on seeking professional help is included in the information sheet given to participants. Ensuring the mental health and well-being of participants is always our top priority.

Analytic Plan

Data analysis will be conducted according to the intention-to-treat (ITT) analysis principle, and missing data will be processed using multiple imputations. Descriptive analyses will be used for the distribution of demographics and all outcome variables. Analysis of covariance will be deployed to compare postintervention outcomes between the intervention and TAU groups, controlling for baseline differences. This approach ensures that the observed effects can be attributed to the intervention rather than preexisting differences, thereby enhancing the validity of the results. Generalized estimating equations will be applied to process data from repeated measures to initiate subgroup analyses and to assess differences in the efficacy of the intervention among participants with different work experiences, emotional states, and mindsets. Because of the cluster randomization, a 2-level analysis will be conducted [58]. Additionally, multilevel regressions will be used to test group effects, time effects, and their interactions on outcome variables. A *P* value of <.05 will be considered statistically significant, and all statistical analyses will be performed using SPSS (version 26; IBM Corp).

Data Quality Assurance

Respondents can review and change their answers through a "back" button. The investigators will be responsible for the quality control of the data. Data with response times that are too long or too short, as well as expired responses, will be excluded. Completion times from the pilot study will be used to determine thresholds for early or late submissions. The first entry will be kept to avoid duplicate entries. Two attention-checking items are embedded to identify careless responses.

Protocol Amendments

In general, the research will be conducted following the protocol. The protocol should be seriously and carefully revised and reapproved by the ethics committee of the PI's university if major modifications are necessary for any reason or if the change will impact the conduct of this study and the interests of the participants. Minor adjustments that do not have significant impacts on this study and participants will be recorded for subsequent supplementation of ethical and trial materials.

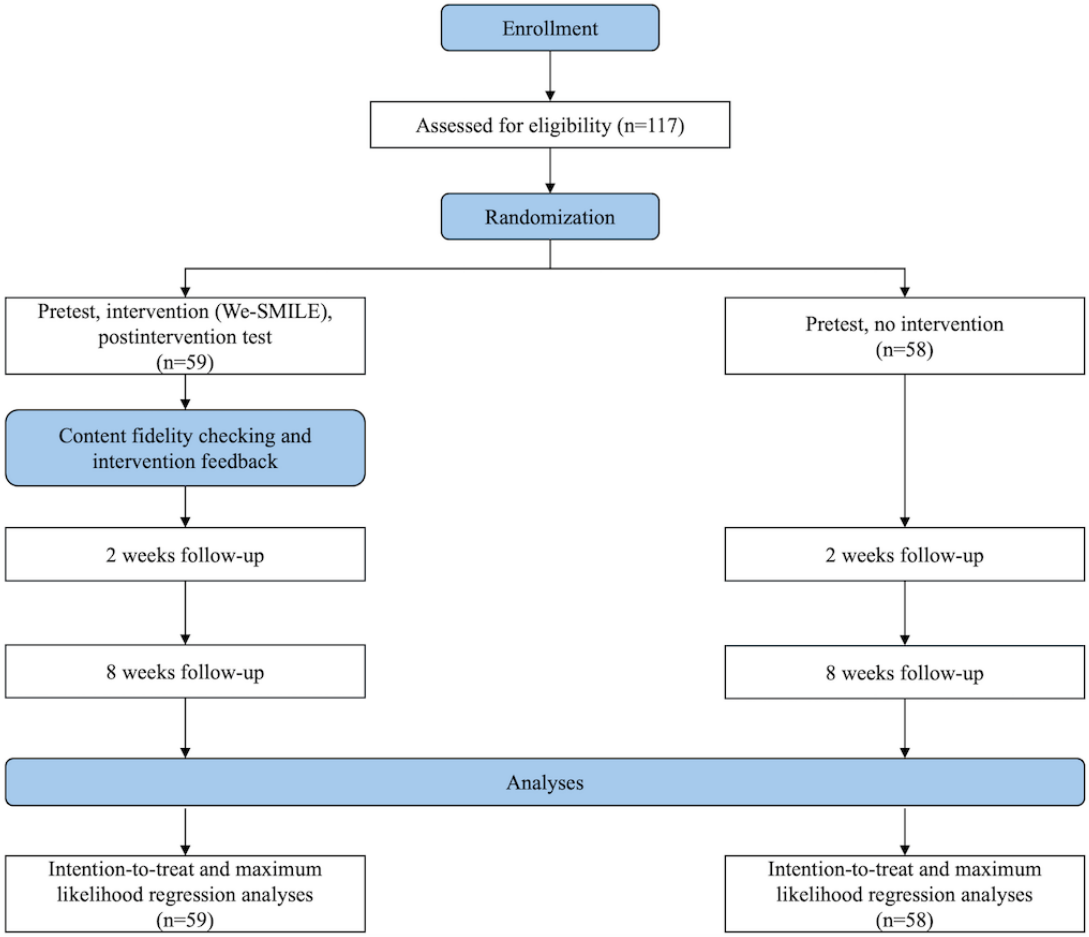
Ethical Considerations

This study has received research ethics approval from the institutional review board of the PI's university (HSEARS20240512001-01). Students who click the link sent by supervisors and teachers will first read the information sheet and sign the consent form. The participants can decide when to start and withdraw from the intervention. The primary investigators will be responsible for the management of research data. All identifying information of participants will be anonymized during the research process, including data analysis, results reporting, and publication. The data will be generated directly from the web-based survey platform and will be stored at the PI's university. All database files will be password-protected and can only be accessed by direct researchers. Researchers who have permission to access the data will be appropriately trained to maintain data confidentiality, integrity, and basic data security measures. All data and backups will be maintained till 5 years after the completion of the research. Each eligible participant will be contacted by the research team and receive HK $100 (US $12.87) supermarket vouchers after completing all the questionnaires.

Results

The project was funded by the Departmental Teaching and Learning Grant of the Department of Applied Social Sciences at PI's university (grant 8AL1). Recruitment began in May 2024, and data collection is expected to end in April 2025. Data collection is currently underway. The results are scheduled to be released in August 2025. We plan to issue a publication and may also disseminate the results at conferences. The flow of this study is shown in Figure 5.

Figure 5. CONSORT diagram. CONSORT: Consolidated Standards of Reporting Trials; We-SMILE: Web-Based Single-Session Intervention of Mindset on Intelligence, Failure, and Emotion.



Discussion

Principal Findings

The purpose of this study is to initiate a randomized controlled trial among prepracticum social work and counseling students, assessing the efficacy and acceptability of a digital integrated growth mindset intervention (We-SMILE). It is expected that the We-SMILE group will present lower anxiety related to practicum and more positive secondary outcomes compared to the TAU group. Although this is a single-session, web-based self-help intervention, its efficacy, effectiveness, and sustainability should not be overlooked, as it may continue to serve a useful purpose beyond the project period [44].

We-SMILE is an innovative, convenient, and promising intervention for prepracticum training with a focus on the growth mindset. The We-SMILE will be the key deliverable of the proposed project and has several remarkable advantages. First, We-SMILE is theory-based. Extant interventions with similar core concepts from Western or local practice have been found effective in improving mental health [28,36,40]. Second, patient and public involvement and the coproduction process involving students and fieldwork supervisors ensure We-SMILE to be a tailor-made intervention for practicum trainees. Third, the web-based and nonstigmatizing natures increase accessibility and flexibility for young individuals. Once the efficacy of We-SMILE is established, the integrated mindset prepracticum intervention can help hundreds of students be psychologically prepared for fieldwork training. While providing mental support, it can also supplement practicum education as a readily accessible module to enhance the training outcomes of social work and counseling students. Additionally, this study will provide clear implementation protocols and strategies to increase transparency. The intervention study can be replicated, developed, and referenced as a basis for future research and the design of single-session growth mindset interventions.

Strengths

Based on previous research indicating the lack of interventions targeting prepracticum training, the proposed study fills this gap by focusing on improving the growth mindset in this particular population. The project will benefit multiple parties. The immediate beneficiaries will be social work and counseling students. The intervention is designed to tune trainees' mindsets regarding how they perceive the learning process, feedback, failure, and emotion. It could help prevent a high level of anxiety and fear about receiving negative feedback and facilitate students building resilience in fieldwork training. Second, it could benefit fieldwork supervisors. We-SMILE offers a flexible intervention option as a concise psychoeducational tool that seamlessly fits into prepracticum preparation. It does not require an extra workload for supervisors and can easily be distributed for students' needs and reference. Alternatively, the intervention can be used as a specialized component of the existing

prepracticum training or incorporated into classroom teaching. Third, it may benefit the social work and counseling programs as a whole. We-SMILE provides an accessible intervention to assist social work and counseling students in transitioning into future workplaces with lower levels of distress, better self-efficacy, and becoming mentally prepared, which will in return improve the outcome and quality of education programs.

Limitations

Some limitations in this intervention require further consideration and refinement. First, this study only targets students in social work and counseling programs. The number of participants in each cohort will be limited. We may not be able to recruit a sufficient sample size if practicum trainees are occupied by coursework and internships and become too busy to complete the intervention course. There is a need to expand the scope of implementation by including a larger sample in the future to demonstrate that the intervention could be adapted into training for other education and health care domains. Second, as this study does not differentiate individuals with various levels of anxiety states, the effectiveness in reducing anxiety may not be significant for those students with no or low levels of anxiety, thus, it may affect the overall statistical significance. Therefore, we may conduct subgroup analyses to address this issue.

Conclusion

This study aims to develop a digital single-session integrated growth mindset intervention (We-SMILE) and to evaluate its efficacy and acceptability using a 2-arm randomized controlled trial among practicum trainees of social work and counseling programs. If proven effective, our study will provide a potential model for the implementation of a brief, low-dose, single-session intervention. In return, We-SMILE may also contribute to the development of accessible, highly adaptable, low-cost, and sustainable interventions in mental health education on a larger scale.

Acknowledgments

This work was supported by the Departmental Teaching and Learning Grant of the Department of Applied Social Sciences at The Hong Kong Polytechnic University (grant 8AL1). We thank social work students who served as student helpers in the coproduction of the intervention, including Oscar Cheung, Alfie Li, and Tim Lam. We also thank the students in the pilot study who provided helpful comments for intervention improvement. The social work or counseling program leader, supervisors, and student assistants contributed greatly to the development and conduct of the intervention and are gratefully acknowledged.

Data Availability

Data generated and analyzed during this study is not publicly available due to privacy and confidentiality issues but can be obtained by contacting the corresponding author upon reasonable request.

Authors' Contributions

SZ proposed this study concept, was responsible for the intervention design, funding acquisition, study supervision, paper writing, review, and revision. YW participated in the intervention design, data collection, paper writing, and revision. AX worked on the intervention design and paper revision. and SSKW, KY, and JTYL facilitated the data collection. All authors read and approved this paper.

Conflicts of Interest

None declared.

Multimedia Appendix 1
CONSORT-eHEALTH checklist (V1.6.1).
[PDF File (Adobe PDF File), 948 KB - resprot_v14i1e67234_app1.pdf]

Multimedia Appendix 2
SPIRIT checklist.
[DOC File , 119 KB - resprot_v14i1e67234_app2.doc]

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Abbreviations

CONSORT-EHEALTH: Consolidated Standards of Reporting Trials of Electronic and Mobile Health Applications and Online Telehealth
DASS: Depression Anxiety Stress Scales
ITT: intention-to-treat analysis
PC-SMILE: Parent-Child Single-Session Mindset Intervention on Intelligence, Failure, and Emotion
PI: principal investigator
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials
TAU: training as usual
We-SMILE: Web-Based Single-Session Intervention of Mindset on Intelligence, Failure, and Emotion

Edited by A Schwartz; submitted 07.10.24; peer-reviewed by KW Tay; comments to author 09.12.24; revised version received 23.12.24; accepted 03.03.25; published 27.03.25.

Please cite as:
Wang Y, Xi A, Wong SSK, Yam K, Leung JTY, Zhu S
Efficacy of a Web-Based Integrated Growth Mindset Intervention on Reducing Anxiety Among Social Work and Counseling Practicum Trainees: Protocol for a 2-Arm Randomized Controlled Trial
JMIR Res Protoc 2025;14:e67234
URL: https://www.researchprotocols.org/2025/1/e67234
doi:10.2196/67234
PMID:

Protocol

Ayurveda Management of Menorrhagia (Raktapradara): Protocol for a Randomized Controlled Trial

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Abstract

Background: In India, heavy menstrual bleeding or menorrhagia (*Raktapradara*) constitutes about 15% to 20% of all gynecological admissions in an institution. Of these, 43% of patients are aged 20-40 years. This condition is worsening because of the high prevalence of anemia among Indian women. Menorrhagia can have a significant impact on women's lives. Medical treatment is usually the first choice in excessive bleeding, but it reduces menstrual blood loss by only 50%, and up to 50% of women undergo surgical treatment within 5 years. However, none of these treatments proved their definite efficacy in spite of the high price and side effects. This condition presents a major financial burden on health care services. In Ayurveda, encouraging work has been done on the compound drug *Ashokarishta*, and the drug *Trinakantamani pishti* is indicated in Ayurvedic classics and the *Ayurvedic Formulary of India*. Also, these medicines have been used in Ayurvedic practice for a long time. However, no clinical trial has been carried out on these formulations.

Objective: The primary objective is to evaluate the efficacy of Ayurvedic intervention in the management of menorrhagia, and the secondary objective is to assess the efficacy of Ayurvedic intervention on the quality of life of the women with menorrhagia.

Methods: This ongoing study is an open-label, interventional, randomized controlled trial, with a sample size of 140 in the treatment and control groups combined (including 20% dropouts), and will be carried out within the duration of 36 months. Participants in the treatment group will receive Ayurvedic treatment, that is, 20 mL of *Ashokarishta*, 250 mg of *Trinakantamani pishti*, and 1 iron and folic acid tablet (100 mg of elemental iron and 1.5 mg of folic acid) twice a day orally for 3 months. Participants in the control group will receive a 500-mg tranexamic acid tablet thrice a day for 7 days from the first day of menses for 3 cycles and 1 iron and folic acid tablet twice a day orally for 3 months. The primary outcomes are changes in the amount of uterine bleeding evaluated by the Pictorial Blood Loss Assessment Chart, changes in the duration of bleeding, and attainment of a normal quantity of blood loss during the interval of cycles. The secondary outcome is changes in the Menorrhagia Impact Questionnaire.

Results: As of December 2024, a total of 79 patients have been enrolled. Data analysis should be completed by February 2026. The study will be reported following standard guidelines for reporting randomized controlled trials. Clinical results will be disseminated through conferences and peer-reviewed publications in a relevant journal.

Conclusions: The Ayurvedic approach may provide an evidence-based therapeutic tactic for the management of menorrhagia.

Trial Registration: Clinical Trial Registry India CTRI/2023/05/052929; https://tinyurl.com/3cd6mxrn

International Registered Report Identifier (IRRID): DERR1-10.2196/60801

(JMIR Res Protoc 2025;14:e60801) doi:10.2196/60801

KEYWORDS

Ashokarishta; Trinakantamani pishti; tranexamic acid; menorrhagia; Raktapradara

Introduction

Normal menstrual bleeding is cyclical, with 3-5 days in durations and 50-60 mL of bleeding in normal color, as described in Ayurvedic classics. However, when the normal menstrual bleeding pattern is altered in reference to duration, amount, color, and cycle, the conditions are called *Artavadushti*; *Raktapradara* is one of them, and it is comparable to menorrhagia. In India, menorrhagia constitutes about 15% to 20% of all gynecological admissions in an institution. Of these, 43% of patients are aged 20-50 years. This condition is worsening because of the high prevalence of anemia among Indian women [1]. Heavy menstrual bleeding (HMB) can have a significant impact on women's lives. HMB or menorrhagia is clinically defined as greater than or equal to 80 mL blood loss per menstrual cycle [2,3]. It is, however, the woman's perception of her own menstrual loss that is the key determinant in a referral and, indeed, subsequent treatment. In allopathic medicine, various medical treatment options are available, but many women proceed to surgery due to treatment failure or hormonal side effects. Surgery introduces the risk of bowel, bladder, and ureteric damage, as well as hemorrhage, infection, and even death [4]. So, there is a clear unmet clinical need for better medical treatments for this benign but incapacitating condition. *Ashokarishta* is a compound drug, consisting of 14 drugs described in the *Stree rogadhikara* (female disorders) section of the *Bhaishajya Ratnavali* book of Ayurveda [5]. The *phalashruti* (benefits at the end of the composition) of this medicine says that, by using the medicine for more than one month, it cures pain due to menorrhagia, fever, several types of hemorrhages, hemorrhoids, etc. *Trinakantamani pishti* [6,7] is a drug also mentioned for *Raktapradara* (HMB or menorrhagia) in Ayurvedic classics. As the effect of this medicine is mainly in bleeding disorders, it was decided to evaluate its efficacy in *Raktapradara* (Table 1). Some encouraging work has been done on the effect of *Ashokarishta* [8-10] on *Raktapradara*, but no work has been carried out on *Trinakantamani pishti* along with *Ashokarishta*. Tranexamic acid is a safe and effective form of medical therapy in women with menorrhagia; it also increases the quality of life in these women [11]. So, this study is planned to evaluate the efficacy of Ayurvedic treatment modalities in the management of menorrhagia and to assess the efficacy of Ayurvedic intervention on the quality of life of the women with menorrhagia, compared to the control intervention (tranexamic acid).

Table 1. Details of the investigational products.

Drug and components	Botanical name	Part used	Quantity
Trinakantamani pishti			
1. Trinakantamani	__[a]	—	1 part
2. Distilled rose water	—	—	As needed for *mardana* (triturate)
Ashokarishta			
1. Ashok	*Saraca asoca* L.	Stem bark	100 parts
2. Water for decoction (*kashaya*), reduced	—	—	256 parts
3. Guda (jaggery)	*Saccharum officinarum*	—	200 parts
4. *Dhataki*	*Woodfordia fruticosa* (L.) Kurz.	Flower	16 parts
5. *Ajaji*	*Nigella sativa* L.	Fruit	1 part
6. *Mustak*a (*musta*)	*Cyperus rotundus* Linn.	Rhizome	1 part
7. *Sunthi* (ginger)	*Zingiber officinale* Roxb.	Rhizome	1 part
8. *Darvi* (*daruharidra*)	*Berberis aristata* DC.	Stem	1 part
9. Utpala	*Nymphaea stellata* Willd.	Flower	1 part
10. *Haritaki*	*Terminalia chebula* Retz.	Whole plant	1 part
11. *Bibhitaka*	*Terminalia bellirica* (Gaertn.) Roxb.	Whole plant	1 part
12. *Amalaki*	*Phyllanthus emblica* L.	Whole plant	1 part
13. *Amrasthi* (*Amra*)	*Mangifera indica* L.	Endosperm	1 part
14. *Jiraka* (*sveta jiraka*)	*Cuminum cyminum* L.	Fruit	1 part
15. *Vasa*	*Adhatoda vasica* Nees.	Root	1 part
16. *Chandana* (*sveta candana*)	*Santalum album* Linn.	Heart wood	1 part

[a]Not applicable.

Methods

Study Setting

This study will be conducted at Vardhman Mahavir Medical College and Safdarjung Hospital, New Delhi, India.

Eligibility Criteria

Inclusion Criteria

Participants will include those aged 20-50 years with menorrhagia—that is, regular (21-35 days) cycle with HMB loss, subjectively or objectively defined (Pictorial Blood Assessment Chart [PBAC] score of more than 100 points) [12], or prolonged bleeding (bleeding more than >7 days) for 3 consecutive cycles—who are willing and able to participate in the study.

Exclusion Criteria

Participants with any of the following will be excluded: anemia (hemoglobin level <7%); hypertension; diabetes mellitus; hepatic or renal disease; cardiac disease; organic lesions of the reproductive tract due to conditions such as tuberculosis, carcinoma, and congenital deformities; pelvic inflammatory disease or cervicitis; evidence of malignancy, cervical intraepithelial neoplasia, or cervical carcinoma; history of untreated sexually transmitted disease or being HIV positive; past history of atrial fibrillation, acute coronary syndrome, myocardial infarction, stroke, or severe arrhythmia in the last 6 months; lactating women; current or previous use of oral contraceptive pills, glucocorticoids, antiandrogens, ovulation induction agents, antidiabetic drugs, antiobesity drugs, or other hormonal drugs recently (unless there is a washout period of 1 month); hypersensitivity to the trial drugs or any of their ingredients; currently participating in any other clinical trial or participated in past 6 months; or any other condition that the principal investigator thinks may jeopardize the study.

Study Interventions (Investigational Products)

Participants in the treatment group will receive 250 mg of *Trinakantamanipishti* twice a day orally before meals, 20 mL of *Ashokarishta* twice a day orally before meals, and 1 iron and folic acid tablet (100 mg of elemental iron and 1.5 mg of folic acid) twice a day orally after meals for 3 months. The treatment group's medicines (investigational products) will be procured from Good Manufacturing Practices–certified pharmacies, namely, Indian Medicines Pharmaceutical Corporation Ltd. and Central Ayurveda Research Institute, along with the Certificate of Analysis to ensure the quality and safety of the medicines. The study drugs will be kept in a secure place and will only be supplied to the participants under the guidance of the investigator. A record will be maintained for the drug dispensed.

Any discrepancies between amounts dispensed and returned will be explained.

Participants in the control group will receive a 500-mg tranexamic acid tablet thrice a day for 7 days from the first day of menses for 3 cycles and 1 iron and folic acid tablet twice a day orally for 3 months.

Strategies to Improve Adherence to Study Protocol

The compliance of taking trial drugs will be assessed at each visit during the follow-ups (30-day intervals) by assessing the approximate quantity consumed. The participants will be asked to return the empty container of medicine at the time of each follow-up visit. Repeated reminders will be given over the phone or through family members and project staff for regular taking of medicine.

Outcome Measures

Primary Outcome Measures

Primary outcome measures are changes in the amount of uterine bleeding evaluated by the PBAC, changes in the duration of bleeding, and the attainment of a normal amount of blood loss during the interval of cycles, evaluated at baseline, the end of every cycle up to 3 cycles, and follow-up visits.

Secondary Outcome Measure

The secondary outcome measure is changes in the Menorrhagia Impact Questionnaire (MIQ) [13], evaluated at baseline, the end of intervention period, and follow-up visits.

Safety Outcomes

The safety of the trial intervention will be evaluated by recording the incidence of adverse events on every scheduled follow-up visit. All adverse events during the study timeline will be recorded and monitored per the Good Clinical Practice Guidelines. The investigator will report the same to the institutional ethics committee and the sponsors at the earliest opportunity. To assess the safety, hematological and biochemical investigations such as complete blood count and liver and kidney function tests will be done at baseline and the end of the intervention period.

Sample Size

To calculate the sample size, we anticipated a difference of 70 units in average PBAC score after treatment between the two groups (*Trinakantamanipishti* along with *Ashokarishta* vs tranexamic acid tablet), with an SD of 137 units based on the results of the previous study [14]. With 95% confidence level (α=.05) and 80% power, the number of patients to be enrolled in the study was calculated using the following formula:

where $Z_{1-\alpha/2}$=1.96, $Z_{1-\beta}$=0.84, σ=137, and δ=70.

Expecting a dropout rate of 15%, the number of patients is estimated to be 60 + 9 = 69. Thus, approximately 70 patients should be enrolled in each group.

Randomization and Allocation

A randomization chart will be generated with the help of computer-generated random numbers. Participants will be randomized in a ratio of 1:1 to either of the two groups. The randomization schedule will be strictly controlled and remain with the biostatistician/data analyst. Sequentially numbered, sealed, opaque envelopes will be used to conceal the allocation.

Study Procedure

The participants will be screened for menorrhagia as per the inclusion criteria. Prior to any trial-related activity, the investigator will give the verbal information and written information in a printed form about the trial to the participant, parents, or guardians to read and understand. The investigator would ensure that the participants are fully informed about the aims, procedures, discomforts, and expected benefits of the trial. It must be emphasized that participation is voluntary, and participants have the right to discontinue the trial at any time without any prejudice. A voluntary, signed informed consent will be obtained from the participants prior to any clinical trial–related procedure.

After the screening, if the participants are found to be suitable, then they shall be enrolled in the study after signing the consent form. The required investigations will be carried out, and subsequently, within one week or as soon as laboratory values are received and found to be within permissible limits, the participants will be enrolled in the study, and that day will be considered visit 1 or the baseline visit. The treatment will be given to the participants after fulfilling all the formalities as per the protocol. The subsequent follow-ups will be on the 30th day (visit 2), the 60th day (visit 3), the 90th day (visit 4), the 120th day (visit 5), and the 150th day (visit 6; ie, completion of active treatment). Participants will visit the study site 6 times during the trial. The details of the activity during each visit are presented in Table 2 and Figure 1.

Table 2. Study schedule.

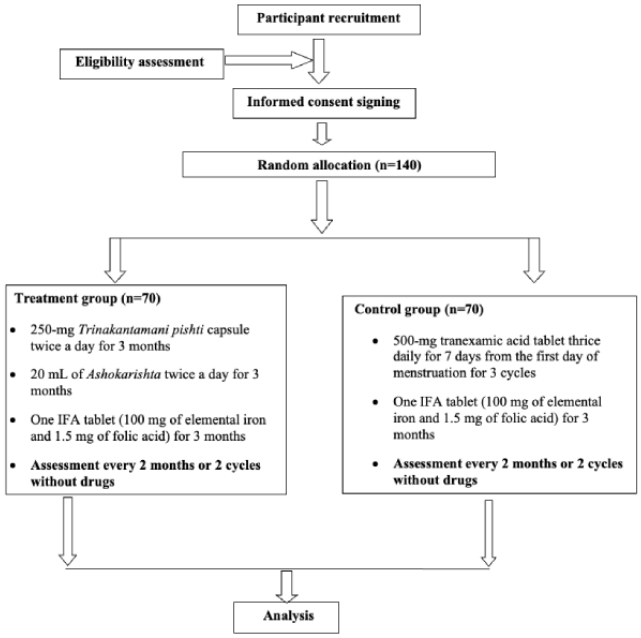
Components	Screening	Baseline (visit 1)	30th day (visit 2)	60th day (visit 3)	90th day (visit 4)	120th day (visit 5)	150th day (visit 6)
Informed consent	✓						
Demographics and medical history		✓					
Laboratory investigations	✓		✓		✓		
Assessment of clinical signs and symptoms		✓	✓	✓	✓	✓	✓
Assessment of the MIQ[a]		✓	✓	✓	✓	✓	✓
Clinical examination	✓						
Assessment of the PBAC[b]		✓	✓	✓	✓	✓	✓
Assessment of ADRs[c]			✓	✓	✓		
Assessment of drug compliance			✓	✓	✓		
Issue of trial drugs every 20 or 30 days							

[a]MIQ: Menorrhagia Impact Questionnaire.

[b]PBAC: Pictorial Blood Loss Assessment Chart.

[c]ADR: adverse drug reaction.

Figure 1. Flowchart of the study procedure.



Timelines With Deliverables

The total study period spans 36 months and is divided into four distinct phases. During the initial phase, which lasts from months 1 to 6, efforts will focus on procuring standard trial drugs and finalizing laboratory arrangements. Additionally, tasks such as staff recruitment, equipment procurement, and finalization of case report forms (CRFs) will be undertaken. The second phase, covering months 7 to 23, will be dedicated to the recruitment of participants for the study. Subsequently, months 24 to 34 will constitute the treatment period, during which participants will undergo interventions as per the study protocol, with follow-up assessments conducted accordingly. Finally, in the last phase spanning months 35 to 36, data compilation, analysis, report preparation, and publication will be the primary activities, culminating in the dissemination of study findings.

Laboratory Tests

The laboratory tests (hematological tests, biochemical tests, and ultrasonography) will be conducted in a National Accreditation Board for Testing and Calibration Laboratories–accredited laboratory. Hematology (hemogram, lipid profile, fasting blood sugar and postprandial blood sugar levels, and hemoglobin A_{1c} level); liver function test; kidney function test; venereal disease research laboratory test; HIV test; hepatitis B surface antigen test; ultrasonography (transabdominal sonography or transvaginal sonography); coagulation profile; hormonal test like thyroid profile, serum prolactin test, serum follicle-stimulating hormone test, and serum luteinizing hormone

test; routine urine culture; and microscopic urinalysis will be carried out at baseline and the end of the treatment (90th day). Coagulation profile will also be done at the middle of treatment (30th day).

Data Collection, Management, and Analysis

The data collection will include all information in the CRFs. All participants will be assigned an enrollment number, which will be used on CRFs and electronic databases. Consent forms and CRFs will be stored in locked cupboards, and electronic databases will be password protected. The data will be entered using the double-entry method for accuracy. All data will be accessible to the principal investigator and coinvestigators during and after the study has been completed and will be available to sponsors and monitors as required. Data will be stored for 5 years before being destroyed. In case of dropout, 10% data will be inserted through the imputation technique. Proper documentation will be done to ensure its accurate interpretation and verification. The analysis will be done by the Central Council for Research in Ayurvedic Sciences statistical unit.

Statistical Methods

Continuous variables will be presented as mean, SDs, medians, and ranges. Categorical variables will be summarized with frequencies and percentages. When inferential analyses will be conducted for continuous variables, they will be tested for normality. Nonparametric methods will be used to compare nonnormal data. Within-group comparison will be done using a paired *t* test (1- or 2-tailed, as suitable), while between-group comparisons will be done using an independent sample *t* test (1- or 2-tailed, as suitable) for the data following normal distribution. Nonnormal data within the group will be compared using the Wilcoxon sign rank test, while between groups comparison will be done by using the Mann-Whitney *U* test. Categorical data between groups will be compared using the chi-square or Fisher exact test. A 2-sided *P* value of <.05 will be considered statistically significant. Per-protocol and intention-to-treat analyses will be carried out at the end of the study. All data will be analyzed using Stata (version 16.1; Stata Corp).

Ethical Considerations

This research protocol had been reviewed and approved by the institutional ethics committee of Vardhman Mahavir Medical College and Safdarjung Hospital (S. No. IEC/VMCC/SJH/NOTE/2023-Feb/06). Participants will receive an information sheet with the research details given in two languages (Hindi and English). Voluntary signed informed consent will be obtained from the participants before any clinical trial–related procedure. The participants will be informed by the investigator that all trial data recorded will be treated with strict confidence. During documentation and analysis of the trial, the individual participant will only be identified by their enrollment number.

Participant confidentiality will be guaranteed, and only researchers will have access to the data. Participants are nominally compensated for their loss of wages and transportation costs by paying an amount of IND 100 (US $1.19) for every visit to the hospital during the study period.

Data Safety and Monitoring

The safety of the trial intervention will be evaluated by recording the incidence of adverse events on every scheduled follow-up visit. All adverse events during the study timeline will be recorded and monitored per the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use's Guideline for Good Clinical Practice. The investigator will report the same to the institutional ethics committee and the sponsors as soon as possible.

For facilitating appropriate reference standards for scientific, ethical, and safety issues before the trial begins, this protocol has been developed according to the 2013 SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) and CONSORT (Consolidated Standards of Reporting Trials) statements [15].

After completion of the study on 25% of the total participants, the data will be analyzed for the safety of the trial drugs. The project monitoring committee will monitor the trial's progress through review meetings and site visits as per the requirement to ensure strict adherence to the trial protocol and correct completion of the CRF.

Drug Compliance

The compliance of taking trial drugs will be assessed at each visit during the follow-ups (30-day intervals) by assessing the approximate quantity consumed. The participants with equal to or more than 80% compliance will continue in the study. The participants will be asked to return the empty container of medicine at the time of each follow-up visit. Repeated reminders will be given over the phone or through family members and project staff for the regular taking of medicine.

Prior and Concomitant Medication

Participants will receive clear instructions not to take any medication other than the trial drugs for any condition without prior consultation with the investigators. The investigator will advise participants to promptly report any additional signs, symptoms, or unusual occurrences and to seek guidance accordingly. Additionally, the investigator will diligently document any other medications taken by the participants for comprehensive recordkeeping.

Rescue Medication

Permission will be given for the use of rescue medication for alleviating any emergency condition as per the discretion of the investigator. It will be documented in detail in the CRF.

Results

As of December 2024, a total of 79 patients have been enrolled. Data analysis should be completed by February 2026. The study will be reported following standard guidelines for reporting randomized controlled trials. Clinical results will be disseminated to the public through conference presentations and peer-reviewed publications in a relevant, open-access journal.

Discussion

Conclusion

Ayurveda scholars correlate *Raktapradara* with menorrhagia (National Ayurveda Morbidity Code: EL-4) based on the similarities in causes, clinical features, and treatment. This paper describes the protocol for the Ayurvedic management of menorrhagia. We undertook a randomized controlled trial to objectively assess the efficacy of Ayurvedic treatments for the management of menorrhagia and compared it with standard conventional treatment. The changes are assessed objectively by using the PBAC score and MIQ as the outcomes for participants with menorrhagia.

Studies have demonstrated promising results of some Ayurvedic interventions for managing *Raktapradara*. With this study, we aim to observe the effectiveness and safety of Ayurvedic management using the formulations of *Ashokarishta* and *Trinakantamani pishti* in reducing symptoms associated with menorrhagia, such as HMB. If beneficial, this study could contribute significantly to integrative approaches for managing menorrhagia.

Strengths and Limitations

The strengths of this study include its randomized design and the inclusion of enough participants to allow for adequate statistical power for subgroup analyses. This study uses the PBAC score and MIQ, which are well-validated instruments to assess menorrhagia.

One potential limitation of this study is that the investigators were aware of the participants' group assignment, and therefore, bias in favor of any particular group cannot be excluded. However, every effort was made to ensure blinding of the participants during the group allocation. An independent evaluator blind to study conditions was responsible for administering all study measures. The protocol may also serve as a reference for the planning of similar clinical trials.

Acknowledgments

The authors are thankful to the institutional ethics committee, for approving the protocol, and to the Vardhman Mahavir Medical College and Safdarjung Hospital, for allowing the study to be conducted at their facilities. The study was funded by the Central Council for Research in Ayurvedic Sciences, New Delhi, India. Patients and/or the public were not involved in the design, conduct, reporting, or dissemination plans of this research.

Data Availability

The findings will be disseminated to the public through conference presentations and published in open-access, peer-reviewed journals. Analyzed data will be made available for interested researchers with a reasonable request after the publication of the results.

Authors' Contributions

SR, SM, US, SO, and BG developed the protocol. SR and SM registered the protocol and generated the first draft of the manuscript. SM revised the manuscript according to suggestions. The manuscript was reviewed and approved by all authors.

Conflicts of Interest

None declared.

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Abbreviations

CONSORT: Consolidated Standards of Reporting Trials
CRF: case report form
HMB: heavy menstrual bleeding
MIQ: Menorrhagia Impact Questionnaire
PBAC: Pictorial Blood Loss Assessment Chart
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials

Edited by A Schwartz, T Leung; submitted 22.05.24; peer-reviewed by BR Tubaki, Aminuddin; comments to author 04.12.24; revised version received 07.01.25; accepted 21.02.25; published 31.03.25.

Please cite as:
Rajput S, Mata S, Saxena U, Ota S, Gupta B
Ayurveda Management of Menorrhagia (Raktapradara): Protocol for a Randomized Controlled Trial
JMIR Res Protoc 2025;14:e60801
URL: https://www.researchprotocols.org/2025/1/e60801
doi:10.2196/60801
PMID:

Protocol

Cooperative Virtual Reality Gaming for Anxiety and Pain Reduction in Pediatric Patients and Their Caregivers During Painful Medical Procedures: Protocol for a Randomized Controlled Trial

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Abstract

Background: The hospital experience is often marked by fear and pain, particularly for children undergoing medical procedures. Sedation is commonly used to alleviate patient anxiety, but it poses additional health risks. Caregivers, usually the parents, also experience emotional distress during the child's hospital stay, which can further exacerbate the child's anxiety and pain. While various interventions exist to ease patient distress, few consider the emotional well-being of caregivers.

Objective: This study aims to explore the effectiveness of a cooperative virtual reality (VR) game as a novel nonpharmacological solution to reduce anxiety and pain for both pediatric patients and their caregivers during medical procedures. Specifically, we aim to investigate whether the VR game "Sweet Dive VR" (SDVR), designed for children aged between 6 and 12 years to play with 1 caregiver, can alleviate anxiety and pain during different types of needle punctures and Kirschner-wire removal.

Methods: A prospective multicenter randomized clinical trial will be conducted. Eligible participants will be identified by scanning the hospital information system, and group allocation will follow stratified randomization. During the medical procedure, patients in the VR condition will play SDVR with a caregiver present, while patients in the control group will listen to a recording of gently crashing waves. Data collection will be carried out through self-reports of patients and caregivers using visual analog scales and questionnaires at 2 measurement time points: before and after the intervention. In addition, observation by the interviewers will occur during the intervention to capture emotional and pain reactions as well as interaction quality between patients and caregivers and smoothness of the procedure flow using a structured observation protocol. The measured variables will encompass patient affect and pain, caregiver affect, player experience, patient experience, and the flow of the procedure.

Results: As of November 2024, we enrolled 39 patients and caregivers, 28 of whom completed the study. Data collection is still ongoing.

Conclusions: Cooperative VR gaming, as exemplified by SDVR, emerges as a promising intervention to address anxiety and pain in pediatric patients while involving caregivers to support the emotional well-being of both parties. Our approach strives to foster positive shared experiences and to maintain trust between children and caregivers during emotionally challenging medical situations.

Trial Registration: German Clinical Trial Register (DRKS) DRKS00033544; https://drks.de/search/en/trial/DRKS00033544

International Registered Report Identifier (IRRID): DERR1-10.2196/63098

(JMIR Res Protoc 2025;14:e63098) doi:10.2196/63098

KEYWORDS

virtual reality; extended reality; mixed reality; serious game; video game; pain; anxiety; stress; child; caregiver; patient experience; well-being; medical procedures; punctures; distraction; intervention

Introduction

Background

Fear and pain characterize the hospital experience. Children, due to a lack of understanding of the situation, often show extreme anxiety reactions even in objectively harmless situations such as magnetic resonance imaging [1]. Hence, the patient's anxiety and stress can complicate treatment procedures and interfere with the healing process [2-4]. As a result, it is a common practice to sedate patients by administering medication. However, the use of such medication is associated with additional health risks [5], particularly in the context of child development [6]. An additional factor that can influence the emotional experience of child patients is their caregivers, in most cases a parent. Caregivers are also under extraordinary emotional pressure during the child's stay in hospital. If a medical procedure causes intense fear or pain, it can strain the caregiver-child relationship, especially if the child perceives the caregivers as siding with medical staff instead of supporting them—for example, by helping to physically restrain the child [7]. As a result, anxiety, stress, and pain of patient and caregiver can mutually depend on and reinforce each other [8]. While there are numerous pharmacological and nonpharmacological options to ease the patient, the experience of the caregivers is rarely the focus of such interventions.

Therefore, it is advisable to explore nonpharmacological solutions to reduce anxiety and pain. Distracting patients from the medical situation in a controlled manner is an approach that has proven successful for a large variety of media such as movies, music, or toys [9]. The use of immersive technologies such as digital games and virtual reality (VR), in particular, has been shown to be effective in reducing anxiety and pain in a variety of medical situations in numerous studies, especially for needle-related procedures, burn care, and in dental medicine [9-13]. However, these solutions typically address only the patient, which may lead to patients and caregivers feeling disconnected from each other. VR has the potential to result in patients feeling separated from their caregivers due to the sensory shielding provided by wearing a head-mounted display (HMD), which is necessary to create the desired level of immersion. This, in turn, could have an unintended anxiety-increasing effect.

Approach

We are pursuing a new approach in our work: we have developed the cooperative, asymmetrical VR game "Sweet Dive VR" (SDVR) that involves the patient and a caregiver equally in the gameplay and promotes joint communication [14]. In this way, both parties are distracted from the intimidating medical situation without being artificially separated from each other. Involving caregivers in the game, thereby creating positive shared player experiences, can be a way of maintaining children's trust and reducing feelings of helplessness for both children and caregivers [15]. In addition to the game-related interaction with the child, the caregivers are given the task of reacting to certain steps of the medical procedure (eg, the application of a disinfectant or an oxygen cannula) by triggering in-game events. In this way, we achieve synchronization of the virtual world with the patient's real-world sensory impressions, which is intended to preserve and strengthen immersion for the patient on the one hand, while supporting the caregivers' sense of agency. SDVR was designed for children aged between 6 and 12 years and for application during needle-related procedures, in particular port punctures, bone marrow punctures, central and peripheral venous catheterization, and venipunctures. However, we are also planning to test our approach with more painful procedures, such as Kirschner-wire removal.

Objectives

While several different works have successfully used VR games as a distraction during painful procedures [14-16], SDVR is, to the best of our knowledge, the first game that involves both the patient and the caregiver and aims to enhance the emotional experience of both. This study aims to evaluate the effectiveness of using cooperative VR games during medical procedures to improve patient and caregiver experiences. Specifically, we examine whether SDVR can reduce patients' anxiety, pain, and agitation; improve cooperation; and positively influence caregivers' emotional states compared to a control condition in which a calming atmosphere is created by playing natural ocean wave sounds to promote relaxation.

Methods

Hypotheses

In this study, we investigate whether targeted distraction from anxiety- and pain-inducing medical procedures through cooperative VR gaming can reduce experienced pain and anxiety while fostering well-being for both the patients and their caregivers. A list of our hypotheses is presented in Textbox 1. Hence, the primary outcome of the study is a reduction in pain and anxiety ratings of the patient (hypothesis 1) as well as an improvement in the caregiver's emotional experience (hypothesis 2). Our intervention relies on targeted distraction through sensory immersion for the patient as well as cognitive immersion and game fun for the patient and caregiver. Thus, distraction from the medical procedure represents a further end point of the study (hypothesis 3 and hypothesis 5).

The smooth execution of the medical procedure, characterized by the cooperativeness of the patient and caregiver, the needlessness of sedation or fixation, and an uninterrupted flow, will be assessed as a secondary end point (hypothesis 4). Moreover, this study aims to evaluate the quality of SDVR with respect to the player experience of both patient and caregiver (hypothesis 5).

Textbox 1. A list of hypotheses.

Hypothesis 1: patient affect and pain

a. Patients playing Sweet Dive VR (SDVR) during the procedure will report reduced levels of *anxiety* compared with those in the control group.

b. Patients playing SDVR during the procedure will report reduced levels of *pain* compared with those in the control group.

c. Patients playing SDVR during the procedure will exhibit decreased *motoric activity* compared with those in the control group.

d. *Observer's* ratings of *patient cooperation* during the procedure will be improved in the SDVR group compared with those in the control group.

e. *Caregivers'* ratings of patient *pain* will be lower in the SDVR condition than in the control condition.

f. *Caregivers'* ratings of patient *anxiety* will be lower in the SDVR condition than in the control condition.

g. *Observers'* ratings of patient *pain* will be lower in the SDVR condition than in the control condition.

h. *Observers'* ratings of patient *anxiety* will be lower in the SDVR condition than in the control condition.

Hypothesis 2: caregiver affect

a. Caregivers in the SDVR group will experience more *positive emotions* during the procedure compared with those in the control group.

b. Caregivers in the SDVR group will experience fewer *negative emotions* during the procedure compared with those in the control group.

c. *Observer's* ratings of *caregiver cooperation* during the procedure will be improved in the SDVR group compared with those in the control group.

Hypothesis 3: player experience

a. The more positive the player experience of the patients in the SDVR group is, the lower will be the *patients'* intensity of *anxiety* during the procedure.

b. The more positive the player experience of the patients in the SDVR group is, the lower will be the *patients'* intensity of *pain* during the procedure.

c. The more positive the playing experience of the *caregivers* in the SDVR group, the less negative will their *emotional experience* be.

Hypothesis 4: patient experience

a. In the SDVR condition, more patients will have a feeling of *being in control over the situation* than those in the control condition.

b. In the SDVR condition, more patients will report being *distracted* from the procedure than those in the control condition.

c. The number of *patients* reporting that SDVR reduced their *agitation* will be greater than those reporting that listening to ocean waves reduced their agitation.

d. *Patients* in the SDVR condition will be more *surprised by the pain* than those in the control condition.

Hypothesis 5: flow of the procedure

a. The *observers'* rating of the *overall quality of the procedure* will be higher in the SDVR condition than in the control condition.

As interviewing children about their emotional and physical experience is a methodological challenge due to various biases, and because we strive for an objective assessment of the patient's and caregiver's experience, we follow a comprehensive, holistic approach in our methodology and the instruments used. In addition to the patients' and caregivers' self-reported emotional experiences, we also ask the caregivers to assess the patient's anxiety and pain. In addition, the interviewers use a structured observation protocol to assess the patient's experience, the gaming situation, and the course of the medical procedure.

Potential Confounding and Influencing Factors

The meta-analysis carried out by Eijlers et al [11] indicates that VR-based distraction from anxiety and pain is more efficacious in younger children than in older children. Age and gender influence the perception of pain and anxiety during medical procedures. Younger children tend to report more pain during procedures such as venipuncture [16]. In self-reporting, girls tend to report more pain than boys [17]. However, older children and boys tend to rate pain and anxiety differently compared to younger children and girls [17]. Age and parental predictions of distress are substantial predictors of pain and anxiety on blood tests [18]. Therefore, age and gender will be considered as possible influencing factors in the analysis.

Our intervention addresses a range of medical procedures that have shown to be highly anxiety- and stress-inducing in pediatric patients but can generally be performed without anesthesia. It is possible that patient anxiety and pain ratings differ for different procedures and that these perceptions influence the effect of our intervention.

Fundamental anxiety as a patient characteristic (ie, trait anxiety) is also a likely influencing factor for anxiety and pain ratings [19]. Furthermore, there is evidence in the literature of a link between perceived anxiety and postoperative recall of pain [20], which could influence patients' retrospective assessment of their pain. Therefore, we will consider the assessment of the caregivers and the observation of the interviewers in our study.

A well-documented phenomenon that negatively impacts the VR gaming experience is simulator sickness, which includes symptoms such as nausea, dizziness, headaches, and eye strain. There is evidence that children are less likely to react to VR exposure with these negative symptoms [21], but there have been few studies on the possible relationship between age and different forms of visually induced motion sickness. Nevertheless, we will record any indications of simulator sickness before and after the intervention as the described symptoms may relate to patients' general health state. We have elaborated more on that topic in the Methods section, under the Simulator Sickness subsection.

Previous hospital experience, particularly about the previous interventions of the same or similar nature, as well as needle-related phobias and trauma, can influence the patient's emotional response to the medical situation and will therefore be documented during screening. The actual diagnosis will also be recorded to assess the overall psychological situation of the patient and caregiver.

Ethical Considerations

This study was approved by the ethics committee of the medical faculty of the University of Duisburg-Essen (22-10873-BO). The ethics committees of the other study centers, Universitätsklinikum Hamburg-Eppendorf, Germany, Ethik-Kommission der Ärztekammer Hamburg (approval 2023-200739-BO-bet) and Ethikkommission des Universitätsklinikum Schleswig-Holstein, Lübeck, Germany (approval 2023-708), also saw no ethical or legal objections to this study.

All patients and caregivers will be fully informed about the background and procedure of the study during the recruitment process before they consent to participate in the study. Both the legal guardians and the children must give their written consent to participate in the study. They will be informed about the protection of their personal data and their digital rights in accordance with the European General Data Protection Regulation.

During the onboarding process, the collected data will be pseudonymized. An individual, random participant ID will be created during enrollment and stored with the patient ID separate from the survey answers. Once data collection is complete, the pseudonymization table will be deleted so that the data are anonymous from this point on. The children will be informed of the possibility that they might undergo the procedure in the control group without HMD and sedation or anesthesia. Participants in the control group will be allowed to try the game after completing the medical procedure.

Study Design

The study presented here is a prospective multicenter randomized nonblinded clinical trial. This study refers to protocol version 19 (March 1, 2023), which is registered in the German Clinical Trials Register (DRKS00033544). Any changes to the protocol will be submitted as an amendment to the responsible ethics committee of the University Hospital Essen for approval and filed in the DRKS. Data collection will take place at the University Hospital Essen, the University Hospital Schleswig-Holstein in Lübeck, and the University Hospital Hamburg-Eppendorf, all 3 located in Germany. Patients in the VR condition will play the game SDVR with 1 caregiver during the medical procedure. The beneficial effects of VR and digital games in distracting from anxiety and pain compared to the standard of care (ie, no intervention for distraction or sedation) have been demonstrated in numerous studies [9,11-13]. Therefore, our study particularly focuses on the effect of the shared gaming experience and addresses both the patient and the caregiver as recipients of the distraction and mood-enhancing intervention. Furthermore, to avoid the results being biased simply by the patient's experience of getting an "extra treatment" and additional attention from the medical staff during participation in the study, we will compare the experimental condition with a control condition in which the patients and caregivers will also receive special treatment. Acoustic relaxation techniques are straightforward and unobtrusive to implement in medical procedures, making it possible to address both patients and caregivers simultaneously. In contrast to guided imagery, which requires active mental engagement—often challenging in stressful or painful situations—nature sounds offer a passive form of relaxation. This passivity makes them more accessible and appealing across a range of ages and cognitive abilities. Another option could be passive music therapy; however, natural sounds present a more universally neutral and calming experience, as they bypass personal musical preferences and the emotional resonance often associated with music. Therefore, we chose to play a recording of ocean waves to foster a calming atmosphere during the procedure.

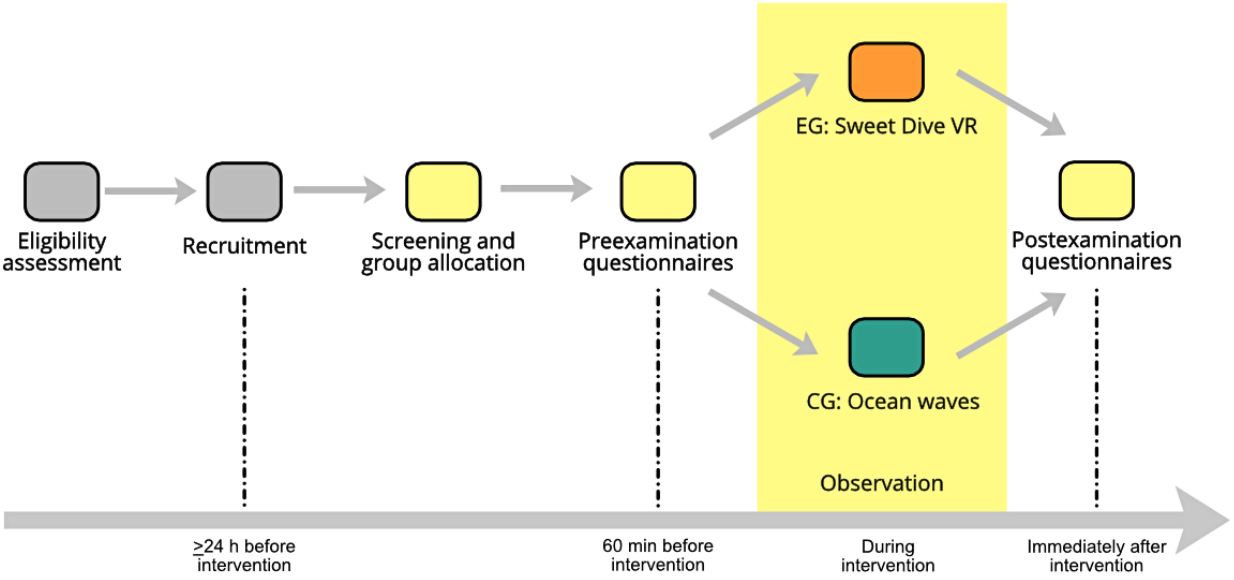
Procedure

A diagram of the study procedure is shown in Figure 1. Patients meeting the eligibility criteria (Textbox 2) will be identified in the hospital information system. Patients and their caregivers will then be contacted by telephone or during their next stay in the hospital. They will be fully informed about the background and aim of the study, the procedure, and the 2 experimental conditions. Patients and caregivers will then have at least 24 hours to consider whether they want to participate. Refusals and their reasons will be recorded anonymously.

If they agree to participate, patients and caregivers will be asked to give their written consent. During registration, the patients will then complete the screening questionnaire together with an interviewer, based on which the randomized, stratified group allocation will be automatically performed. All questionnaires aimed at patients will be completed together with the interviewers. The task of the interviewers is to read out the questions and items if necessary and to help with comprehension problems. The interviewers are trained accordingly so that they do not interfere with the patient's response behavior and do not suggest answers.

The participants will be requested to arrive 60 minutes before the actual appointment. During this time, the patients and caregivers will fill out the preexamination questionnaires in parallel. The participants will be reminded once again that participation is voluntary and that they can withdraw their participation at any time.

Figure 1. Study procedure timeline. Participants are assigned to either the experimental group (ie, Sweet Dive VR; SDVR) or the control group (ie, ocean waves). Pre- and postexamination questionnaires are administered to patients and caregivers. The interviewers assess the situation during the intervention using an observation protocol. CG: control group; EG: experimental group.



Textbox 2. Participant inclusion and exclusion criteria.

Inclusion criteria

- Age 6 to 12 years (applies for patients only)
- Procedure possible without sedation or anesthesia (applies for patients only)
- Sufficient knowledge of German (applies for patients and caregivers)
- Ability to hold and operate a game controller (applies for patients and caregivers)

Exclusion criteria

- Visual impairments (eg, lack of stereo vision and color blindness; applies for patients only)
- Severe cognitive impairments (as assessed by the caregivers and physicians; applies for patients and caregivers)
- Diagnosed with epilepsy (applies for patients only)

Termination criteria

- Desire to end participation (applies for patients and caregivers)
- Clear signs of severe simulator sickness (applies for patients only)
- Extreme pain (applies for patients only)
- Extreme anxiety (applies for patients only)
- Other adverse events (applies for patients and caregivers)

In the SDVR condition, patients and caregivers will receive a verbal, written, and illustrated explanation from the interviewer about the process, goal, and controls of the game as well as a brief introduction to the background story either as a short video or in the form of a short picture story. The caregivers will be instructed that they can start the game using the buttons on the controller and trigger events in the game that correspond to the treatment steps.

After the patients and caregivers have entered the examination room, in the SDVR group, the interviewer will help the patient put on the HMD and hand them the controller. The caregivers will receive the game controller and can then start the game session. In the control condition, the audio file will be played from a tablet or notebook.

We made special efforts to make the setup process as straightforward and quick as possible to enable noninvasive and seamless integration into the medical procedure. The VR app starts automatically as soon as the HMD is switched on (ie, the so-called “kiosk mode”). The necessary realignment of the perspective in the virtual world to the patient’s position can be triggered simply by pressing a button on the game controller. The technical setup process, including a functional test of all components (eg, Bluetooth connection to the game controller), takes just 5 minutes on average and can be prepared before the

actual treatment. Setting up and adjusting the HMD for the patient and handing over the game controller to the caregiver takes a further 1 to 2 minutes on average.

During the procedure, the interviewer will observe the medical situation, the patient's reactions, and the interaction between the patients and the caregivers. The observations will be documented in an observation protocol.

At the end of the intervention, the postexamination questionnaires will be completed by the patients and caregivers. Interruptions and premature terminations of the intervention will be recorded, and the reasons will be noted. Children in the control condition will be allowed to try out the game after the end of the experiment.

If a participant wishes to terminate the intervention or if one of the termination criteria described in Textbox 2 is met, the intervention will be discontinued immediately, and the participant will return to the standard of care, and a note will be made in the observation protocol.

Participants

Sample

Patients requiring port puncture, lumbar puncture, peripheral or central venous catheter insertion, or Kirschner-wire removal will be enrolled, each with 1 caregiver. Given the complexity of the planned study setting and its integration into the clinical processes, we performed a sensitivity analysis to ensure an appropriate test strength and sample size. We anticipate that the recruitment of 78 patients and caregivers each is feasible. On the basis of a power analysis with the G*Power software [22] and starting from a 2-sided *t* test with a significance level of α=.05 and a test power of 80%, we determined that a medium-size effect of approximately Cohen *d*=0.64 can be achieved with a corresponding sample size of 39 participants per group. In view of these statistical parameters and considering the objectives of the study, we decided that recruiting 26 participants in each of the 3 participating study centers would provide an appropriate balance between practical feasibility and statistical power.

Randomization and Stratification

Assignment to the experimental conditions will be automated by a study management software. The recruiters will have no opportunity to influence the assignment at any time. Allocation will use the method of stratified randomization using a minimization algorithm. Consequently, the patient-related variables (ie, strata) used for sample stratification, are as follows: (1) trait anxiety (State-Trait Anxiety Inventory for Children–trait anxiety), (2) age, (3) type of intervention, (4) previous experience with the procedure, and (5) sex. The minimization algorithm attempts to allocate a new patient to a group in such a way that the difference between the 2 groups is minimal for each stratum. If no clear allocation can be achieved with this procedure, a random allocation will be made.

Material

Experimental Condition: SDVR

The players' mission will be to catch as many fish as possible for a medical examination after a cargo ship lost a container filled with candy. The patient and 1 caregiver will play the game cooperatively. The core mechanic of SDVR is attracting and catching fish. To attract a fish, the patient can drop a piece of candy into the water by pressing a button. A transport box moves horizontally on the upper edge of the screen from left to right and back. When the box is precisely above the fish, the patient must press another button at the right moment to bring it down and cover the fish. In the next step, the patient must inform the caregiver verbally so that the caregiver can press a button on the gamepad to move the box upward. The fish is then considered to be collected, and the process can start all over again. The number of fish collected will be shown to the VR player in a head-up display (Figure 2). The gameplay is infinite; that is, there is no fixed game end or goal. This way, we can respect the variable length of the treatment.

Figure 2. In "Sweet Dive VR," the patient must attract a fish with candy and move the box down in the right moment to collect it. Next, the caregiver must move the box up again. The head-up display in the upper-left corner indicates the number of collected fish (top row) and events associated with the medical procedure triggered by the caregiver (bottom row).

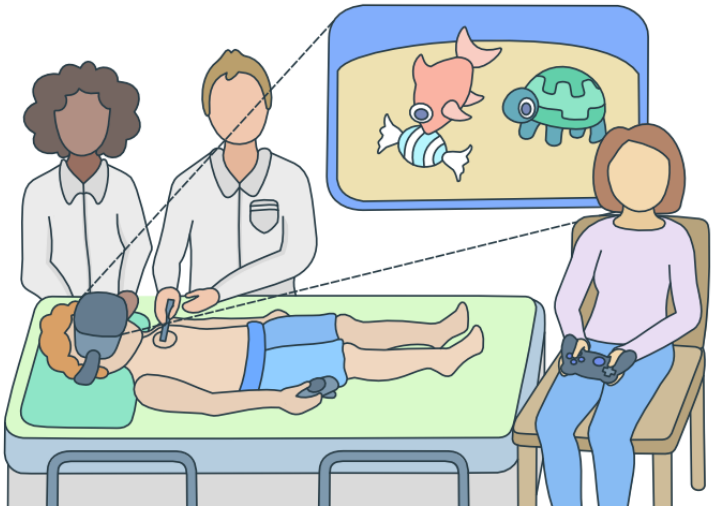
The game was designed to be played in a supine position (Figure 3). Consequently, the player's perspective has been adjusted so that, while lying on their back, they not only look up at the virtual sky (ie, the virtual water surface as in the case of SDVR) but can also see the horizon and the ground. By slightly shifting the virtual camera, a natural visual impression is possible, suggesting that the player is standing. In numerous previous

tests, we have not registered any negative effects such as simulator sickness.

The key feature of our game design is the inclusion of a caregiver in the gameplay as a second player. Through the asymmetrical game design [23], we can distract both the patient and caregiver from the treatment and create a shared positive experience. While both players must cooperate to pursue their shared objective (ie, catching the fish), they have different mechanics at their disposal to achieve that objective. However, not only are the actions available to the 2 players different but also the information about the game world is different. While the patient can see the game world via the HMD, the caregiver lacks all visual and auditory cues about the current game state (Figure 3). Thus, the caregiver is completely dependent on the communication of their child. Consequently, a high degree of concentration on the game events and the verbal communication of both players is required, which thus becomes an essential mechanic of the game and enhances the immersion of both players [14]. With the children giving verbal instructions to their caregivers, the game is designed to support their feeling of being in control over the situation. Moreover, the strong focus on communication between caregivers and children should enhance the sense of familiarity, security, and connectedness within the emotionally challenging situation. In addition to interacting with the child through the game, caregivers are assigned the task of responding to specific steps of the medical procedure (eg, the application of a disinfectant or an oxygen cannula) by triggering corresponding in-game events. This approach synchronizes the virtual world with the patient's real-world sensory experiences, thereby preserving and enhancing the patient's immersion. Concurrently, it grants caregivers a sense of agency and participation in the medical situation, reinforcing their involvement in the process.

As this study focuses on the description of the research protocol for the clinical evaluation of our approach, we refrain from delving deeper into the design rationale here and refer to the planned publication elsewhere.

Figure 3. Schematic representation of the medical procedure and the patient-caregiver interaction in the asymmetric game design.



Control Condition: Audio Recordings of Ocean Waves

The research field of environmental psychology explores the positive effects of natural environments on human experience [24], including in medical contexts [25,26]. It has been shown that exposure to natural environments can reduce acute and anticipatory stress. Annerstedt et al [27] showed a stress-recovery–promoting effect of birdsong in a virtual forest scenario. Liszio et al [28] have shown that the audiovisual presentation of virtual underwater environments significantly reduces acute and anticipatory stress. However, research on the effect of solely auditive presentation of nature sounds on the emotional experience of patients in medical situations is scarce; however, there is some evidence in the literature. Moreover, several studies indicate a significant reduction of patient anxiety and agitation during percutaneous coronary intervention [29] and coronary artery bypass graft surgery [30,31] when listening to nature sounds.

In the control condition, a 30-minute recording of ocean waves will be played instead of the VR game. Recording will start with a 1-minute introduction by the same soothing voice that narrates the companion character "Turtle" in SDVR. From then on, only the sound of the waves will continue.

Hardware

Patients in the VR condition will play the game with a Pico G2 4K HMD (Figure 4, left). The device is a stand-alone HMD in which all calculations are performed on the device itself, so that no additional computer is required. The HMD has 3 df and can therefore only be used when sitting or lying down. User inputs are made via the associated controller, which resembles a simple remote control. A larger touchpad is located on the controller, which works like the directional pad on a typical game controller. In addition, the controller has a trigger button that is operated with the index finger. It can be controlled with 1 hand using either the left or right hand. We chose this hardware for the following reasons: the housing is comparatively easy to disinfect, as all external components are either hard plastic or rubber. Comparable devices from other manufacturers typically use foam covered with fabric for the face pad and elastic fabric for the headbands, which do not meet health care hygiene standards. Furthermore, no user account from third-party

providers is required for operation. Apps can also be started in a so-called kiosk mode, that is, the corresponding app starts automatically when the device is switched on, which makes it much easier to use in the fast pace of everyday clinical practice. Finally, the standard controller's small design and reduced number of buttons simplify operation with small hands. Children have no problems holding the controller and reaching all the buttons with their fingers. The symmetrical design allows operating the controller with either the left or right hand.

For the caregiver, we will use a conventional gamepad as an input device for the game. The gamepad and HMD are connected via Bluetooth. The advantage of using a common gamepad is that many people are familiar with the layout of the buttons and the handling while the acquisition costs are low.

For data collection, we will use tablet PCs. These will also be used to play the recording of ocean waves in the control condition.

Figure 4. The Pico G2 4K head-mounted display with controller (left) and conventional gamepad (right) used in the experimental condition during the medical procedure.

Psychometric Assessment

Emotional Experience

State and Trait Anxiety

The State-Trait Anxiety Inventory is an established questionnaire for measuring anxiety [32] (Table 1). It was developed to measure both state anxiety and the personality characteristics of anxiety (ie, trait anxiety). The questionnaire consists of 2 scales, one for assessing state anxiety and one for assessing trait anxiety. In this study, we will use the German translation provided by Laux et al [33].

For the child survey, we will use the German translation of the adapted State-Trait Anxiety Inventory for Children [19]. This adaptation is characterized by a reduced number of 20 per scale items and a simplified response scale as compared to the original State-Trait Anxiety Inventory. In addition, the rating options are reduced to 3, ranging from 1 (low anxiety) to 3 (high anxiety).

In addition, we will implement a visual analog scale (VAS), which provides an effective method of assessing children's affective state as it offers a simple and easy to understand way of quantifying emotions. We will use the scale "Anxiety" by Gräßer et al [34]. This is based on a scale from 0 (not at all) to 10 (very strong). By simultaneously presenting an illustration the children can identify with and scaling the values from 0 to 10 on a line, children can express their emotional experience in a precise and differentiated way. For comparability between the children's self-report and the impressions of the caregivers and the interviewers, we will also ask the caregivers and the interviewers to rate the patients' pain perception on the same VAS.

Table 1. Breakdown of the psychometric instruments administered (ie, questionnaires, visual analog scales, and self-designed questions) for each respondent group and measurement time.

Respondents and measurement time	Psychometric instrument
Children	
Screening	• STAIC-T[a]
Preintervention measurement	• STAIC-S[b] • VAS[c] anxiety • PANAS-K[d] • SSQ-C[e]
Postintervention measurement	• STAIC-S • VAS anxiety • PANAS-K • VAS pain • SSQ-C • Adapted PXI[f] for childreng • Patient experience • Presence
Caregivers	
Preintervention measurement	• PANAS • PANAS-C-P[g] • VAS anxiety (child)
Postintervention measurement	• PANAS • 0-P • VAS anxiety (child) • VAS pain (child) • PXI[h] • Player experienceg
Interviewers	
Observation	• CHEOPS[i] • Self-designed questions for assessing procedure flow

[a]STAIC-T: State-Trait Anxiety Inventory for children–trait anxiety.

[b]STAIC-S: State-Trait Anxiety Inventory for children–state anxiety.

[c]VAS: visual analog scale.

[d]PANAS-K: German translation of the Positive and Negative Affect Schedule for Children.

[e]SSQ-C: Child Simulator Sickness Questionnaire.

[f]PXI: Player Experience Inventory.

[g]PANAS-C-P: parent version of the Positive and Negative Affect Scale for Children.

[h]Sweet Dive VR only.

[i]CHEOPS: Children's Hospital of Eastern Ontario Pain Scale.

Positive and Negative Emotions

To assess the participants' affective state, we will use the positive affect negative affect schedule (PANAS) [35]. The questionnaire consists of 2 separate scales, one for positive affect (PA) and one for negative affect (NA). Each scale comprises a list of words that describe different emotions or moods. Respondents will be asked to indicate the extent to which they felt each of these words either "when thinking about the medical procedure" (before measurement) or "during the medical procedure" (after measurement).

For the caregivers, we will use the original questionnaire translated to German by Janke and Janke and Glöckner-Rist [36]. This version comprises 20 adjectives that describe emotional states. The rating scale describes the intensity with which these emotional states were experienced on a 5-point scale from 1 (not at all) to 5 (extremely). For the 2 dimensions PA and NA, the sum scores are formed from the intensity ratings of the corresponding items.

In addition to describing their own emotional experience, the caregivers assess the children's emotional states using the parent version of the Positive and Negative Affect Scale for Children, which we will use in the German translation provided by

Großheinrich [37]. The scale consists of 2 subscales to determine the children's PA (12 items) and NA (15 items) according to the caregiver's impression on a 5-point scale from 1 (very little or not at all) to 5 (extremely).

The participating children will be administered an adapted version of the original PANAS (PANAS-C) developed by Laurent et al [38]. To our knowledge, because no official German translation of the children's version of the PANAS-C exists, we used this version as a starting point and compared the items with the German translations of the adjectives according to Janke and Glöckner-Rist [36]. As the PANAS-C comprises 30 items, rather than 20 items as in the version by Janke and Glöckner-Rist [36], additional adjectives for which no translation could be found were translated by the authors.

Pain

To measure the children's perceived pain, we will use the VAS "Pain" by Gräßer et al [34], equal to the measurement of anxiety (as mentioned earlier). Again, we will ask the patients, the caregivers, and the interviewers for a rating.

The interviewers will rate the observed pain-associated behavior of the child using the Children's Hospital of Eastern Ontario Pain Scale [39]. It can be used to monitor the effectiveness of interventions to reduce pain and discomfort in young children. The result is a pain score between 4 (no pain) and 13 (severe pain).

Player Experience

Overview

We will use the German translation of the Player Experience Inventory (PXI), which was developed by Graf et al [40], to assess the caregivers' experiences while they play SDVR. The PXI consists of 10 dimensions that describe aspects of the player experience, allowing for a systematic analysis of the game design. Each dimension comprises 3 items, which are rated on a 7-point scale ranging from –3 (strongly disagree) to 3 (strongly agree).

For evaluating the caregivers' experience, we will consider only the following constructs: "ease of control," "goals and rules," "challenge," "meaning," "curiosity," and "mastery and immersion." We will exclude the constructs "progress feedback," "audiovisual appeal," and "autonomy" from the evaluation of SDVR because the game does not have any audiovisual component for caregivers.

To date, there is no suitable and validated version of the PXI for children. As the PXI in its complete form is quite extensive and, in our experience, some item formulations are difficult for younger children to understand, we created a variant by selecting 1 item from each of the 10 dimensions that is clear and easy to understand. In the first round, 3 of the authors—an educator and health play specialist, a pediatric nurse with significant expertise in child-friendly medical language, and an entertainment computing specialist—independently selected 1 item per dimension that, in their opinion, met the criteria of representativeness for the dimension, child-appropriate concept complexity, and child-appropriate language. In the second step, the items for which there was no agreement between the 3 reviewers were discussed until consensus was reached. Moreover, we reduced the response options to a more child-friendly 5-point scale from −2 (strongly disagree) to +2 (strongly agree). It should be noted that this is a tentative, empirically unvalidated version. The data collected in the study may provide the basis for future efforts to develop a suitable player experience metric for children. For the sake of reproducibility and transparency, we included the final list of items in Multimedia Appendix 1.

The interviewers will be asked to assess the child's player experience by rating the statements "The child had fun playing."; "...was completely immersed in the play world."; "...gave the caregiver clear, game-related instructions."; "...understood what his role in the game was."; "...had no problems with the controls of the game"; and "...was optimally challenged by the game" on a 7-point Likert scale.

Presence

According to our assumptions, playing a VR game creates presence, which can be explained as a redirection of the user's attentional focus from the real to the virtual world. Hence, the experience of presence is an indicator of distraction from the medical situation. As there is no questionnaire designed for children to measure their sense of presence, we will use 5 items from the German Igroup Presence Questionnaire [41]. These 5 items describe how conscious the players were of the actual world and how real the virtual world seemed to them. The vocabulary used in these items is less abstract, which makes it easier for children to comprehend. The items are rated on a 7-point scale from 0 (strongly disagree) to 6 (strongly agree).

Simulator Sickness

Simulator sickness is a possible adverse side effect of VR exposure. To diagnose simulator sickness, we will use the Child Simulator Sickness Questionnaire adapted by Hoeft et al [42] and translated to German by us. The questionnaire comprises 7 items describing different symptoms summarized in dimensions "nausea," "oculomotor," and "disorientation." Each symptom is rated on a 3-point scale ranging between 0 ("not at all") and 3 ("very much").

However, it should be noted that our target group will consist of children who are sick. Thus, it is likely that some participants, due to their illness, will experience symptoms that are also associated with simulator sickness. Therefore, we will ask the participants to rate their symptoms before (ie, before measurement) and after (ie, after measurement) the VR exposure.

Patient Experience

We will use several simple self-designed questions to assess specific aspects of the patient experience from the perspective of the children, the caregivers, and the interviewers, including a sense of control, perceived distraction from the medical situation, excitement, and surprise at the onset of pain.

Procedure Flow

The interviewers will be asked to evaluate the course of the medical procedure using the statement "Please evaluate the willingness of the patient and the accompanying person to

cooperate regarding the examination procedure" (1="very uncooperative"; 5="very cooperative"). In addition, they will be asked to rate the overall procedure on a 5-point star scale. We will also track all premature terminations of the intervention and the reasons given by participants, if any.

Data Collection and Analysis

All questionnaires will be completed electronically using the LimeSurvey (LimeSurvey GmbH) software to prevent data loss, incorrect data, or duplicate entries. Data will be stored anonymously on secured servers at the University Hospital Essen. The signed declarations of consent will be stored separately from the data collected. No identifying data will be stored in the dataset. The dataset will be stored separately from security-relevant patient data. Only the persons involved in the data analysis (SL and OB) will have access to the final dataset. Methods of descriptive and inferential statistics will be used to analyze quantitative data.

Results

Data collection is ongoing at the time of publication of this study. As of November 2024, we enrolled 39 patients and caregivers, 28 of whom completed the study (Multimedia Appendix 2 presents the participant flow diagram).

Discussion

Overview

Although anxiety and pain at the hospital cannot always be avoided, there are situations in which the emotional experiences of patients and their caregivers can be improved in a controlled and safe manner using comparatively simple means. VR gaming has proven to be a suitable, effective measure for distracting pediatric patients in pain and anxiety-ridden situations and thus as a nonpharmacological analgesic. We take this approach one step further and involve the caregivers in the game. Therefore, our aim is to make the medical procedure as pain-, anxiety-, and stress-free as possible for patients and their companions to enable the most positive patient experience possible. With our intervention, we aim to increase the cooperativeness of patients and caregivers and thus optimize the course of the medical procedure in terms of minimizing health risks for the patients as well as the necessary time and personnel resources. In the study presented here, we use the VR game SDVR, a cooperative multiplayer game based on cooperation between patient and companion specially designed for this use case.

Challenges

In our effort to enhance the experience for pediatric patients and their caregivers, we acknowledge the challenges associated with maintaining immersion and comfort during medical procedures, particularly when patients are visually and auditorily shielded from the real world; that is, some patients might feel uncomfortable when touched while visually and auditorily shielded from the real world [43]. In this context, it should be noted that there is currently no HMD that has been optimized for children's heads. All existing devices on the market are designed for adults in terms of weight, dimensions, lens distance, and so forth. Consequently, patients may perceive the HMD as a strain and wish to discontinue wearing it during the procedure. In the study, we record such cases and the patients' reasons.

Furthermore, unexpected real-world sensations (eg, phone calls, medical staff coming and going, and noises from medical equipment) that interfere with the virtual environment may "break" immersion and distraction [44]. Our approach addresses these concerns by integrating real-world stimuli into the VR gaming environment, thereby enhancing immersion and minimizing potential disruptions. By allowing the caregivers to trigger events in the game from the outside, real-world stimuli and game-related sensations can be aligned.

We might also encounter patients who are not eager to wear the HMD and engage in the game as they may perceive a sense of losing control over the situation. Previous adverse experiences with the same or similar medical procedures may have resulted in trauma and left patients so emotionally compromised that they perceive any additional treatment (ie, wearing the HMD) as an excessive burden. Reaching such patients with alternative interventions is generally very difficult.

As mentioned earlier, studies show that there is a relation between pain perception and age [16,17]. Against this background, the wide age range of our study is beneficial as it allows us to examine this relationship. In the results report, we will compare our findings with those of other studies to derive potential recommendations on the use of VR game–based pain distraction for pediatric patients of different age groups.

When designing our specific VR application SDVR, we already focused on seamless integration into medical treatment processes. Nevertheless, integrating VR into medical situations brings several challenges, and solutions and workflows must be found. These include the maintenance of the hardware (eg, system updates, battery charging, storage, and disinfection) but also the training of staff in the use of the technology. A VR solution can only provide real added value if it can be easily and safely integrated into the highly standardized processes of the hospital. It must be borne in mind that medical staff are primarily responsible for medical tasks, and experience has shown that, in many cases, they are already working to their capacity. In addition, previous experience and technological expertise cannot always be assumed. If a VR solution does not take these circumstances into account, there is a high risk that the technology will not be accepted and therefore not used. We tried to take these circumstances into account when developing SDVR and our intervention concept and want to use the planned study to check whether we have succeeded.

Limitations

There are some restrictions regarding the study design and methodology. Answering self-report questionnaires about their emotional and perceptual experience can be difficult for younger children. Although we use instruments specially adapted and, where available, validated for children. The interviewers are trained to assist the children in answering the questionnaires without influencing their answering behavior. However, bias cannot be completely ruled out due to children's psychoemotional and cognitive development including language

skills, focus, and motivation. Sometimes the caregivers need to be kept from trying to influence the child when answering the questions. Given the nature of the matter, the study cannot be blinded. Therefore, it is not possible to fully objectify the interviewer's assessment during the intraoperative observation.

The duration of exposure to the alleged anxiety- and pain-reducing stimuli (ie, SDVR and recording of ocean waves) cannot be standardized due to the variable length of the medical procedure. Therefore, it is not possible to determine whether the duration of the intervention influences the experience of patients and caregivers. In addition, the reality of daily practice in the hospital does not allow for a fully standardized, perioperative measurement of the relevant experience-related variables. Therefore, our study protocol defines realistic time frames before and after the procedure, representing a reasonable compromise between temporal proximity to the events and feelings under investigation, integration into hospital operational processes, and standardization with sufficient time for the participants to complete the questionnaires.

Conclusions

This study represents a significant step forward in addressing the challenges of managing anxiety and pain in pediatric medical settings. By harnessing the immersive potential of VR gaming and actively involving caregivers in the process, we strive to create a supportive and stress-free environment for patients and their caregivers. Despite the complexity inherent in our presented study design, we are confident that our work contributes to advancing nonpharmacological interventions in pediatric health care.

Acknowledgments

The authors would like to thank in advance all participating patients and their caregivers who supported us in our research. They would also like to thank in advance the teams at the participating study centers for their cooperation during recruitment. Special thanks to Dr Brigitte Bäuerlein, who lent the authors her voice for Sweet Dive VR. The authors further thank Sarah Haefs for creating the logo and illustrations and Anastasia Chernetskaya for her support in modeling the 3D assets.

Data Availability

The datasets generated and analyzed during this study are available from the corresponding author on reasonable request.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Selection of items derived from the German version of the Player Experience Inventory used to assess player experience in children.
[PDF File (Adobe PDF File), 119 KB - resprot_v14i1e63098_app1.pdf]

Multimedia Appendix 2
CONSORT (Consolidated Standards of Reporting Trails) participant flow diagram.
[PDF File (Adobe PDF File), 56 KB - resprot_v14i1e63098_app2.pdf]

Multimedia Appendix 3
SPIRIT checklist.
[PDF File (Adobe PDF File), 147 KB - resprot_v14i1e63098_app3.pdf]

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Abbreviations

HMD: head-mounted display
PXI: Player Experience Inventory
SDVR: Sweet Dive VR
VAS: visual analog scale
VR: virtual reality

Edited by A Schwartz; submitted 08.07.24; peer-reviewed by I Eker; comments to author 22.10.24; revised version received 28.11.24; accepted 31.01.25; published 31.03.25.

Please cite as:
Liszio S, Bäuerlein F, Hildebrand J, van Nahl C, Masuch M, Basu O
Cooperative Virtual Reality Gaming for Anxiety and Pain Reduction in Pediatric Patients and Their Caregivers During Painful Medical Procedures: Protocol for a Randomized Controlled Trial
JMIR Res Protoc 2025;14:e63098
URL: https://www.researchprotocols.org/2025/1/e63098
doi:10.2196/63098
PMID:

Protocol

Assessing the Noninferiority of a Rhythm and Language Training Serious Game Combined With Speech Therapy Versus Speech Therapy Care for Children With Dyslexia: Protocol for an Investigator-Blinded Randomized Controlled Trial

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Abstract

Background: Specific learning disorder (SLD) of reading skills impacts approximately 7% of children. Speech and reading therapy is currently the gold-standard intervention for improving children's reading abilities. However, intensive interventions are difficult to implement. Recently, numerous studies have investigated the interest of game- and home-based training approaches to enhance children's motivation and facilitate intensive learning activities in home settings. The serious game Poppins Clinical integrates rhythm and specific written language exercises to improve reading skills in children with SLD.

Objective: This study aimed to assess the noninferiority of Poppins Clinical combined with a reading specialist session once every 2 weeks versus a reading specialist session every week, on the reading skills of children with SLD.

Methods: A total of 306 children with dyslexia will be recruited for this study and randomly assigned to either the experimental or control group. Children in the experimental group will use the serious game Poppins Clinical at home for 20 minutes, 5 days a week, and attend 1 reading therapy session every 2 weeks. The control group will participate in one reading therapy session per week. Poppins Clinical combines rhythm and language exercises integrated into an engaging game designed to maintain user motivation. We will use a noninferiority paradigm to assess the clinical impact of both interventions in terms of reading accuracy, reading speed, and reading comprehension. We will also investigate the evolution of phonological and visual-attentional skills. However, we will explore the impact of the protocol on parental stress and children's perception of their difficulties. Finally, we will also assess the cost of medical care and the impact of introducing the serious game Poppins Clinical on reading therapy. To facilitate recruitment and ensure the representativeness of our sample, the evaluation of the children will be conducted via videoconference using standardized tests that have been adapted for videoconference administration.

Results: Patient recruitment is expected to start in December 2024, with study completion by the end of August 2025.

Conclusions: This study should allow us to assess the interest in using the serious game Poppins Clinical in addition to reading therapy to improve reading abilities in children with SLD.

Trial Registration: ClinicalTrials.gov NCT06592911; https://clinicaltrials.gov/study/NCT06592911

International Registered Report Identifier (IRRID): DERR1-10.2196/71326

(JMIR Res Protoc 2025;14:e71326) doi:10.2196/71326

KEYWORDS

dyslexia; serious game; rhythm; randomized controlled trial; non-inferiority protocol

Introduction

Specific learning disorder (SLD) with impairment in reading is a type of SLD classified as a neurodevelopmental disorder according to the *DSM-5* (*Diagnostic and Statistical Manual of Mental Disorders* [Fifth Edition]). The disorder affects reading and spelling abilities as well as related language processing skills such as phonological skills or auditory attention, despite adequate instruction, and in the absence of general cognitive or sensory deficits [1]. Yang et al [2] estimated the prevalence of SLD at around 7% in primary school children, suggesting that this disorder represents a considerable public health challenge.

It is now well established that SLD is caused by problems at the level of phonological representation, characterized by difficulty in accessing or manipulating speech sounds [1]. Recently, several studies revealed a deficit in the temporal processing of speech, which could explain the phonological deficit observed in people with SLD [3-5]. This deficit does not seem to be specific to the processing of speech but applies to the temporal treatment of the auditory signal in general. Effectively, the ability to process rhythm in music is linked with the processing of linguistic prosody in children and adults. However, musical rhythm perception skills predict metaphonological and reading skills [6,7]. People with SLD have difficulty estimating changes in the amplitude of the sound envelope over time [8], processing short durations [5], preattentive processing of vowel duration and voicing establishment [9], and also processing rhythmic information. This is particularly the case in the synchronization of simple rhythmic sequences, such as a metronome, or complex ones, such as music, where people with SLD are more variable [4,10,11]. They also have difficulty identifying whether a sequence is regular or not [11,12]. Rhythm perception and production skills even predict reading skills in children with SLD with reading deficits [12]. Regarding the strong link between rhythm perception and reading skills, several studies tried to improve reading skills in children with SLD through musical training [13]. Among them, some studies specifically focused on the training of rhythm skills. As an example, Flaugnacco et al [12] compared the impact of rhythm training to art training on phonological and reading skills in children with SLD. In this randomized controlled trial including 46 children with SLD, children receiving the rhythm training significantly improved their phonological and reading skills, more than the group of children receiving art training.

The “Recommendations for good practice in the assessment, prevention, and treatment of written language disorders in children and adults” by the Collège Français d’Orthophonie [14] describe three different modes of intervention for patients affected by SLD: (1) corrective treatment targets underlying cognitive deficits (eg, phonological or visual-attentional deficits) and various processes involved in identifying written words (eg, graphophonological conversion, phonological decoding, orthographic memory, and orthographic recoding), (2) adaptive treatment aims to reinforce the reader’s natural compensatory strategies (eg, lexical orthographic memory formation), and (3) compensatory treatment seeks to reduce written language disorders by replacing deficient cognitive functions (eg, using digital aids). These modes of intervention are not mutually exclusive and should be combined or alternated according to a treatment plan defined for each patient. However, when possible, corrective treatment should be the first option applied to a patient. For the intervention to be effective, it must be intensive (5 times a week). Achieving this intensity is not feasible in conventional in-person speech and reading therapy, where therapists are generally limited to scheduling 1-2 sessions per week [15]. Therefore, learning activities must also be carried out at home to ensure sufficient training frequency.

In recent years, there has been growing interest in digital technologies and game-based assessment, training, and rehabilitation methods for neurodevelopmental disorders [16,17]. As defined by Mayer [18], serious games have the motivational and playful characteristics of games, but their main objective is to achieve a measurable change in the player’s skills. The playful nature of these games leads to increased interest and attention from the player, which in turn encourages greater effort [18,19]. However, the digital tool appears to be a preferred learning tool for school-age children [20]. Digital tools also enable the multimodal, sequential, and simultaneous presentation of information, allowing the player to interact with the device in various ways [21]. A recent review of serious games for people with SLD supports their effectiveness in developing reading abilities, particularly those targeting sound and letter association and action video games [22]. In addition, serious gaming could be an ideal medium for training rhythmic skills, as rhythmic synchronization is one of the easiest musical skills to isolate [23]. Furthermore, serious games enable the use of an active musical framework in which body movements, emotions, and intentionality influence each other, maximizing the demands on the audio-motor loop and enhancing anticipatory and predictive processing [24]. Indeed, serious games provide an interesting medium to combine musical training with grapheme-phoneme correspondence, as recommended by recent guidelines [14]. The serious game Poppins Clinical was created to combine written language exercises and rhythm training, allowing children with SLD to practice at home and improve their reading skills. The rhythm training part is the most original component and has been used with children with neurodevelopmental disorders, showing improvement in rhythm skills within the game [25]. A randomized placebo-controlled trial involving 154 children with SLD tested the rhythm training part or a placebo game for 2 months [26]. The results showed improvement in reading accuracy and speed, supporting the

efficacy of Poppins Clinical to improve reading skills in children with SLD. Written language exercises have been added to the rhythm training to match the most recent recommendations [14].

The use of new technologies, including serious games, raises several questions, notably regarding how these new technologies are used in the current health system [27]. Specifically, cost-effectiveness data is lacking. It is crucial to evaluate the impact of a technology compared with its cost [27]. In addition, the impact of a new treatment must also take into account other variables such as treatment adherence or safety. To assess these points, a number of trials use a noninferiority paradigm [28,29]. The objective of these trials is to evaluate if a new treatment can be considered not worse than the gold-standard treatment by an acceptably small amount, with a given degree of confidence [30]. In this type of trial, defining the noninferiority margin is crucial [30]. This margin represents the threshold below which any difference in efficacy is considered clinically acceptable. Elicited health costs can be considered to evaluate the gain of the treatment. These costs may be divided into three types of costs: direct costs related to resources used, indirect costs related to productivity loss, and intangible costs as costs related to pain and endurance [31]. As an example, Schmidt et al [32] identified 31 subcategories of "out-of-pocket" costs such as transportation, insurance, or technology-related costs, that could be considered when looking at health expenditures.

The objective of this paper is to present the methodology of a randomized controlled trial aimed at comparing the effectiveness of Poppins Clinical combined with one reading therapy session every 2 weeks to one reading therapy session per week, on the reading skills of children with SLD, using a noninferiority paradigm. Safety, treatment adherence, and cost will also be considered.

Methods

Study Design and Objectives

This study is an interventional, multicenter, noninferiority randomized trial with two arms. The main objective is to evaluate the noninferiority of Poppins Clinical combined with one reading therapy session every 2 weeks (experimental arm) compared with one reading therapy session every week (control arm) on the reading accuracy (the primary end point) of children with SLD and reading impairment.

Secondary objectives include comparing the experimental group to the control group in terms of safety, reading speed, reading skills, phonological awareness, parental stress, parent quality of life, and text comprehension (secondary end points). Costs related to medical care and therapy between the experimental and control groups are also investigated. This protocol follows SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) guidelines (checklist provided in Multimedia Appendix 1).

Study Population

The study will include 306 participants. The justification for the sample size is given below in the *Statistical Justification of the Sample Size* section.

Inclusion criteria require participants to have a confirmed diagnosis of SLD with a reading deficit, as defined by a speech-language assessment. This diagnosis must align with the *DSM-5-TR* (*DSM-5*, Text Revision) definitions, with reading and/or transcription test scores showing an SD of at least –1.4 or below the 20th percentile, or –2 SD and below the 10th percentile on two such tests. Eligible participants will be children aged 7-11 years, enrolled from CE1 to CM2, who have been receiving reading therapy once a week for less than 2 years. Other criteria include fluency in French or bilingualism in French at home, at least 3 years of schooling in France, and access to a tablet or smartphone at home. In addition, participants must be affiliated with the French National Insurance system, and both the child and their legal guardians must provide informed consent and agree to follow the study protocol. Only one child per family will be enrolled.

Exclusion criteria will exclude individuals who have previously used Poppins Clinical or its earlier version, Mila-Learn (Poppins). Children with unstabilized chronic illnesses, autism spectrum disorders, or documented intellectual disabilities will not be eligible. Participants with vision or hearing impairments that would prevent the use of a tablet or smartphone, as well as those engaged in other interventional studies that may affect the trial's outcomes, will also be excluded.

Study Procedure

First, participants will be informed about the study either by their therapists or via web-based social media platforms. Two clinical sites in Paris and Poitiers, France, will be in charge of the screening and recruitment. Potentially eligible children and their legal representatives will receive study information during an informational visit. If interested, legal representatives will be asked to sign the informed consent form. Speech and reading therapists working with the participants will also be officially informed about the study, and their consent will be collected. The study investigator will then verify whether the participant meets the study criteria and determine their eligibility during an inclusion visit, which can be conducted either on-site or via videoconference. During this visit, verbal assent will also be obtained from the child. Following this, a baseline evaluation (T1) will be conducted by a speech therapist from the clinical site via videoconference, and questionnaires will be provided to both the patients and their legal guardians. These assessments will be performed under the same conditions as renewal evaluations, using standardized tests that have been adapted for videoconference administration.

Patients will then be randomized into one of two groups: the experimental arm or the control arm. Randomization will be carried out by the Contract Research Organization (CRO) using blocks of size six to maintain a 1:1 ratio, with stratification based on the participant's schooling level.

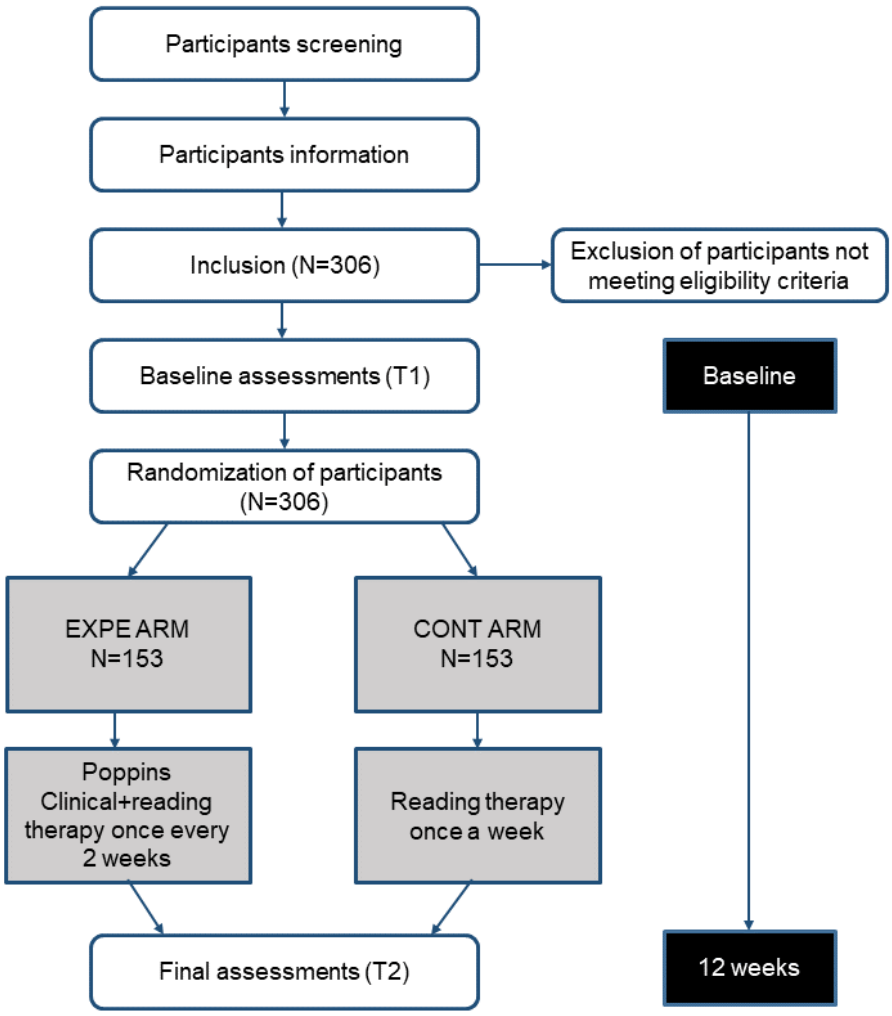
Patients assigned to the experimental arm will undergo 12 weeks of reading therapy, with one session every two weeks. In addition, they will use the medical device Poppins Clinical for 20 minutes per day, 5 days a week, over 12 weeks. The Poppins Clinical device is provided free of charge to families during the three-month training period. Each family must create an account in the game using a specially generated link designed to track

study participants. The patient's playtime is recorded by Poppins Clinical—the time spent on each exercise is tracked, enabling the app to monitor the children's daily playtime. The patient will receive a notification on their tablet every Monday encouraging them to play, and another on Saturday to motivate them to reach the playtime goal. If they have not played during the week, the child will receive an additional notification the following Wednesday to encourage them to play. The first day of training in the Poppins Clinical group must be performed within 2 weeks after the baseline evaluation (T1). Patients in the control arm will continue to receive a weekly reading therapy session, as per common practice in France [15]. To control for potential bias related to the formation of speech and reading therapists, years of graduation and the training courses followed in the last 5 years will be recorded.

A second evaluation (T2) will take place via videoconference 12 weeks (+ or - 14 days) after the first day of training with Poppins Clinical for the experimental arm, or 12 weeks after the baseline evaluation for the control arm. Questionnaires for patients, their legal guardians, and speech and reading therapists will be collected at this time. Please refer to Figure 1 for a flowchart of the study procedures.

Throughout the trial, investigators and evaluators will remain blinded to the patients' group assignments. However, patients and their speech and reading therapists will not be blinded to the allocation. To maintain blinding of the investigators and evaluators, the CRO's safety department will be responsible for recording all adverse events and device deficiencies.

Figure 1. Study procedure flowchart. CONT: control group; EXPE: experimental group.



Experimental Intervention: Poppins Clinical

As aforementioned, we have already examined the impact of the first version of the digital medical device Poppins Clinical on the reading abilities of children with SLD. This version consisted of musical training in the form of a serious game [26]. Based on the new recommendation from the Collège Français d'Orthophonie [14], a new version of Poppins Clinical has been developed that combines the initial musical training program with a written language training program.

Poppins Clinical is now an app available on tablets and smartphones (iOS [Apple Inc] and Android), where children are led to carry out different activities divided into two categories: language activities and musical activities. Depending on the child's performance, the difficulty of the proposed activities is adapted. Poppins Clinical contains several short activities, allowing for a variety of activities within a single session. Each activity lasts an average of 1.40 minutes, ensuring that it does not demand too much sustained attention from the child [33,34]. This structure of short activities ensures a fluid,

coherent, and continuous experience for the user. To offer an experience suitable for as many children as possible (aged 7-11 years, both gamers and nongamers, with a wide range of tastes), the visual and narrative aesthetics of Poppins Clinical align with mainstream video game standards such as Rayman (Ubisoft) and Mario games (Nintendo), which are designed for all audiences.

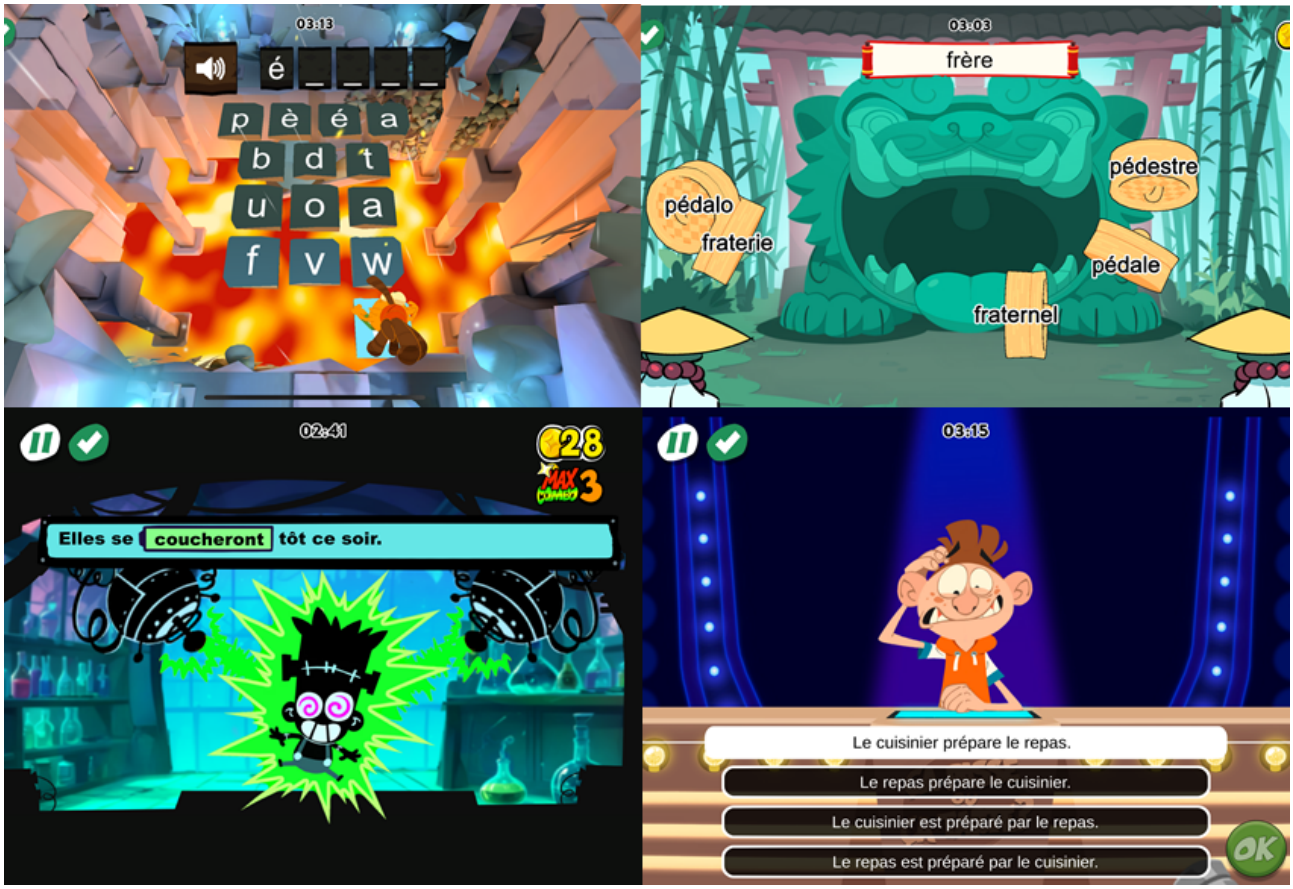
Musical Activities

The musical activities consist of rhythmic tasks described in a previous paper [25]. In summary, all these tasks were designed to work on rhythm, as rhythm appears to be directly related to reading skills, whereas melody is not [35]. However, children with SLD showed deficits in rhythm processing [8,9]. Each task also requires the mobilization of other skills such as attention, inhibition, working memory, and motor skills, which are often impaired in children with dyslexia [36].

Written Language Section

The written language section combines exercises to enhance phonological awareness, reading speed, and writing accuracy (Figure 2). All exercises are proposed to associate phoneme and grapheme as recommended by the College Français d'Orthophonie [14]. Words presented in the game were chosen from the Manulex database, considering their frequency, length, and orthographic difficulty. Syntactic difficulties and vocabulary frequencies were also considered in the selection of sentences and texts presented in the game.

Figure 2. Screenshots of written language tasks from Poppins Clinical.



Four types of exercises have been developed to work on different skills used to access written language:

1. Underlying processes: In Poppins Clinical, various activities are based on the ability to identify the sounds contained in a word (phoneme or syllable), thus calling on phonological and meta-phonological skills. These include activities to classify words according to the sounds that make them up. However, the activities (language and music) are carried out in various forms and require interaction with the digital tool in several ways, calling on visual attention skills, executive functions, and praxis.
2. Graphophonology: Various activities are based on matching graphic representations with their corresponding sounds (syllables and words). The aim is to teach the player to link a graphic form to a phonological representation, in reading activities such as categorizing written words.
3. Orthographic skills: Transcription activities are based on the ability to write words by working on lexical spelling (eg, knowledge of spelling irregularities), grammatical spelling (eg, differentiation of "et" or "est"), inflectional morphology (eg, plural marks), and derivational morphology (eg, recognizing prefix-radical-suffix structures). Activities such as word completion are proposed here.
4. Semantics: Semantics activities are based on understanding written language. This involves knowing the vocabulary, understanding syntactic structures (eg, subordinate clauses) and textual structures (eg, organization of ideas in a text), and making inferences. This involves activities such as

carrying out written instructions or putting a story in chronological order.

Outcomes

The primary outcome of this study is reading accuracy, which will be measured by the number of correctly read words using the EVALEO (Ortho Edition) [37] 2-minute word reading test (EVAL2M). Noninferiority will be evaluated 12 weeks after the start of training with Poppins Clinical for the experimental group or 12 weeks after the baseline evaluation for the control group.

Safety will be assessed by monitoring adverse events reported by patients during the 12-week study duration.

Seven secondary outcomes will also be investigated. Noninferiority in reading speed, measured by the number of words read using the EVAL2M [37], will also be evaluated. In addition, noninferiority in word reading skills (speed and accuracy) and meta-phonological skills will be assessed using respectively the Alouette-R [38] text reading test and the BALE Phoneme Suppression Test [39].

The impact of Poppins Clinical on parents' stress levels and quality of life will be measured using the Parenting Stress Index-Short Form (PSI-SF) and the EQ-5D-5L [40] quality of life questionnaire. Text comprehension will also be assessed through the computerized BMT-i test battery [41], evaluating correct answers to comprehension questions, as well as reading precision and speed. A cost evaluation will be conducted by administering a questionnaire to parents to evaluate the health and economic value of Poppins Clinical. The objective is to determine in each group the direct and indirect health care costs, including, treatment costs (eg, number of appointments and costs of each session) and work-related costs (eg, the number of days off used for health purposes).

A total of 5 exploratory end points will be investigated. The effect of Poppins Clinical on visual attention span will be assessed with the EVALEO test, using correct answer scores. The patient's quality of life and reading and writing difficulties will be evaluated using the PedsQL 4.0 CORE [42] young child report and a self-assessment grid for reading and writing difficulties [43]. The perceptions of parents and speech therapists regarding the study's impact on therapy will be captured via an adapted questionnaire. Finally, predictive factors of training effectiveness with Poppins Clinical will be explored to improve the individualization of the program and the use of the device through connection data.

All the outcomes are described in Table 1.

All outcomes will be evaluated 12 weeks after the start of training for the experimental group or 12 weeks after the baseline evaluation for the control group. Participants of the experimental group will have up to 14 calendar days to start training with Poppins Clinical once the baseline evaluation is completed. The results will be entered into an electronic case report form (eCRF) hosted on the web by the CRO, which will be responsible for data monitoring and treatment.

Table 1. Measured outcomes investigated in the protocol.

Outcome	Measure
Primary outcome	Reading accuracy is measured by the number of correctly read words (EVAL2M)
Safety secondary outcome	Number of adverse events reported during the study
Secondary outcome 1	Reading speed is measured by the number of read words (EVAL2M)
Secondary outcome 2	Word reading accuracy and speed (Alouette-R)
Secondary outcome 3	Cost evaluation
Secondary outcome 4	Phoneme suppression skills (BALE)
Secondary outcome 5	Parental stress levels measured using the Parenting Stress Index Short Form
Secondary outcome 6	Parent's quality of life measured using the EQ-5D-5L
Secondary outcome 7	Reading precision, speed, and comprehension (BMT-i)
Exploratory outcome 1	Visual attention span (EVALEO)
Exploratory outcome 2	Child's quality of life (PedsQL 4.0 CORE)
Exploratory outcome 3	Child's perception of reading and writing difficulties [43]
Exploratory outcome 4	Perception of parents and speech therapists on the impact of the protocol on the child (custom questionnaire)
Exploratory outcome 5	Evaluation of predictive factors of training effectiveness

Statistical Justification of the Sample Size

The sample size determination was based on the primary end point, which is to demonstrate the noninferiority of a follow-up with reading therapy every 2 weeks, in addition to the use of the digital medical device (Poppins Clinical), compared with a follow-up with reading therapy every week, on the evolution of reading accuracy over 12 weeks. The null (H0) and alternative (H1) hypotheses for noninferiority trials may take the following form:

1. H0: experimental (EXPE) is inferior in terms of the mean response, $\mu EXPE - \mu CONT \leq -\Delta NI$.
2. H1: experimental is noninferior in terms of the mean response, $\mu EXPE - \mu CONT > -\Delta NI$.

Where μEXPE is the mean of the outcome in the experimental arm, and μCONT is the mean of the outcome in the control arm. The noninferiority limit, –ΔNI, is defined as the threshold at which the mean difference between the experimental arm and the control arm becomes clinically unacceptable.

The noninferiority margin was determined through a formal expert committee meeting, combining independent experts and investigators. The committee was structured to ensure both independence and relevant expertise. Two independent experts were selected for their complementary expertise: a neuropediatrician who pioneered diagnostic recommendations for learning disorders in France, and a speech therapist who codeveloped the standardized assessment tool used as the primary outcome in this study (EVALEO 6-15). The two investigators of the study, both professors in child psychiatry with extensive research experience in neurodevelopmental disorders, provided their methodological expertise. A fifth expert, a neuropsychologist with experience in written language rehabilitation guidelines and as a reviewer of good practice recommendations, was included as a scientific advisor. All experts were active clinicians and researchers in learning disabilities.

The committee's decision was informed by empirical data from the previous randomized controlled trial (ML-01), showing a natural progression of 7.7 (SD 12.9) correctly read words over 8 weeks in the placebo group [26]. Based on these data and their collective clinical experience, they established that a difference of 5 words or fewer between groups would represent a clinically acceptable margin of noninferiority. This threshold was unanimously approved by the full committee after a structured discussion of potential age-related variations in reading progression.

The SD of the outcome in each group was estimated at 12.7 words from the ML-01 study [26]. The maximum acceptable inferiority for experimental versus control on the primary outcome is therefore expected to be a standardized difference (Cohen d=0.39), which corresponds to a label between small or medium, depending on the guidelines (R effect size package) [44].

Considering a one-sided significance level of 2.5% and a power of 90%, it is necessary to include 137 participants per group (G*Power 3.1). Assuming a 10% drop-out rate, the final estimate is 306 participants in total (or 153 participants per arm).

Statistical Methods

This trial uses a noninferiority and possibly superiority hypothesis testing framework between groups for primary, secondary, and exploratory outcomes. We will report the results in accordance with the noninferiority trials extension of the CONSORT (Consolidated Standards of Reporting Trials) 2010 statement. Tests for noninferiority will be one-sided and performed using a 2.5% significance level. All other tests will be two-sided, performed using a 5% significance level. The type I error rate will be controlled using a hierarchical testing procedure for secondary end points. A subsequent end point will only be tested if the previous end point's test for noninferiority is statistically significant.

Criteria Analysis

According to CONSORT 2010, interpreting a noninferiority trial's results depends on where the CI for the treatment effect lies relative to the margin of noninferiority –ΔNI and the null effect. The lower bound of the one-sided (1–α)×100% CI for the treatment effect must be above the margin –ΔNI to declare that noninferiority has been shown [45].

Once noninferiority is evident, it is acceptable to assess whether the new follow-up appears superior to the reference follow-up, using an appropriate test or CI, with a significance level defined a priori and with an intention-to-treat (ITT) and a per-protocol (PP) analysis. All randomized patients will be included in the ITT analysis, including children assessed at T1 or T2, after the time allowed by the protocol. The PP population will include only participants without major deviations. These patients must have completed at least 50% of the prescribed training time and at least 50% of the reading therapy sessions outlined in the protocol.

In this context, if the noninferiority is shown (based on both ITT and PP analyses), superiority will then be tested for the same primary end point, as described in the European Medicines Agency (EMA) guidelines [46]. Superiority will be tested using a t test at a 2-sided 5% significance level.

The type I error rate will be controlled using a hierarchical testing procedure for secondary end points. A subsequent end point will only be tested if the previous end point's noninferiority test is statistically significant.

Safety Criterion Analysis

The safety population includes all participants who will use the DM Poppins device at least once. This safety population will be used for the safety analysis. Adverse events will be reported by the participant's parents to the CRO's Safety Department or the patient coordinator and will be recorded in the eCRF form. The form will contain all necessary variables to define the date, severity, and relationship to the study device, as evaluated by the investigator (see Textbox 1).

Textbox 1. Summary of descriptive statistics of adverse events and device deficiencies.

For adverse events:

- Type of adverse event
- Severity
- Evolution
- Relationship with the device
- Number of episodes
- Time of onset of the adverse event (defined as the time from first use to the earliest date of the adverse event)
- Number of participants with at least one episode (and percentage)
- Discontinuations will also be summarized.

For device deficiency:

- Type of device deficiency
- Duration of the deficiency

Ethical Considerations

The study protocol was approved by the local ethics committee (Comité de protection des personnes for Sud-Est-1; number 2023-A02723-42) and national regulatory agencies (Agence nationale de sécurité du médicament et des produits de santé and Commission nationale de l'informatique et des libertés; N°IDRCB 2023-A02723-42).

Before consent, the patient and their parents will receive a patient information sheet via email. This document will provide the participant and legal guardian with a comprehensive explanation of the study, including its rationale, procedures, benefits, and risks. It will also emphasize that participation is voluntary and that the participant may withdraw from the study at any time without any negative consequences. In addition, a physician will discuss this information with the participant and legal guardian, allowing them sufficient time and opportunity to ask questions and make a decision about whether to participate in the study.

It will be clearly stated that the participant is free to withdraw from the study at any time and for any reason, without affecting their future care, legal rights, and the obligation to give a reason for withdrawal.

Written informed consent must be obtained from the legal guardian in accordance with local practices and regulations before any study assessments or tests are conducted. Written consent will be obtained by signing and dating the approved consent forms. No study assessments or procedures will be conducted until written informed consent has been provided. A description of the consent process must be documented in the participant's medical record.

The parents will provide their signature at the end of the consent form, and a delegated site team member will countersign it. Consent will be obtained either via an electronic signature or a wet ink signature. A copy of the fully executed informed consent form will be provided to both the participant and their parents (either in paper form or sent electronically via email), and a copy will be securely retained by the site in a restricted-access area.

Identifiable participant details (such as name and date of birth) will be held in a separate database from the research database after receiving the participant's consent. The research database will never hold personally identifiable information. Automatic reminders will be sent to participants by doing a one-time recall of identifiable information, matched with the unique study ID.

Given the patient's condition (specific learning disability with reading deficit) and their age thus potentially being unable to provide written consent, the child will provide verbal assent to participate in the trial. The investigator will read the content of the consent form during the information visit, clearly stating that the child is free to decline their participation at any moment. The consent form is adapted to an appropriate language to facilitate the children's understanding. An audio track of the consent form content will also be sent to the parents via email, in case the child would like to listen to it again. Once the child verbally agrees to participate in the trial, the investigator will sign the consent form (either electronically or wet ink) on their behalf and register it in the eCRF.

An information letter for the speech and reading therapist in charge of the participants will also be sent by email to the participant's parents. Parents will be asked to forward it to the speech and reading therapist to inform them of the study and that compensation is provided for them if the participant participates.

The compensation for the speech and reading therapist aims to cover their involvement in the study (they will receive by email the attribution group of their patient and might be asked to rearrange their session schedule to comply with the study protocol) and to compensate for missed sessions (for speech and reading therapist who follow up with patients in the experimental group). Compensation is disclosed to the speech and reading therapists only after the participant signs the informed consent and is detailed in an email that is directly sent to the speech and reading therapists. For further information, the speech and reading therapist can ask for an appointment

with the dedicated support team (assured by an independent third party), if desired. Speech and reading therapists will be asked to agree to the collection of their personal data (name and email address) to receive information about the study via email and to complete a questionnaire at the end of the trial.

Results

We expect to enroll 306 patients within 6 months from the start of the inclusion phase. Considering that children's participation lasts 3 months, we expect to have the results of this study by the end of August 2025.

Discussion

Principal Findings

The objective of this study is to assess the noninferiority of the serious game Poppins Clinical combined with one reading therapy session every 2 weeks, compared with a reading therapy session every week. To achieve this, we will use a noninferiority trial to measure the acceptance of the new intervention with Poppins Clinical. Our primary outcome will be the number of correctly read words with the EVAL2M test, which is a standard and recent test used in reading therapy. We expect that the experimental group's outcomes will remain within the established noninferiority margin relative to the control group for reading tasks (speed, accuracy, and comprehension), visual span, phonology, and measures of quality of life and parental stress. In addition, we anticipate that the children will be able to adhere to the training program over 3 months when combined with speech therapy sessions, during which the speech therapist can monitor the child's progress. Finally, we expect parents and speech therapists to easily integrate Poppins Clinical–based training into their daily routines. Therefore, Poppins Clinical would demonstrate good integration into the child's care pathway, positively impacting the medico-economic aspects of the treatment, such as improving access to care or simplifying travel for families.

The noninferiority margin represents the maximum clinically acceptable difference between the new treatment and the active control that still allows concluding noninferiority. This margin should be based on a clinical basis, but methods for defining the noninferiority margin can vary widely [47]. The methods used to define the noninferiority margin are frequently not detailed in noninferiority trials, although the choice of the noninferiority margin may strongly impact the conclusion regarding noninferiority trials [47]. Currently, there is no consensus about the best method for defining the noninferiority margin. Previous trials and historical data should be considered if available, however, such data do not always exist. To our knowledge, there is no previous trial or historical evidence regarding the margin that could be clinically relevant in SLD therapy. In that case, the choice of the margin is often based on experts' opinions [29,47]. The clinically significant margin was determined through consultation with an independent expert committee. A threshold of –5 correctly read words was established as the noninferiority margin based on clinical data and expertise. This decision was based on data from a previous double-blind randomized controlled trial showing a natural progression of 7.7 (SD 12.7) correctly read words over 8 weeks [26] and was unanimously approved by a committee of experts combining clinical experience in learning disabilities with methodological expertise.

The choice of population and how to handle missing data may also affect trial results. ITT analyses may favor noninferiority results, while protocol violations may dilute potential differences between the treatment arms, favoring noninferiority results. Therefore, it is preferable to analyze noninferiority trials using both the ITT and PP approach [48]. We will conduct statistical analysis using both the ITT and PP populations. The PP population includes only participants who have completed at least 50% of the training time prescribed by the protocol. To ensure consistency in reading therapy care within the PP population, each participant must complete at least 50% of the reading therapy sessions outlined in the protocol.

We will also conduct noninferiority analysis for reading skills with texts with and those without meaning. The use of several reading tests will allow us to explore different aspects of reading such as accuracy, speed, and comprehension. The use of two texts, with and without meaning, should help us address the possible compensation that patients might use during reading by relying on the context of the text to increase their performance [49]. To avoid an effect between the test and retest for the evaluation of reading understanding, we will use two different texts between the pretest and posttest. Both texts come from the EVALEO 6-15 [37] and are equivalent in terms of syntactic complexity, word frequencies, and length.

However, we will look at the medical costs in both groups during the study. Effectively, the benefit of a new treatment may also be considered in terms of time consumption (eg, transportation and appointments), costs for the family and the patient, as well as costs for society, as speech and reading therapy are reimbursed by the social health insurance in France [28,29]. Gentili et al [50] conducted a literature review on the impact of medical costs of the use of digital health interventions. It appears that more and more evidence suggests a generally favorable effect of digital interventions in terms of costs and health outcomes. The findings show a positive impact, especially for studies that implemented a new mobile app or a web portal intervention, as is the case for Poppins Clinical. Benefits seem to be particularly important in rural areas [50].

Finally, we will perform questionnaires to assess the quality of life and perceived reading difficulties of the patient. Effectively, it is important to evaluate if the impact of an intervention is perceived by the patient and should have an impact on their daily life [51]. However, we will take into account parents' and speech therapists' perceptions of the impact of the protocol on reading therapy in terms of motivation, satisfaction, and time dedicated to work at home and in-person therapy. We seek to evaluate if the introduction of home training with the serious game Poppins Clinical may negatively or positively affect family time and reading therapy. We will track the stress of parents, as the introduction of home training could be time-consuming and raise behavioral problems (such as rejection to use the device). However, most web- and game-based interventions used with patients with SLD are well accepted by patients and

their parents [52,53]. Home training may benefit the link between the child and the parents, supporting their interaction and giving them a structured environment to help the child make new learning [54].

Some limitations can be identified in our study. First, the participants are not blinded to their group allocation. This was not feasible, as the protocol affects the frequency of reading therapy sessions, and it would have been unethical to reduce the number of reading therapy sessions to replace them with a placebo. In addition, we will conduct multiple analyses, which could increase the risk of a Type I error. To control for this, we will use a hierarchical testing procedure for secondary end points. A subsequent end point will be tested only if the previous end point's noninferiority test is statistically significant. Finally, we cannot control what reading therapists do during therapy sessions. However, we will monitor the training of the reading therapists by recording their year of certification and any recent training they have completed.

Conclusion

We plan to conduct a single-blind randomized controlled trial to compare the effect of the serious game Poppins Clinical, combined with a reading therapy session every 2 weeks, to reading therapy alone every week on reading skills in children with SLD. To compare the clinical impact of both interventions, we will use a noninferiority design. We will also explore phonological and visual-attentional skills and the impact of the intervention on children, parents, speech and reading therapists, and patient care organizations. The trial results will be submitted to a research journal and summarized for the study participants.

Acknowledgments

We would like to thank Monique Touzin, Catherine Billard, Prof Fabrice Denis, Catherine Grosmaitre, and Michel Habib for their contributions throughout the various stages of this project. We also thank the investigative centers and physicians who facilitated this work, including Joana Matos, Alice Oppetit Clément Villiers, Cécile Pernossi, Claire Lechevalier, Manon Ranvier, and Anne Delepine. This work was supported by the Plan France 2030 (France's national investment strategy program).

Data Availability

The datasets generated or analyzed during this study are available upon reasonable request from the corresponding author.

Authors' Contributions

CG: methodology, writing—original draft; MD: methodology, statistical plan; SC, DC, FV, and JX: methodology, Writing—review & editing; HP and BF: methodology, Writing—review & editing.

Conflicts of Interest

FV is the CEO of Poppins, the company that developed Poppins Clinical. MD and CG are employees at Poppins. DC reports a relationship with Poppins that includes equity or stocks.

Multimedia Appendix 1
SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) checklist.
[PDF File (Adobe PDF File), 242 KB - resprot_v14i1e71326_app1.pdf]

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Abbreviations

CONSORT: Consolidated Standards of Reporting Trials
CRO: Contract Research Organization
DSM-5: Diagnostic and Statistical Manual of Mental Disorders (Fifth Edition)
DSM-5-TR: Diagnostic and Statistical Manual of Mental Disorders (Fifth Edition, Text Revision)
eCRF: electronic case report form
EMA: European Medicines Agency
H0: null hypothesis
H1: alternative hypotheses
ITT: intention-to-treat
PP: per-protocol
PSI-SF: Parenting Stress Index-Short Form
SLD: specific learning disorder
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials

Edited by A Schwartz; submitted 15.01.25; peer-reviewed by S Bertoni; comments to author 11.02.25; revised version received 28.02.25; accepted 04.03.25; published 03.04.25.

Please cite as:
Grossard C, Descamps M, Cadoni S, Pellerin H, Vonthron F, Xavier J, Falissard B, Cohen D
Assessing the Noninferiority of a Rhythm and Language Training Serious Game Combined With Speech Therapy Versus Speech Therapy Care for Children With Dyslexia: Protocol for an Investigator-Blinded Randomized Controlled Trial
JMIR Res Protoc 2025;14:e71326
URL: https://www.researchprotocols.org/2025/1/e71326
doi:10.2196/71326
PMID:

Protocol

Testing a Machine Learning–Based Adaptive Motivational System for Socioeconomically Disadvantaged Smokers (Adapt2Quit): Protocol for a Randomized Controlled Trial

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Abstract

Background: Individuals who are socioeconomically disadvantaged have high smoking rates and face barriers to participating in smoking cessation interventions. Computer-tailored health communication, which is focused on finding the most relevant messages for an individual, has been shown to promote behavior change. We developed a machine learning approach (the Adapt2Quit recommender system), and our pilot work demonstrated the potential to increase message relevance and smoking cessation effectiveness among individuals who are socioeconomically disadvantaged.

Objective: This study protocol describes our randomized controlled trial to test whether the Adapt2Quit recommender system will increase smoking cessation among individuals from socioeconomically disadvantaged backgrounds who smoke.

Methods: Individuals from socioeconomically disadvantaged backgrounds who smoke were identified based on insurance tied to low income or from clinical settings (eg, community health centers) that provide care for low-income patients. They received text messages from the Adapt2Quit recommender system for 6 months. Participants received daily text messages for the first 30 days and every 14 days until the end of the study. Intervention participants also received biweekly texting facilitation messages, that is, text messages asking participants to respond (yes or no) if they were interested in being referred to the quitline. Interested participants were then actively referred to the quitline by study staff. Intervention participants also received biweekly text messages assessing their current smoking status. Control participants did not receive the recommender messages but received the biweekly texting facilitation and smoking status assessment messages. Our primary outcome is the 7-day point-prevalence smoking cessation at 6 months, verified by carbon monoxide testing. We will use an inverse probability weighting approach to test our primary outcome. This involves using a logistic regression model to predict nonmissingness, calculating the inverse probability of nonmissingness, and using it as a weight in a logistic regression model to compare cessation rates between the two groups.

Results: The Adapt2Quit study was funded in April 2020 and is still ongoing. We have completed the recruitment of individuals (N=757 participants). The 6-month follow-up of all participants was completed in November 2024. The sample consists of 64% (486/757) female participants, 35% (265/757) Black or African American individuals, 51.1% (387/757) White individuals, and

16% (121/757) Hispanic or Latino individuals. In total, 52.6% (398/757) of participants reported having a high school education or being a high school graduate; 70% (529/757) smoked their first cigarette within 30 minutes of waking, and half (379/757, 50%) had stopped smoking for at least one day in the past year. Moreover, 16.6% (126/757) had called the quitline before study participation.

Conclusions: We have recruited a diverse sample of individuals who are socioeconomically disadvantaged and designed a rigorous protocol to evaluate the Adapt2Quit recommender system. Future papers will present our main analysis of the trial.

Trial Registration: ClinicalTrials.gov NCT04720625; https://clinicaltrials.gov/study/NCT04720625

International Registered Report Identifier (IRRID): DERR1-10.2196/63693

(JMIR Res Protoc 2025;14:e63693) doi:10.2196/63693

KEYWORDS

smoking cessation; mHealth; socioeconomically disadvantaged, biochemical verification; machine learning

Introduction

Background

Cigarette smoking is a serious public health problem and the leading cause of preventable disease, disability, and death in the United States [1]. While overall smoking rates have decreased, smoking rates among individuals who are socioeconomically disadvantaged remain high [2-5]. Individuals who are socioeconomically disadvantaged are affected disproportionately from smoking-related diseases [2-5]. Individuals who are socioeconomically disadvantaged may be less likely to try to quit smoking (eg, due to lower self-efficacy and maladaptive beliefs) and are less likely to use evidence-based strategies (such as quitlines).

Computer-Tailored Health Communication via Texting: A Potential Approach

One strategy to engage these individuals is by using computer-tailored messages delivered via texting. Computer-tailored health communication involves the use of computer programs to select the best personalized message for an individual. This form of communication has been effective in enhancing motivation to quit and supporting cessation [6-12]. In a systematic review, computer-tailored messages showed higher cessation rates than nontailored messages (relative risk 1.17, 95% CI 0.97-1.41). Computer-tailored messages work because participants are more likely to engage and carefully process personally relevant messages [13]. Thus, methods to increase the relevance of the message may increase the effectiveness of the smoking cessation intervention. Computer-tailored messages delivered via texting over phones may be particularly attractive for individuals who are socioeconomically disadvantaged. Mobile phone ownership is now nearly universal (95%) [14], and these rates are consistent across socioeconomically disadvantaged groups (less than high school education, 92% and those earning <US $30,000, 92%). The texting app is the most commonly used app on mobile phones [14].

The Adapt2Quit Intervention: Leveraging Machine Learning for Tailored Cessation Support

In our National Institutes of Health–funded trial, we are testing Adapt2Quit, which uses machine learning algorithms (ie, recommender systems) to computer-tailor messages for an individual and deliver them via texting [15]. Recommender systems can be programmed to continuously learn from user feedback and improve personal relevance and customer engagement [15]. Adapt2Quit also includes proactive texting facilitation to the state quitline in which participants are asked if they want to be referred to the quitline, and those who agree are referred to the quitline. Quitlines are programs in the United States that offer evidence-based support (eg, counseling and medications) to individuals who smoke. These individuals can either directly contact quitlines using the number 1-800-QUIT-NOW or be referred by a health care provider or tobacco cessation programs. Although quitlines have been established in all 50 US states, they are vastly underused. The use of texting to promote quitline use could potentially increase quitline use, and thereby increase the effectiveness of the smoking cessation intervention for the participants.

Preliminary Evidence Supporting Adapt2Quit

In our preliminary studies, Adapt2Quit increased engagement and 30-day point-prevalence effectiveness over a standard messaging that randomly selected these messages [16]. In a subanalysis among those who reported lower education (n=49), the average rating of the messages was higher on more days than the average ratings of true comparison messages (77% vs 23%; $P<.01$). This pilot study showed the potential of the Adapt2Quit trial among individuals who are socioeconomically disadvantaged. Since the beginning of the trial, we have completed another randomized controlled trial that tested the machine learning algorithm compared to standard messaging among those who were recruited via social media [17]. In the other trial, there was no significant difference in 6-month point-prevalence smoking cessation (adjusted odds ratio 0.81, 95% CI 0.61-1.08) between the recommender system (146/412, 35.4% of participants with outcome data) and messages tailored by standard messaging based on participants' baseline readiness to quit groups (156/389, 40.1% of participants with outcome data). However, the other trial differs from the current trial being reported in that the messages were delivered via email, it did not target individuals who are socioeconomically disadvantaged, and the system did not facilitate referral to the quitline. Furthermore, another group has evaluated a similar recommender system approach for message selection in a pilot trial for self-reported smoking cessation [18]. However, additional studies testing recommender systems are needed to uncover the potential of these systems for increasing the

effectiveness of computer-tailored smoking cessation interventions.

Theoretical Basis for the Adapt2Quit Intervention

The Adapt2Quit intervention is based on the self-determination theory (SDT). SDT-based interventions support autonomous decisions and are designed to increase intrinsic motivation and self-regulation and they have been shown to improve motivation and cessation outcomes among those who smoke [19-24]. Three innate psychological needs are theorized to promote self-motivation: autonomy, relatedness, and competence [19]. Autonomy reflects the need to engage in behaviors with a sense of choice or personal endorsement [25]. Autonomy support can be provided by acknowledging an individual's unique perspective and offering choice [25,26]. Relatedness reflects the degree to which an individual feels connected to and understood by others. Competence is a feeling of being capable and is akin to self-efficacy, the belief that one can bring about desired outcomes. By supporting autonomy, relatedness, and competence, health behaviors are more likely to be internalized and maintained. Specific examples of how Adapt2Quit supports the SDT are provided in Textboxes 1 [27] and 2. Our aims and hypotheses align with our proposed model, which suggests that relevant personal messages from the Adapt2Quit system will enhance system engagement. This increased engagement is expected to improve internal processes (ie, the SDT constructs measured using the Perceived Competence Scale [PCS]), leading participants to adopt cessation-supporting behaviors (external processes such as quitline and nicotine replacement therapy [NRT] use), ultimately resulting in smoking cessation.

Textbox 1. Examples of mapping the self-determination theory to Adapt2Quit.

- Autonomy: participants can control how often they want to rate the messages with the system. Autonomy increases as the participant's ratings influence the messages they receive, providing an enhanced feeling of control over the intervention. Furthermore, Adapt2Quit facilitates quitline access but does not impose it. Participants are asked if they want to contact the quitline. Only if the participant responds positively, our system will initiate a quitline referral. Autonomy is increased as the participant controls if and when they choose to interact with the quitline. Our messages will focus on persuading the smoker to use quitline.
- Relatedness: in addition to the smoker profile, Adapt2Quit's recommendations are based on feedback from thousands of smokers who previously engaged with the recommender system. Relatedness increases as the system learns and adapts to the ratings feedback of each new smoker. The Adapt2Quit messages database includes peer-written messages [27]. Messages from peers may enhance relatedness because they reflect shared experiences, allowing smokers to more easily identify with the message content [27].
- Competence: Adapt2Quit messages are designed to improve motivation, educate, and increase a smoker's confidence and skills related to smoking cessation. Content includes appropriate strategies and treatments, as cues and reminders to encourage use, which were developed based on current guidelines on smoking cessation. Our pilot showed that Adapt2Quit increased the adoption of cessation-supportive behavior.

Textbox 2. Specific aims.

Aim 1: Adapt2Quit engagement—heterogeneity of Adapt2Quit recommender system engagement

- Hypothesis 1a: among Adapt2Quit participants, those with higher engagement levels (ie, completed more ratings) will have greater scores on the Perceived Competence Scale (PCS).

Aim 2: behavioral processes—internal processes (self-determination theory constructs) and external "processes" or cessation-supportive actions comparing Adapt2Quit and the comparison group (texting facilitation to quitline)

- Hypothesis 2a: Adapt2Quit participants will have greater scores on the PCS than comparison participants.
- Hypothesis 2b: Adapt2Quit participants will adopt more cessation-supporting actions (quitline use and nicotine replacement therapy) than comparison smokers.

Aim 3: effectiveness—6-month smoking cessation in Adapt2Quit versus the comparison group

- Hypothesis 3a: (primary outcome) Adapt2Quit participants will have greater smoking cessation rates (6-month point-prevalence biochemically verified) than comparison participants.
- Hypothesis 3b: (mediation analysis) measured internal and external processes will mediate the effect of Adapt2Quit on smoking cessation.

Paper Objective

This paper describes the protocol and status of our ongoing randomized controlled trial testing the Adapt2Quit intervention among individuals from socioeconomically disadvantaged backgrounds who smoke. Our comparison participants receive the biweekly texting facilitation messages but do not receive the motivational messages recommended by the Adapt2Quit intervention. Our protocol description includes the intervention and comparison system as well as the description of the analyses of the primary and secondary hypotheses listed in the following sections. Since recruitment for our study has finished, we describe the demographics of the participants we have recruited. Our follow-up data collection is in progress.

Methods

Study Design and Setting

This study is a 2-arm randomized controlled trial comparing participants who received smoking cessation text messages selected by the Adapt2Quit recommender system plus a texting

facilitation approach to connect participants to the quitline with participants who received the texting facilitation but no smoking cessation text messages. Study participants were blinded to group assignments. They were recruited from health systems in diverse geographic areas. Recruitment started in April 2020 and was completed in March 2024. Our target sample size was 750 individuals from socioeconomically disadvantaged backgrounds who smoke.

Ethical Considerations

The Adapt2Quit study has been approved by all participating institutions' institutional review boards (IRBs), including Baystate (BH-20-123) and Johns Hopkins (IRB00280942), with the University of Massachusetts Chan Medical School (UMass Chan) IRB (H00018991) being the central IRB. The study is listed in ClinicalTrials.gov (NCT04720625). It is being carried out in accordance with the Helsinki Declaration, and all participants have signed an informed consent form before enrollment in the study. Participants have been informed that they have the right to withdraw their consent at any point during the study, and the reason for their withdrawal will also be documented if the participant so wishes. The participants have received compensation for completing study activities. They received US $25 for completion of baseline, US $25 for the 6-month follow-up, US $50 for completing the carbon monoxide (CO) verification assessment, and an additional US $50 for participation in the qualitative interview. Upon randomization, all patients have been assigned an individual ID number so their data remain anonymous.

Inclusion and Exclusion Criteria

The inclusion criteria were as follows: an individual who smokes, comes from a socioeconomically disadvantaged background, speaks English, who is active in care (having at least 2 clinical visits in the past 2 years), and who has a texting-enabled mobile l phone. We used insurance status to identify participants as socioeconomically disadvantaged [28]. In the United States, people can receive health insurance or health care payment coverage from several sources including through their employer, other private health insurance companies, or through government-supported programs. Individuals who have these government-supported programs are more likely to be from socioeconomically disadvantaged groups. For our study, we used Medicare (a government-funded program for older adults and those with disabilities) and Medicaid (a state and federal program for low-income individuals) to identify individuals from socioeconomically disadvantaged backgrounds. We determined smoking status by asking participants if they had smoked at least 100 cigarettes and their current smoking frequency (Multimedia Appendix 1). Those who responded "yes" to 100 cigarettes and "some" or "every day" were included.

The exclusion criteria were as follows: adults who were unable to consent, individuals who were not yet adults (ie, aged <18 years), prisoners, people with Alzheimer disease, and pilot study participants.

Recruitment

Recruitment was spread over the 3.5 years of the study. Study participants were recruited at urban and rural health care settings across 3 health care systems in the United States (UMass Memorial Medical Center, Baystate Health, and Johns Hopkins University). We used an opt-out recruitment strategy, with some variations between the three sites. At all 3 sites, after obtaining a Health Insurance Portability and Accountability Act waiver, potential participants who met our inclusion criteria in the clinical data warehouse were identified. At the UMass Chan and Baystate Medical Center, an initial invitation letter with a self-addressed, stamped opt-out postcard was sent to those eligible from the local site principal investigator outlining the study's purpose. Johns Hopkins University's site used emailed study invitation letters with instructions to opt-out via email instead of or in addition to mailed letters and "opt-out" postcards for those without an email address. Instructions were provided on how to opt-out by email. At all sites, individuals who opted out or whose email was returned undelivered within 2 weeks were removed from the recruitment list.

Screening, Informed Consent, and Baseline Data Collection

Potential participants were phoned up to 4 times to determine their interest and were screened for eligibility. Before starting the first recruitment call, the research staff sent an automated introductory text message to potential participants who would be called that day. During the phone call, participant eligibility was assessed (Multimedia Appendix 1). Eligible participants were asked to provide informed consent for study participation, were asked to complete the baseline data, and were then randomized to treatment. The screening session, informed consent, and baseline data collection were conducted via Zoom (Zoom Communications, Inc) or by phone.

Once randomized, after completion of the baseline survey (Multimedia Appendix 1), the Adapt2Quit intervention participants received 5 initial motivation messages and were asked to provide a rating. The recruitment staff viewed the rating in real time to confirm whether the participant understood and was comfortable with the system. The staff emphasized the importance of rating their messages to intervention participants. The research staff explained the quitline facilitation process and smoking status texting assessment to both groups and reiterated the importance of completing the ratings to intervention participants. Those randomized to the control group received only the texting facilitation and smoking status but did not receive the motivational messages, and instructions were provided accordingly.

Randomization

Separate randomization tables were created for each site to enhance the balance between the two groups. Participant allocation to study arms was based on a permuted block scheme in which treatment assignments were made within blocks so that numbers assigned to each treatment arm are equal after a block has been filled. Blocks of various sizes (2, 4, and 6) were used in random order to facilitate allocation concealment. As in our prior technology-based trials, we embedded

randomization within the technology [29,30]. After completing the screening, informed consent, and baseline data collection, the research staff entered the participant ID and participant mobile phone number from the survey into a web-based system, which then assigned the allocation based on the randomization table. Using this technique, participants and staff were blinded to allocation during the initial session. The research staff were subsequently unblinded to provide personalized training for the intervention and control groups, as noted.

Intervention and Comparison

Intervention: The Adapt2Quit Recommender System

The Adapt2Quit recommender system uses a machine learning algorithm to select the best message for a participant from a motivational messaging database. We programmed Adapt2Quit to select messages based on the following: (1) the smoking status of the participant and (2) the ratings database (both from prior study participants and current participants) [16,31-33]. We discuss the recommender system components in subsequent sections. The system has multiple components.

Component 1: The Motivational Messages Database

The messages include 261 messages, including 206 expert- and 55 peer-written messages (Multimedia Appendix 2) [27]. We developed the expert-written messages through an iterative group review process guided by theoretical frameworks and existing smoking cessation guidelines [34]. Peer-written messages were written by current and former people who smoke, responding to a web-based survey. Our methods for developing this messaging database and its characteristics have been published [27]. Briefly, the expert messages written by smoking cessation providers and researchers were more "biomedical" (ie, avoidance, behavioral strategies, and health), while peer messages had more "social" and "real-life" content (ie, expectations, money, quality of life, attitudes, and friends) [27]. Our messages were assessed to be readable for someone with at least a fifth grade–level education (Flesch-Kincaid Grade level 5.5). In total, 19.9% (52/261) of the messages were peer messages. Overall, 52.9% (138/261) of the messages provided information about behavioral treatments (eg, substitution and distraction); 39.8% (104/261) contained motivational content, such as reasons to quit; 26.8% (70/261) included health-related information, such as the risks of smoking to physical and cognitive functioning; and 19.9% (52/261) addressed how seeking social support or smoking impacted social interactions with family and friends. Multimedia Appendix 2 lists example messages.

Component 2: Ratings Database

The algorithm uses 2 types of ratings data to generate the following recommendations.

First, ratings from prior study participants. More than 1000 participants have rated our messages using the influence rating question (see definition in the Data Elements, Statistical Analysis, and Power Calculation for Specific Aims section) resulting in 18,920 ratings [16,32,33]. We chose the influence rating question after a pilot test in which we asked participants to rate each message on 4 aspects: influence, emotional response, relevance, and preference [33]. We found that all these aspects were highly correlated. In developing the algorithms for the recommender system, we compared ratings by different user profile characteristics. Of the 20 messages rated most highly by participants with less than a high school education, only 3 messages were rated in the top 20 by college graduate participants. Adapt2Quit considers all these variations for message selection.

Second, current ratings from participants in the intervention group using 2-way texting. Adapt2Quit is also programmed to learn from the explicit ratings of participants receiving the messages. Thus, when a participant is sent a text message, it will be accompanied by a question (see definition in the Data Elements, Statistical Analysis, and Power Calculation for Specific Aims section) asking the participant to rate the text message using the influence ratings question. The participant can choose how frequently they wish to rate the text messages. In addition to improving the system, our participants in the pilot studies noted that rating the messages helped them to cognitively process the messages better and remember their content.

Component 3: Machine Learning Algorithm

In our prior publications, we have described our algorithm development in detail [16,32,33]. For the purpose of this paper, we describe our approach and the functioning of the system in brief. We used a strong generalization protocol that involved completely separating test users from train users, learning a model using all the train users' ratings, freezing all non–user-specific parameters, and finally training the user-specific parameters on a subset of each test user's observed ratings. We evaluated several recommender methods for accurate prediction, including K-nearest neighbors, probabilistic matrix factorization, collective matrix factorization, and the Bayesian probabilistic matrix factorization (BPMF) [33]. In evaluating rating prediction methods, we used a range of standard performance metrics including root mean squared error, Kendall tau-b, and normalized discounted cumulative gain. In all these tests, BPMF was identified as the best single model. For example, comparing the root mean squared error metric between the different algorithms, there was a small but statistically significant gap (P=.01) between the BPMF and other algorithms as determined by a paired t test with Bonferroni correction. The BPMF model estimates a probability distribution over a joint embedding of users and items into complementary latent spaces. The rating of the given user supplies for a given item is approximated by the expected value of the product of the latent user and item factor vectors representing the user-item pair, with the expectation taken over the uncertainty in embeddings.

The intervention participant experience is as follows: during baseline registration, the intervention participant will be asked to rate 5 messages. The recommender system will use these ratings to select the first message. As the intervention unfolds, the participant will be asked to rate each message, and the system will learn and adapt to these ratings [16,32,33]. In the backend, each time the program needs to select a message for an individual, the program sends all the prior ratings provided by the participant and the messages rated by the participant.

The system also sends demographic information of the participant. The algorithm then selects the next messages based on these data from the list of messages that have not been sent to the participant. The algorithm was also programmed to choose only from among those messages that matched the participant's readiness to quit status. All participants will receive a new message every time. When they do not rate the message on a particular day, our system will have the 5 messages rated at baseline and the ratings of the prior participants to fall back upon to pick a new message. Because the machine learning algorithms operate as a black box, in our prior study, we conducted an analysis of our messages to uncover the black box of the algorithms and understand the message selection process and have published our results [35].

Flow of the Intervention

Participants in the intervention group receive motivational messages, texting quitline facilitation, and texting assessment of smoking status.

Motivational messages selected by the Adapt2Quit recommender system including ratings for user feedback. Participants receive daily motivational messages for the first 30 days and every 14 days until the end of the study. As noted, participants were asked to read these messages and provide their ratings. They were able to choose how frequently they rated messages.

For texting quitline facilitation, participants in both study arms were asked (via text message) if they were interested in being referred to the quitline every 14 days or until the participant responded "yes" to this question. We have followed current best practices in SMS text messaging to connect users to the quitline as described in the study by Krebs et al [36], who, after assessing multiple message frames, found that including a self-efficacy frame was the most effective. If participants request to be connected, a member of the study team refers them to quitline via a secure web form provided by the Massachusetts and Maryland quitline. As per their standard protocol, once quitline staff receive notice of participant interest, they proactively call the participant and engage in counseling.

For texting assessments of smoking status, participants were asked, "What is your current smoking status?" every 30 days over a 6-month period.

Comparison

To isolate the effect of the Adapt2Quit recommender system, comparison participants do not receive tailored motivational messages but receive the texting quitline facilitation and the texting assessment of smoking status with the same frequency as intervention participants.

Six-Month Data Collection Procedures

Overview

Six-month follow-up was conducted via telephone using the REDCap (Research Electronic Data Capture; Vanderbilt University) system to collect the data. Participants had the option to complete the REDCap survey on their own, with research staff sending the secure REDCap link by either email or text or mailing a paper survey to the participant. The system is designed to first collect the main outcome data and then branch into any intervention or control-specific questions. This way the staff is blinded to the participants' assignment when the primary outcome data are collected. To maximize retention, participants were asked upon enrollment to provide 2 alternate telephone numbers, their physical and email addresses, and any other contact information, as applicable. All this contact information was used in making multiple attempts to reach participants to complete their follow-up assessment, which includes sending a thank you letter and incentives for completing the 6-month visit. Participants in both groups will receive a US $25 incentive for completion of the 6-month follow-up and an additional US $50 for completing the CO verification assessment. A web-based tracking system was used to automatically alert staff about participants due for the 6-month follow-up measure to facilitate timely assessments.

Qualitative Interviews

After completion of the 6-month follow-up visit, intervention participants will be invited to complete the qualitative interview to deepen the understanding of potential mechanisms and ways to improve the next generation of the Adapt2Quit intervention (Multimedia Appendix 1). We are using a purposeful sampling approach to recruit interview participants (n=30). Purposeful sampling is a technique widely used in qualitative research for the identification and selection of information-rich cases for the most effective use of limited study resources [37]. We will select participants based on the extent of engagement with Adapt2Quit, use of the quitline, and eventual quitting success. Study coordinators will contact participants who agree to be interviewed to complete the audio-recorded qualitative interviews. The interviews will be conducted by phone and will examine a series of topics following the hypothesized path model presented in the research strategy (Adapt2Quit increases engagement, which results in external and internal processes causing the participant to implement smoking cessation–supporting behaviors; Multimedia Appendix 1). Across these topics, our goal is to understand what participants value most and to elicit recommendations for further system enhancement. Interviews are semistructured, allowing for natural conversation with opportunities to explore unanticipated issues, and will be no longer than 30 to 45 minutes in duration. All qualitative interview participants will be asked to provide verbal consent before participating in the interview and being audio recorded. For participation in the qualitative interview, participants will receive US $50.

Data Elements, Statistical Analysis, and Power Calculation for Specific Aims

Data are collected throughout the study at several time points via text-based ratings, quitline use, assessments, questionnaires, and CO readings. Our main outcomes are described subsequently.

Completion of Ratings

Each Adapt2Quit message is accompanied by the influence ratings question as follows: "Please type the number below to indicate whether you agree with this statement—How much does this message influence you to quit smoking"—on a 5-point

Likert scale (strongly disagree to strongly agree). Our program tracks the ratings completed for each participant.

Internal Processes

Perceived competence, a key SDT construct, will be measured using the previously validated PCS [23]. The 4-item scale assesses the participant's feelings of being able to stop smoking permanently ("I feel confident in my ability to not smoke," "I now feel capable of not smoking," "I am able to not smoke anymore," and "I am able to meet the challenge of not smoking"). Responses are scored on a 7-point scale from 1 (strongly disagree) to 7 (strongly agree), and individual items are averaged to create a scale mean. In prior work [23], PCS was reliable (α=.95) at the 6-month follow-up [23]. We will assess PCS at baseline and at the 6-month follow-up visit.

External Processes (Quitline and NRT)

Quitline use is assessed using data collected from the quitline. We will send a list of our users and ask quitline to provide data on these users, such as the number of contacts between the smoker and the counselor. We will use the time to first call completed with the quitline counselor as our primary quitline measure. NRT is self-reported (yes or no).

Six-Month Cessation

Assessment of the 6-month smoking cessation is collected using the 7-day point-prevalence question [38]: "Do you currently smoke cigarettes (smoked even 1 puff in the last 7 days)?" Point prevalence can capture an intervention's delayed effects. A psychometric analysis comparing continuous, prolonged, and point-prevalence outcomes found that point prevalence had the highest concurrent validity [38]. The 7-day window provides an appropriately stringent measure to account for a cross-sectional snapshot. Using the CoVita Smokerlyzer breath CO monitor, participants who self-report quitting at the 6-month follow-up will be asked to complete biochemical verification remotely (the device will be mailed to them) or in person. Because of the variability of the device, participants will be asked to repeat the test 3 times. The average of these values will be used for our analyses [39]. Participants will be classified as tobacco users if their CO measurement is >6 ppm [40]. Participants completing remotely will be asked to conduct the test over videoconference, where our staff will monitor and guide them. To complete the biochemical verification, whether in person or remotely, study participants will receive a US $50 gift card.

Data Analysis

Statistical Analysis and Power Calculations

To preserve randomization, all primary analyses will be on an intent-to-treat basis. Secondary analyses will explore dose-response effects among those with variable levels of adherence to the intervention. All analyses will be 2-sided, and the α error level will be set at .05. We will begin by examining univariate statistics (means, medians, SDs, frequencies, percentages, and 95% CIs) and distributions of the variable of interest. We will examine the balance of participant characteristics by study groups and account for any imbalances in our multivariable analysis. To address sex as a biological variable, we will stratify the analyses by male and female to evaluate whether the mechanisms and outcomes are modified by sex. We will test group differences either using chi-square tests of independence (categorical variables), *Z* test, or a 2-tailed *t* test (continuous variables), or the equivalent nonparametric tests depending on the distribution of the variables. Baseline differences between the intervention and control group will be established based on standardized differences, rather than on tests of statistical significance.

Aim 1: Adapt2Quit Engagement

Aim 1 is analyzed within the intervention group (N=375). Engagement will be defined as the number of daily ratings divided by the total number of rating opportunities (percentage of ratings completed).

Hypothesis 1a

Among Adapt2Quit participants, those with higher engagement levels (completed more ratings) will have greater scores on the PCS. For hypothesis 1a, we will explore the distribution of the PCS at baseline and the averaged PCS scores during follow-up. Furthermore, we will analyze the distribution of engagement. It is likely that these distributions will be nonnormally distributed. In this case, we will transform the distribution into something approximating normality or choose a nonparametric test to assess the correlation between engagement and the PCS. We will generate a generalized linear model with the averaged follow-up PCS score as the dependent variable and engagement as the independent variable, adjusting for demographic characteristics that vary between highly engaged and less-engaged individuals and for baseline PCS measurements.

Power for Hypothesis 1a

We have considerable *power* to detect relatively small correlations for secondary analyses. As a preliminary power estimate, if we assume a normal distribution and α=.05, we have 80% power to detect a correlation coefficient as small as 0.2 with 200 patients. For larger, more meaningful correlations, we have well over 90% power starting at a sample of 375.

Aim 2: Behavioral Processes

Hypothesis 2a

Adapt2Quit participants will have higher scores on the PCS than control participants. To analyze hypothesis 2a, we will first create a generalized linear model where the dependent variable is the averaged PCS score during follow-up (see the section Hypothesis 1a), the independent variable is randomization group, and the baseline PCS score is included as a covariate. Furthermore, to fully use the repeated measures of the PCS, we will develop a random effects interrupted time series model evaluating the change in slope of PCS over time, comparing the Adapt2Quit intervention and comparison group. This will be implemented using a segmented regression to evaluate changes in slope early in the intervention and sustain change over time in the latter months of the 6-month follow-up.

Power for Hypothesis 2a

In a prior smoking cessation study, the mean (SD) of PCS was 4.79 (1.96) [23]. On the basis of these results, for power calculations, we assumed a meaningful difference in the

averaged PCS score to be equal to 1 SD, assumed the mean in control to be 4.79, and set α at .05. To detect a difference of 1 SD, we have 99% power with a sample of 120 participants per group, further demonstrating power for aims 1 and 2.

Hypothesis 2b

Adapt2Quit participants will adopt more cessation-supporting actions (quitline and NRT) than control participants. For hypothesis 2b, the independent variable is again the randomization group. Each dependent variable will be modeled separately. There are several ways to analyze quitline use, including time to first call completed (time from baseline when the first call with the counselor was conducted in a number of weeks) or whether the participant used the quitline and the number of contacts between the patient and counselor. We chose the time to first call completed with the quitline counselor because it matters how quickly the intervention succeeded in motivating participants to call the quitline (if the call happened in the first few days of the intervention or later). The participant may initiate the call, or the counselor can call the participant following a texting referral.

Power for Hypothesis 2b

Analysis and the power calculation for time to first call completed is similar to the hypothesis 3b analysis. The use of NRT will be assessed via self-report at the 6-month follow-up. To analyze NRT use, a dichotomous variable, we will create a logistic model with the use of NRT (yes or no) as the dependent variable and randomization as the independent variable.

Aim 3: Effectiveness

Hypothesis 3a: Primary Outcome

Adapt2Quit participants will have greater smoking cessation rates (6-month point-prevalence biochemically verified) than control participants. For our primary outcome, we will follow recommendations from the Society for Nicotine and Tobacco Research and other experts. While we will attempt to minimize dropout rates loss to follow-up (missing outcomes) in trials such as ours cannot be fully averted [41]. Penalized imputation (missing=still smoking) is not a conservative approach and can be biased (against a group), especially when there is a differential missing between the groups [41]. Thus, the recommended approach is to use inverse probability weighting [42]. In this approach, the first step is to develop a logistic regression model to predict nonmissingness using variables that are found to be different between study participants with and without missing data. The next step is to calculate the inverse probability of nonmissingness and use it as the weight in a logistic regression model to compare the cessation rate between two study groups [43]. Along with inverse probability weighting, we will present penalized imputation and a complete case analysis (limited to those with complete data) as sensitivity analyses. We propose to biochemically verify participants who self-report quitting smoking using a CO meter.

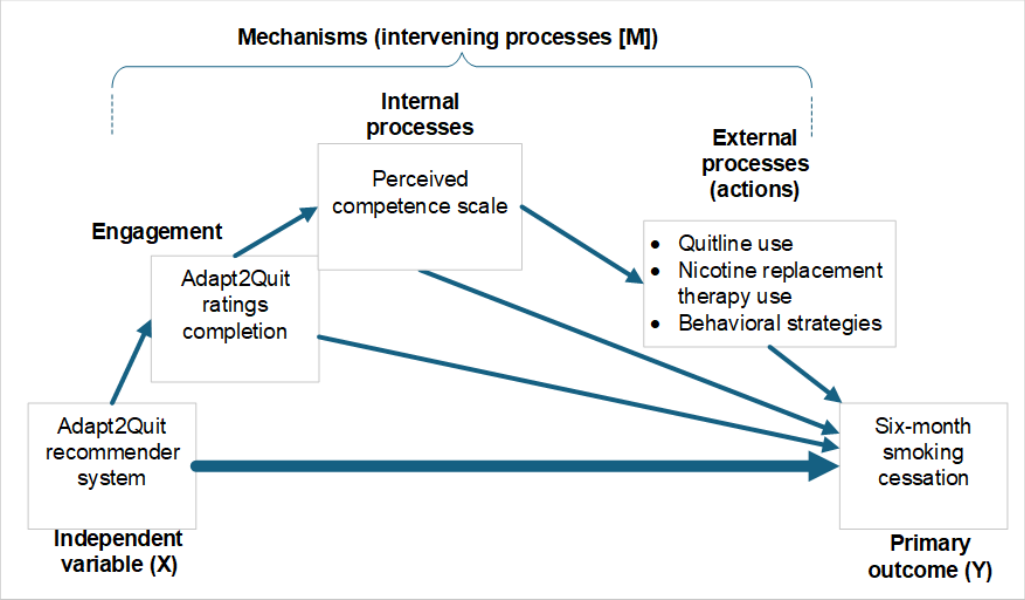
Power for Primary Outcome (Hypothesis 3a)

In our prior National Cancer Institute trial, we observed an absolute 9% difference in the standard messaging versus no-messaging control group [29]. We expect socioeconomically disadvantaged groups to have lower cessation rates than non–socioeconomically disadvantaged groups. Thus, we calculated power using a range of control cessation rates from 7% to 9%. We started at 7%, because it is the estimated rate at which the general population of all individuals who smoke quit without any intervention [34]. On the basis of the recommender enhancements (and further pilot data), we saw an additional marginal difference of 6% at 30 days (even higher for African American individuals who smoke) and expect this difference to continue and expand over time as the recommender system continues to learn and adapt to the individual; however, to be conservative and recognizing the potential difficulty in impacting behavior in this population, we chose to power for a small difference, namely 7%. Although our hypothesis is directional, we have chosen to adopt the commonly used conservative approach of 2-sided tests for all our power calculations. On the basis of a 2-sided chi-square test of equal proportions, α=.05, for all these base rates, we will have 80% power with 600 participants (N=300 per arm). Considering loss to follow-up, we plan to oversample by 25% and thus have budgeted for a total of 750 participants to complete baseline and be randomized. On the basis of our prior experience recruiting from clinical systems, we expect the dropout rate to be lower than the 25% we have assumed in our calculations.

Hypothesis 3b: Mediation Analysis

Measured internal and external processes will mediate the effect of Adapt2Quit on smoking cessation. Adapt2Quit is expected to result in several interconnected processes (Adapt2Quit increases personal relevance, thereby improving system engagement, which results in increasing the external and internal processes, causing the participant to implement cessation-supporting behaviors resulting in smoking cessation; Figure 1). We will explore the pathways using modern mediation and structural equation modeling (SEM) techniques. Mediation occurs when an independent variable (X) leads to a given outcome (Y) through an intervening process (M). In our case, the independent variable is the Adapt2Quit recommender (X), and the outcome will be 6 months of smoking cessation (Y). Perceived competence and adoption of cessation-facilitating behaviors (use of quitlines, use of NRT, and adoption of behavioral strategies) are all potential mediators (M). The mediation analyses will focus on each individual process variable, using the classic mediation principles modified from Barron and Kenny [44]. This approach requires 3 regression models and decomposes the total effect (*c*) of the independent variable (X) into a direct component (*c'*) and an indirect or mediated component (c-c'). Limitations to the modified Barron and Kenny approach include the fact that more complex mediation pathways with multiple steps are not allowed. Thus, we will implement SEM using Mplus as the covariance analysis software. SEM allows for the simultaneous estimation of multiple regression equations representing complex mediation pathways, allowing errors to be correlated across equations. Furthermore, constructs may be represented as latent variables to relax the assumption of no measurement error. An array of diagnostic tests (eg, root mean square error of approximation and comparative fit index) are available to examine model quality.

Figure 1. Hypothesized path model depicting associations among constructs. NRT: nicotine replacement therapy.



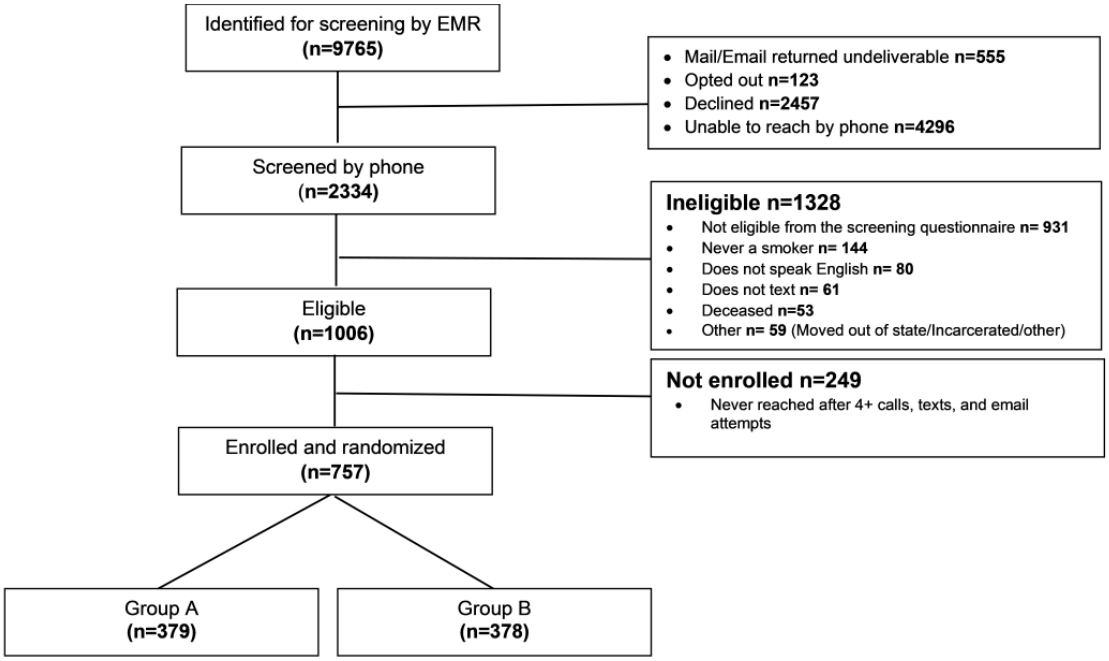
Qualitative Interview Analysis

We will transcribe the interviews verbatim and will use the rapid qualitative analysis method to code the transcripts. The rapid qualitative method uses triangulation and iterative data analysis to quickly develop a preliminary understanding of a situation from the insider's perspective [45-47]. In this method, primary topics or "domains" will be taken from the topics addressed in the interview guide to create summary templates. Two research team members will each code at least 10% of the interview transcripts, and coding checks will be completed to ensure interrater reliability. We will use the summary templates to create a matrix to analyze each domain's depth and breadth of data. From these, we will identify study themes and subthemes using the matrix. The research team will collaboratively and iteratively review, discuss, and sort the data to refine the initial themes and subthemes and highlight the most salient quotes. Recordings collected during interviews will be deidentified using subject ID numbers. No identifiable information, such as a full name, will be collected in the recording. Identifiers will be collected separately and will be stored in an encrypted form. Recordings will be transcribed and deidentified. They will be stored in a secured UMass Chan drive specified for the study within the UMass Chan IS regulated environment, where only UMass Chan study staff will have access to them. Recordings, and all other data collected in this study, will be retained and destroyed in accordance with Standard Operating Procedure Human Research Protection-800. Transcripts of audio or video recordings as well as the audio or video recordings themselves will be fully destroyed 6 years from the conclusion of the study period or at the request of the individual to whom that data belongs.

Results

This trial was funded in April 2020 and is currently ongoing. As of May 2024, we had enrolled 757 participants, and 591 (78.1%) of them had completed the 6-month follow-up interviews (Figure 2). We anticipate that data analysis and final manuscript preparation will occur in late 2025. Multimedia Appendix 3 provides the demographic and screening survey responses of 757 participants.

Figure 2. CONSORT (Consolidated Standards of Reporting Trials) diagram. EMR: electronic medical record.



Discussion

Principal Findings

This study protocol describes a randomized controlled trial to test a machine learning algorithm–based, computer-tailored health communication system for smoking cessation. We hypothesized that the intervention will impact mechanisms of action—specifically engagement, competence (a theoretical construct), and adoption of cessation-supportive actions—as well as demonstrate effectiveness in promoting smoking cessation. Our system will test these hypotheses among individuals who are socioeconomically disadvantaged, a group disproportionately affected by smoking.

Because of the potential for wide reach and effectiveness, texting programs (especially texting) have been increasingly adopted in real-world settings worldwide (public health and within health care systems) [48-50]. For example, the World Health Organization has helped establish texting programs for smoking cessation in several countries, including Costa Rica, Tunisia, and India [51]. The US Department of Health and Human Services established a Text4Health Task Force in 2010 to promote health text messaging programs in the United States [48]. In 2017, 55% of state quitlines offered texting programs (up from 20% in 2012) [34,52]. There is now growing evidence that these programs can be effective. An evaluation of SmokefreeTXT (a free evidence-based smoking cessation program offered by the US National Cancer Institute) reported that point-prevalence abstinence for smokers who initiated treatment at completion of the 42-day program was 7.2% (3% at the 6-month follow-up) [53]. Leaders have called for continued innovations to increase the effectiveness of these health messaging programs, especially to increase effectiveness with smokers from socioeconomically disadvantaged backgrounds.

Our study will provide important evidence on whether a more personalized approach using machine learning can encourage quitline use and support smoking cessation, compared to a text-based referral to quitline. In previous papers, we described our pilot studies testing the Adapt2Quit intervention [16,35,54]. Furthermore, our prior large randomized controlled trial compared the Adapt2Quit intervention to a system that delivered messages based on participants' baseline readiness to quit [17]. In that trial, we recruited participants online as well as through referrals from friends and family. In addition, messages were delivered by email rather than by text, as is being done in this trial. The previous study also did not include biochemical verification of smoking cessation. Beyond the potential benefit of computer-tailored messaging, our system aims to actively engage participants with the quitline. Quitlines have proven to be effective in supporting people to quit smoking, yet using a quitline and attending counseling sessions is a significant step for individuals from socioeconomically disadvantaged backgrounds who smoke. Currently, only 2% to 3% of people who smoke use the quitline, with usage rates even lower among individuals from socioeconomically disadvantaged backgrounds [34]. Prior research has shown that it is possible to use a low-intensity intervention such as texting to increase motivation and the use of cessation resources among people who smoke [55].

In addition to our system, one group compared a similar recommender system in a pilot trial to a system that selected messages based on a knowledge base. They compared the message appreciation, engagement with the system, and one's own self-reported smoking cessation status (7-day point prevalence) [18]. Another group developed a recommender system for smoking cessation and promoting physical activity [56]. This group described an experiment they conducted to identify the optimal approach for selecting messages. In addition, a systematic review examined the potential of using another machine learning approach—reinforcement

learning—for similar purposes [57]. Together, these approaches highlight the potential of the use of machine learning approaches to enhance a widely used behavioral intervention: computer-tailored health communication.

Because we have completed recruitment for our study, we also provide the characteristics of our participants. Our recruitment method, using an opt-out strategy at 3 different health care systems, was able to successfully recruit a diverse sample. A third of our sample (265/757, 35%) are Black, and 16% (121/757) self-identified as Hispanic or Latino. There may be several factors for our successes, including that our intervention is a low-intensity intervention using a texting model that is widely available. Furthermore, our procedures for screening, baseline, and follow-up are all remote, which may have reduced barriers to recruitment. Participants in our study indicated higher motivation levels than the general population. This is an artifact of our recruitment strategy that people who are more motivated participate in a study about tobacco cessation. This more representative sample implies that our study findings will be more generalizable to the US population.

Strengths and Limitations

We describe the protocol for a rigorous evaluation of behavioral intervention among individuals from socioeconomically disadvantaged backgrounds. Since recruitment for our study is complete, we also present participant characteristics. Using an opt-out recruitment strategy across 3 different health care systems, we successfully recruited a diverse sample, which has been challenging to achieve for clinical trials. Our fully remote procedures for screening, baseline, and follow-up may have reduced barriers to recruitment. Notably, 35% (265/757) of our sample identified as Black and 16% (121/757) as Hispanic or Latino. This more representative sample suggests that our study findings will be more generalizable to the US population. One limitation is that our participants reported higher motivation levels for quitting smoking than the general population, which is likely due to the recruitment strategy attracting those who were more motivated to participate in a tobacco cessation study. Because we only used insurance status to determine socioeconomically disadvantaged, some participants may not align with all characteristics that may describe socioeconomically disadvantaged.

Conclusions and Future Work

Our project is the first to rigorously test the use of a recommender system for smoking cessation among individuals from socioeconomically disadvantaged backgrounds who smoke. In this paper, we have reported on protocols for conducting a rigorous trial. In addition to our primary analyses for the 3 aims, we will conduct exploratory analyses to assess the heterogeneity of treatment effects across these subgroups, which could yield valuable insights for future tobacco cessation efforts. Our follow-up papers will report on the results of our trial following the analysis plans described in this paper. Future studies will also explore implementing texting interventions in various clinical and public health settings.

Acknowledgments

The Adapt2Quit intervention is funded by the National Cancer Institute (grant R01CA240551), starting in April 2020.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Telephone screening script, consent form, baseline survey, and 6-month follow-up survey.
[PDF File (Adobe PDF File), 716 KB - resprot_v14i1e63693_app1.pdf]

Multimedia Appendix 2
Example motivational messages (expert and peer).
[DOCX File , 22 KB - resprot_v14i1e63693_app2.docx]

Multimedia Appendix 3
Participant demographic and screening survey responses (N=757).
[DOCX File , 31 KB - resprot_v14i1e63693_app3.docx]

Multimedia Appendix 4
SPIRIT-AI checklist.
[XLSX File (Microsoft Excel File), 15 KB - resprot_v14i1e63693_app4.xlsx]

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Abbreviations

BPMF: Bayesian probabilistic matrix factorization
CO: carbon monoxide
IRB: institutional review board
NRT: nicotine replacement therapy
PCS: Perceived Competence Scale
REDCap: Research Electronic Data Capture
SDT: self-determination theory
SEM: structural equation modeling
UMass Chan: University of Massachusetts Chan Medical School

Edited by A Schwartz; submitted 01.07.24; peer-reviewed by J Thrasher, N Albers; comments to author 21.08.24; revised version received 26.11.24; accepted 17.03.25; published 16.04.25.

Please cite as:
Kamberi A, Weitz B, Flahive J, Eve J, Najjar R, Liaghat T, Ford D, Lindenauer P, Person S, Houston TK, Gauvey-Kern ME, Lobien J, Sadasivam RS
Testing a Machine Learning–Based Adaptive Motivational System for Socioeconomically Disadvantaged Smokers (Adapt2Quit): Protocol for a Randomized Controlled Trial
JMIR Res Protoc 2025;14:e63693
URL: https://www.researchprotocols.org/2025/1/e63693
doi:10.2196/63693
PMID:

Protocol

Text Message Intervention to Facilitate Secure Storage and Disposal of Prescription Opioids to Prevent Diversion and Misuse: Protocol for a Randomized Controlled Trial

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Abstract

Background: Nonmedical use of prescription opioids remains a critical public health issue; 8.5 million people in the United States misused opioids in 2022. Most people obtain prescription opioids for misuse from family or friends. Thus, facilitating secure storage and disposal of opioid medications during and after treatment is needed to prevent medication diversion and subsequent misuse.

Objective: The primary objective of this study is to test the feasibility and efficacy of a novel intervention that uses a persuasive, informational SMS text message reminder system to enhance the impact of secure storage and disposal of unused opioid medications. We hypothesize that the SMS text message intervention will increase secure storage during treatment and disposal of prescription opioids after treatment.

Methods: We will use a 2-arm randomized controlled trial to test the intervention for feasibility and efficacy. Participants (aged 18+ years who have received an opioid prescription in the past 2 weeks) will be randomly assigned to either receive the SMS text message intervention or standard-of-care educational materials. Participants in the intervention will receive 4 SMS text messages related to secure storage and 3 messages related to disposal. All participants will complete baseline, midpoint (day 25), and postintervention (day 45) evaluation surveys. We will test whether receipt of the intervention is associated with two primary outcomes, which are (1) secure storage of prescription opioid medication (locked vs unlocked) and (2) disposal of unused prescription opioid medication (disposed vs not disposed). We will use multiple logistic regression to test the main hypotheses that the intervention will be positively associated with secure storage (locked vs unlocked) and disposal (yes vs no) behaviors, which will allow us to control for demographic variables known to influence the outcomes. This protocol represents the entire structure of the randomized controlled trial.

Results: Recruitment for the randomized controlled trial was launched in April 2024, and data collection was completed in December 2024. The final sample size is 484. Data analyses for the main hypothesis will be completed by May 2025, and the main hypothesis manuscript will be submitted for publication by May 2025.

Conclusions: Results from this study will indicate whether a text message reminder system can increase secure storage and disposal behaviors for individuals who receive opioid medication. This type of intervention has the potential to be integrated into

currently used health care delivery systems, such as prescription pickup reminders at pharmacies. Thus, the intervention is scalable across systems of care, thus expanding the reach of secure storage and disposal programs to prevent prescription opioid misuse.

Trial Registration: ClinicalTrials.gov NCT05503186; https://clinicaltrials.gov/study/NCT05503186

International Registered Report Identifier (IRRID): DERR1-10.2196/60332

(JMIR Res Protoc 2025;14:e60332) doi:10.2196/60332

KEYWORDS

prescription opioid; storage; disposal; text message intervention; randomized controlled trial; mobile phone

Introduction

Statement of the Problem

Despite efforts in the United States to reduce the number of opioid prescriptions through prescribing guidelines [1,2] and drug monitoring programs [3,4], mortality rates due to the nonmedical use of prescription opioids have remained high since their peak in 2010 [5]. National data estimates that 6.1 million people met the criteria for opioid use disorder and 8.5 million (3%) misused prescription opioids in 2022 [6]. The majority of people obtain prescription opioids for misuse from family or friends, with or without their knowledge [6]. Furthermore, many opioid medications go unused; a meta-analysis of postoperative opioid consumption for acute pain by US adults found that 61% of medications [7] remain after treatment. Unused prescriptions can lead to medication diversion, which is the primary source of prescription opioids for misuse [6]. Facilitating secure storage and disposal of opioid medication during and after treatment is needed to prevent medication diversion.

In an early response to the opioid crisis, the Office of the National Drug Control Policy disseminated a plan that included secure storage and disposal of unused opioid medications as key strategies for prevention [8]. This plan specified the need to educate patients on the proper storage and disposal of prescription medications. The Centers for Disease Control and Prevention recommends that medication is stored out of reach of children and pets and opioid medications should be stored in a locked cabinet or drawer [9]. The US Food and Drug Administration (FDA) endorses multiple methods to dispose of unused prescription opioids when they are no longer needed, including medication take-back days, disposal boxes, mail-back programs, and deactivation kits [10,11]. Currently, the FDA also recommends flushing certain types of medications in the toilet or putting them in the trash if other options are not available [12]. The guidance on flushing unused medications is in contradiction to that provided by the US Environmental Protection Agency [13].

Despite the release of the Office of the National Drug Control Policy plan over a decade ago and guidance on secure storage and disposal from federal agencies [9,10,12,13], evidence suggests uptake of the simple behavior of secure storage and disposal is limited. For example, in a study of a nationally representative panel of 1032 adults who had been prescribed an opioid medication, only 8.6% (n=89) stored their medication in a locked location [14]. Similarly, in a study of 113 patients prescribed opioids for cancer pain, only 15% (n=17) locked their opioids while 36% (n=41) stored opioids in plain sight; however, 73% (n=82) indicated a willingness to store their medications in a locked location [15]. Across multiple studies of individuals prescribed opioids for chronic and acute pain, less than a third reported disposal of unused opioid medications [16-19]. Hence, there is significant room for improvement in opioid medication storage and disposal practices.

There is emerging evidence that a more targeted intervention at medical facilities may enhance the secure storage and disposal of unused opioid medications. Several studies have examined the provision of an educational pamphlet to patients who receive an opioid prescription for acute pain [20-23]. In general, the educational pamphlets contained brief information about nonmedical prescription opioid use and instructions for secure storage and disposal. All studies found statistically significant intervention effects on self-reported storage and disposal of unused prescription opioids [20-23]. That is, a targeted intervention to facilitate secure storage and disposal by patients receiving an opioid prescription improved the uptake of these preventive behaviors. However, the rates of utilization of these practices remained low. Across these studies, secure storage did not improve and 48% (45/86) to 78% (37/170) of patients who received an educational pamphlet still did not dispose of their unused opioid medications, which indicates that additional intervention is warranted.

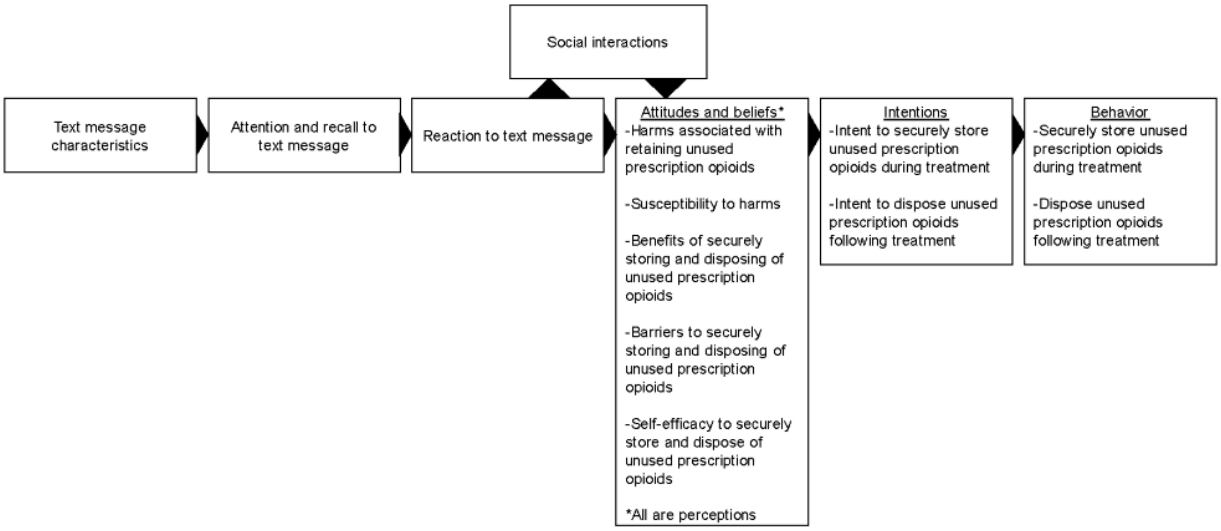
The high prevalence of opioid prescriptions that are not fully used demands an intervention that can scale widely. The widespread adoption and instantaneous nature of mobile phones make them a promising vehicle for economical and systems-based interventions. Almost all (1442/1502, 96%) of US adults have a mobile phone with SMS capabilities [24], indicating that text interventions have the potential to serve as a universal intervention delivery method. Digital health systems have already been implemented in pharmacies. Many pharmacies have established systems that alert patients via text message when medications are ready to be picked up. Patients report that they prefer to receive health information from medical practices via SMS text messages over other forms of communication [25]. Half of pharmacy patrons already use existing pharmacy-based text reminders and smartphone apps [25]. Thus, delivering reminders about the secure storage and disposal of prescription opioids via SMS text messages represents a scalable intervention across systems of care.

Theoretical Frameworks

The study is informed by 2 theoretical frameworks (Figure 1). First, the Message Impact Framework [26] suggests that message characteristics affect the extent to which the message will be

noticed and later recalled. An individual's reaction to the message impacts their knowledge, attitudes, and risk beliefs, which in turn impact intentions and actual behavior. Furthermore, exposure to messages can elicit interpersonal communication and social interactions which further spread and influence individuals' attitudes, beliefs, and reactions to the messages. Second, the Health Belief Model (HBM) [27] posits that messages will generate behavior change if they target perceived barriers, benefits, threats, and self-efficacy specific to the behavior. Specifically, attitudes and beliefs pertaining to perceived seriousness and susceptibility to harms result in the formation of a perceived threat. Along with perceived threats, beliefs about the benefits of and barriers to performing a behavior paired with self-efficacy to do so influence whether an individual will perform the behavior. A cue to action, such as an SMS intervention, serves as a trigger or motivator to perform the behavior, such as securely storing and disposing of prescription opioid medications.

Figure 1. Conceptual framework.



Objective

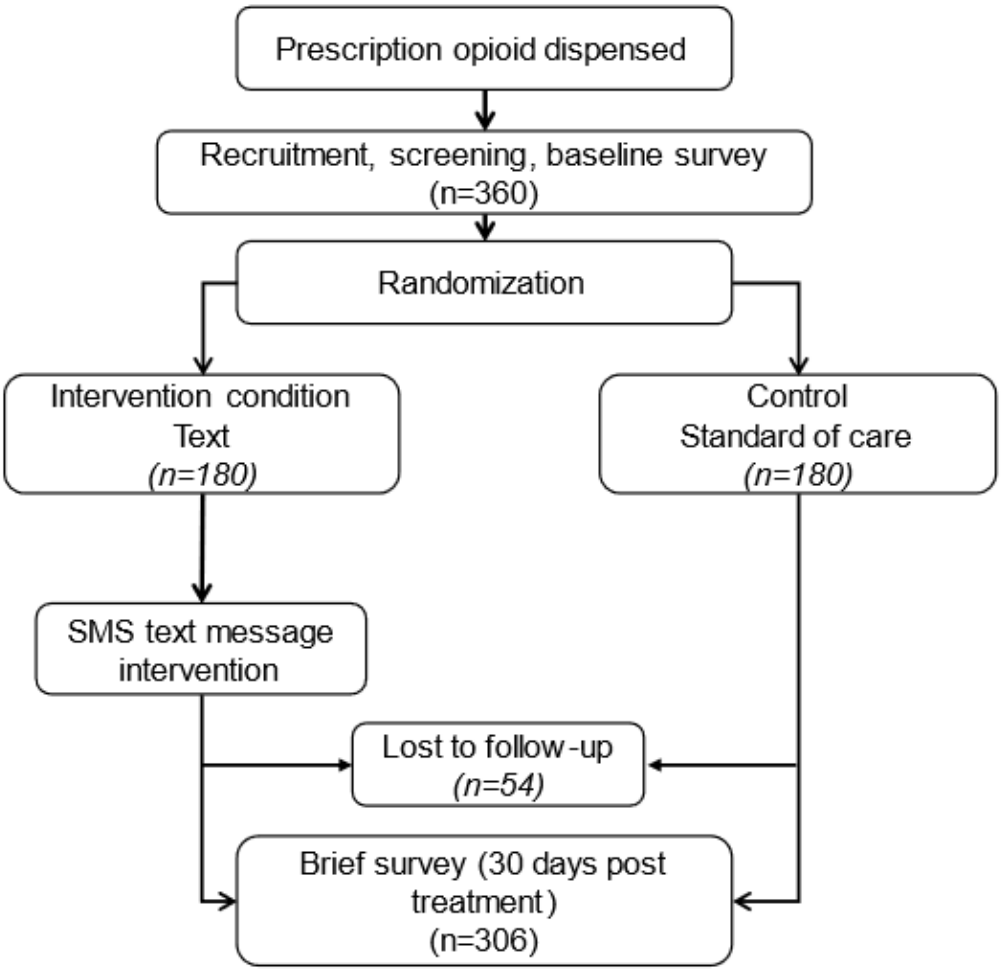
The overall objective of the study is to test the feasibility and efficacy of a novel, evidence-informed strategy that uses a persuasive, informational SMS text message reminder system to expand the impact of secure storage and disposal programs. Our central hypothesis is that the implementation of an SMS text message intervention will increase the secure storage of opioid analgesics during treatment and disposal following treatment.

Methods

Overview

This study uses a 2-arm, single-blinded, randomized controlled trial (RCT) design (Figure 2). Participants are randomly assigned into either the SMS text message intervention condition or a standard-of-care control group. Participants will complete baseline, midpoint (day 25), and postintervention (day 45) evaluation surveys, described further in this study. The primary trial site is Wake Forest University School of Medicine.

Figure 2. Planned randomized controlled trial study design.



Ethical Considerations

This protocol has been approved by the Wake Forest University School of Medicine Institutional Review Board (IRB; IRB00102139).

The consent form will be self-administered on REDCap (Research Electronic Data Capture; Vanderbilt University). Potential participants will review the consent without the assistance of a study team member and will be directed to the study team if they have any questions. In lieu of a signature, participants will be informed that they should "click 'I agree to participate' at the end of the consent form" to provide their authorization to participate in the study. The consent form will use language approved by the Wake Forest University School of Medicine IRB that is designed for readability and includes the general topic of the study, the name of the principal investigator, the principal investigator's contact information, the IRB approval number, and the phone number of the IRB at Wake Forest University School of Medicine. Participants will be reminded that they are not required to answer questions (other than for eligibility), that they can end participation at any time, and that there is no obligation to participate. Given that participants for the RCT may be patients at a participating institution, they will be reminded during the consent process that participation will not impact their treatment or future access to medications.

To recruit participants, we will maintain a spreadsheet that has identifiable information of individuals who have met the study criteria stored electronically on a secured device and IRB-approved cloud system. The purpose of this spreadsheet is to ensure that potential participants are not invited to participate more than once. After ascertaining consent to participate, unique identifiers will be assigned to participants, and identifiers will be stored separately from the data. To minimize the likelihood of a breach in confidentiality, data will be collected and stored in REDCap, a secure web application for building and managing online surveys, and on a secure and encrypted storage system maintained by Wake Forest University School of Medicine IT security.

All participants in the RCT will be provided with incentives following completion of the baseline survey, midpoint survey, and postintervention surveys, in the form of an electronic US $25 Amazon gift card per survey. Participants will be asked if they are willing to upload a photo of their prescription opioid bottle or box for an additional US $5 Amazon gift card. The maximum amount of money that a participant may receive for participation in this study is US $80. Electronic gift cards will be provided via SMS text message to study participants.

Participants

Eligibility

Individuals are eligible to participate if they are 18 years of age or older, able to read and speak English, own a cell phone with the capability of receiving SMS text messages, within 14 days of being dispensed a prescribed opioid medication, and have an opioid prescription that is for 30 days or less.

Sample Size

We plan to enroll 360 participants (n=180 per condition) based on assumptions from an RCT using a text intervention that encouraged parents to vaccinate their adolescent child [28] and an RCT that assessed the delivery of a deactivation product with educational material by medical staff on self-reported disposal of unused opioids [29]. Power calculations based on proportions of vaccine completion for the group exposed to the SMS text message intervention (0.49) and the unexposed group (0.30) [28] indicate a total of 230 participants will be needed to detect a difference in the impact of an SMS text message intervention. Power calculations based on the proportions of disposal for the group who received the deactivation product intervention (0.72) and the unexposed group (0.56) [29] indicate a total of 306 participants will be needed to detect a difference in the disposal of unused opioid medications. We based our sample size on the more conservative estimates [29]. To account for a 15% (12/79) loss to follow-up [21], we plan to recruit an additional 54 participants for a total of 360 participants.

Recruitment

We will use a multimethod approach to recruit participants for the RCT. Potential participants will be identified through the Advocate Health electronic health records. Biweekly, we will receive medical record numbers of Advocate Health patients who were recently prescribed an opioid medication. These individuals will be sent an SMS text message via their Advocate Health MyChart inviting them to participate in the RCT. We will also post flyers in local pharmacies with study information. Participants will be directed to a self-administered consent form programmed in REDCap. If the participant consents to participate, they will complete the self-directed web-based eligibility screener.

Screening and Randomization

If the individual is eligible to participate in the RCT, they will transition immediately from the eligibility screening questions to the baseline survey questions. Following completion of the baseline survey, a study team member will be notified so they can randomize the new participant to study condition. Randomization will occur within REDCap using simple randomization procedures to randomly assign participants to the intervention or control conditions. Randomization will be stratified by biological sex of the participant. An external module has been integrated into REDCap to confirm that each new participant is unique based on their phone number and email address.

Intervention

Procedures (Intervention Condition)

Participants in the intervention group will receive a series of SMS text messages to securely store prescription opioids during treatment and dispose of unused prescription opioids. Twilio will be used to deliver text messages to participants. Twilio is a third-party web service that integrates with REDCap, allowing users to send survey invitations and alerts or notifications to participants as SMS text messages or voice calls. It acts as a conduit between participants' mobile devices and the REDCap project. The intervention will last for 45 days and will start immediately following the completion of the baseline survey. All participants randomized to the intervention study condition will receive 7 identical SMS text messages over the course of the intervention. Participants will receive 4 SMS text messages about storing their medications before the midpoint survey which will take place on day 25 of the research study. SMS text messages about the disposal of unused medications will begin after day 31 of the intervention to ensure that all participants would have completed their treatment regimen. Participants will receive 3 SMS text messages about disposing of their unused medications before the postintervention survey, which will take place on day 45 of the research study. Participants will receive 1-2 SMS text messages about storing and disposing of their unused medications per week, reflecting participant feedback from the first phase of this study, which focused on the development of the SMS text message content (Textbox 1) [29]. The order in which all SMS text messages are delivered will be randomized. The recommendations for storing medications have been endorsed by the Centers for Disease Control and Prevention [9], and recommendations for disposal are currently endorsed by the FDA [10].

Textbox 1. Participant-derived SMS text messages.

Storage messages

- It is your prescription, not theirs. Keep your medication hidden and out of reach.
- Locking up your prescription pain pills could save a life. Keep them in a locked location such as a cabinet or box.
- Your favorite hiding spot could save a life. Keep your pain pills where someone would not look for them.
- Your prescription can become someone else's addiction. Lock up your pain pills.

Disposal messages

- Dispose of your unused medications. You may save the life of someone you love. Dispose in a way that works best for you: Return them to the pharmacy, use a home disposal kit, or mix pills with an undesirable substance and put in your trash.
- Discarding your unused pain pills could save a life. Dispose in a way that works best for you: Return them to the pharmacy, use a home disposal kit, or mix pills with an undesirable substance and put in your trash.
- Your prescription can become someone else's addiction. Safely discard unused or expired medications. Dispose in a way that works best for you: Return them to the pharmacy, use a home disposal kit, or mix pills with an undesirable substance and put in your trash.

Control Condition

Individuals who are assigned to the study control condition will receive the standard of care provided to them from their prescribing physician and dispensing pharmacist. Immediately after completing the postintervention survey, participants will receive information on ways to securely store and dispose of unused opioid medication. This information will be provided in the REDCap survey.

Data Collection and Measures

Evaluation

Participants will complete 3 evaluation surveys. Each evaluation will be delivered via a secure link to a web-based REDCap survey. The baseline survey will be completed directly following study enrollment. A midpoint survey will be sent 25 days after study enrollment, and a final postintervention survey will be delivered 45 days after study enrollment. The baseline survey assesses sociodemographic characteristics, information about the prescribed opioid medication, and past medication storage and disposal behaviors. The midpoint and postintervention surveys ask about how the participant has been storing their opioid medication, if they are still using their opioid medication, if they have disposed of their medication, and their intent to dispose of their medication. Participants assigned to the intervention study condition will provide feedback on the SMS text message intervention in the postintervention survey. Those who were assigned to the control study condition will share what they would like to receive in an SMS text message intervention. All surveys will also query perceptions in alignment with the HBM (eg, perceived barriers, and benefits) [27] about securely storing and disposing of their opioid medications.

Primary Outcomes

We will use 2 primary outcomes based on data from the postintervention survey. Pertaining to storage of opioid medications, participants will be asked, "Where do you usually store your prescribed pain medication?" with response options of (1) in an unlocked box, closet, cabinet, or drawer; (2) in a locked box, closet, cabinet, or drawer; (3) in a purse, backpack, or other carrier; (4) out in the open; (5) other; or (6) unsure where kept. We will create a binary variable for storage of locked (in a locked box, closet, cabinet, or drawer) versus unlocked (all other responses) to test study hypotheses. Related to disposal behaviors, for participants that indicate they had no leftover medications, we will create a binary variable based on the disposal method of the medication (put in the trash, used deactivation product, used a prepaid mail-back envelope, flushed in the toilet, returned them to the pharmacy, or took them to law enforcement agency) versus not disposed (gave them to friend or family member or something else).

Secondary Outcome

For participants who indicate they have medication from their prescription leftover, we will create an intention to dispose variable based on the item "What do you intend to do with your remaining prescription pain medicine?" The binary variable will denote intent to dispose (put them in the trash, use deactivation product, use prepaid mail-back envelope, flush in the toilet, return to pharmacy, or take to law enforcement agency) versus do not intend to dispose (keep them, gave them to friend or family member, or something else).

Other Measures

At the baseline and postintervention time points, we will assess measures derived from the HBM including self-efficacy (eg, I know how to properly dispose my prescription medication), barriers (eg, I do not have access to a locked location where I can securely store my prescription pain medication), benefits (eg, disposing my unused prescription pain medications can stop someone else from taking them), perceived severity (eg, I think there are risks to having prescription pain medication in my home), and perceived susceptibility (eg, I worry about having prescription pain medication in my home). At the midpoint and postintervention time points, we will also assess the SMS text messages themselves using items derived from the Message Impact Framework, including whether the participant felt the SMS text messages grabbed their attention, were easy to understand, and made them think about the risks of having prescription pain medicines in their homes.

Data Management

Before ascertaining consent to participate, we will maintain a spreadsheet stored electronically on a secured device and IRB-approved cloud system that has the name, phone number, and email address of individuals identified via Advocate Health electronic health records who have met study eligibility criteria. This spreadsheet will include the date we contacted the individual and the way in which we contacted them. The purpose of this spreadsheet is to ensure that an individual is not invited to participate more times than approved by the IRB. This spreadsheet will also have a unique identifier, which will be linked to data pertaining to their prescription number, medication list (ie, opioid prescription only), age, gender, and race or ethnicity. We will retain this information for use in the event that they consent to participate in the study. The spreadsheet will be destroyed once recruitment has closed. To minimize the likelihood of a breach in confidentiality, data will be collected and stored in REDCap, a secure web app for building and managing web-based surveys, and on a secure and encrypted storage system maintained by Wake Forest University School of Medicine IT security. Public access to deidentified data will be made public at the conclusion of the study.

Data Analysis

Design and Data Preparation

Analyses will be conducted to assess group differences on the two primary dichotomous outcomes, which are (1) secure storage of the opioid medication (locked vs unlocked) and (2) disposal of unused medication (disposed vs did not dispose). We will use a modified intention-to-treat (ITT) design. While an ITT design minimizes bias and type 1 error, it is often considered a conservative approach that may increase type 2 error [30]. A modified ITT design allows for the exclusion of some randomized subjects in a justified way to achieve the goal of minimizing both type 1 and 2 errors [30]. For this study, we will retain the ITT approach by including all participants regardless of their compliance with the SMS text message intervention. We will modify the ITT approach by excluding participants who do not have outcome data since we will not have a mechanism to assess their storage or disposal behaviors, which could inflate type 2 error if retained in analyses. We will first test for group equivalence in demographic and household characteristics of the participant, diagnosis and treatment, and information about the prescribed opioid (eg, type, number of pills, and duration of treatment). Group differences are not expected in the context of randomization; however, if one of these variables is associated with both a condition and an outcome variable, we will include it as a covariate in subsequent analyses using that outcome. Data will be compiled and screened for integrity, outliers, missing values, and violations of the assumptions of logistic regression. Missing values will be handled in regression analyses using full maximum likelihood estimation.

Statistical Analyses

We will use multiple logistic regression to test the main hypotheses that the intervention will be positively associated with secure storage (locked vs unlocked) and disposal (yes vs no) behaviors, which will allow us to control for demographic variables known to influence the outcomes. We will use a 2-step logistic regression to predict each outcome. In step 1, demographic variables will be entered into the model. We will retain variables significantly associated with the outcome at a significance threshold of $\alpha<.05$. In step 2, the intervention condition will be entered into the model.

Results

Recruitment for the RCT was launched in April 2024, and the first participant enrolled in the study in June 2024. The primary completion date, defined as the date on which the last participant in a clinical study completed the postintervention survey, was in December 2024. The final sample size is 484. Data analyses for the main hypothesis will be completed by May 2025, and the main hypothesis manuscript will be submitted for publication by May 2025.

Discussion

Contributions to the Literature

The overall objective of the study is to test the feasibility of a novel, evidence-informed strategy that uses a persuasive, informational SMS text message reminder system to expand the impact of secure storage and disposal programs. Our central hypothesis is that the implementation of an SMS text message intervention will increase the secure storage of opioid medication during treatment and disposal following treatment. The intervention will be tested with a 2-arm, single-blinded, RCT design. Participants in the intervention group will receive a series of 7 SMS text messages about securely storing prescription opioids during treatment and disposing of unused prescription opioids. The SMS text messages have been developed and refined by end users of the intervention [31].

The status quo is to encourage secure storage and disposal of unused prescription opioids with the implementation of disposal programs [28,29], community-wide awareness campaigns [32], educational pamphlets [20,21], and drug deactivation products [29,33] delivered by medical providers. Current research indicates the need for improved interventions that effectively facilitate secure storage and disposal of unused prescription opioids. Our study adopts an evidence-based intervention strategy, SMS text messages on mobile phones, for a novel purpose—facilitation of secure storage and disposal of prescription opioids. We use a theoretically driven and user-derived messaging delivered in an SMS text message intervention during a critical window of need following receipt of a prescription opioid medication. The findings from the proposed study have the potential to be scalable across multiple systems of care and expand new horizons for medical systems to use existing digital technologies to improve patient care.

Limitations

Several limitations may impact this study. Individuals will be eligible to participate within 14 days of receiving their opioid medications. Thus, individuals with shorter prescriptions may receive SMS text messages about secure storage after they have completed treatment and receive SMS text messages about

disposal after they have already disposed of their unused medication. We will only recruit individuals who have an opioid prescription for 30 days or less, so findings may not be generalizable to patients who have more than a 30-day prescription. We will not be able to control exposure to external messaging about storing or disposing of opioid medications, but we will be assessing self-reported exposure to messaging. While we will be able to track the delivery of all SMS text messages, we cannot assess if they are received or read by the study participants. A systematic, 2-phase approach was used to refine the text messages for the SMS text message intervention using both focus groups and a Qualtrics (Silver Lake) panel [31]. It is possible, but unlikely, that the SMS text messages will not resonate with or be well received by the participants in the RCT. The RCT is being conducted during an election cycle. Participants may be getting more SMS text messages than usual during this period, which may detract from their attention to the study text messages.

Conclusion

Upon successful completion of the study, we will have developed and pretested a systems-level, scalable intervention using mobile technology for the secure storage and disposal of unused prescription opioids, which could be implemented in pharmacies and other medical systems. This contribution is expected to be significant in that facilitating secure storage and disposal of unused prescription opioids should reduce the accumulation of these medications that would otherwise be accessible for nonmedical use. Due to the decreased availability of unused prescription opioids, we would expect to see a decline in the prevalence of nonmedical prescription opioid use and associated consequences. Without the identification of strategies that effectively and universally facilitate secure storage and disposal of unused opioid medications, opioid medications with misuse potential will remain in communities, increasing the likelihood for nonmedical prescription opioid-related morbidity and mortality.

Acknowledgments

Research reported in this publication was supported by the National Institute on Drug Abuse of the National Institutes of Health under award R34DA051710. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health. The authors gratefully acknowledge the use of the services and facilities of the Wake Forest Clinical and Translational Science Institute (CTSI), funded by the National Center for Advancing Translational Sciences (NCATS), National Institutes of Health, through Grant Award UM1TR004929.

Data Availability

Deidentified data collected during this study are available from the corresponding author upon reasonable request.

Authors' Contributions

KLE contributed to conceptualization, methodology, investigation, resources, writing – original draft, writing – review and editing, supervision, project administration, and funding acquisition. MJC contributed to conceptualization, methodology, investigation, writing – original draft, writing – review and editing, and funding acquisition. DWH contributed to conceptualization, methodology, investigation, writing – review and editing, and funding acquisition. JTJ contributed to conceptualization, methodology, investigation, resources, writing – review and editing, and funding acquisition. ARR contributed to conceptualization, methodology, investigation, writing – review and editing, and funding acquisition.

Conflicts of Interest

None declared.

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Abbreviations

FDA: US Food and Drug Administration
HBM: Health Belief Model
IRB: institutional review board
ITT: intent-to-treat
RCT: randomized controlled trial
REDCap: Research Electronic Data Capture

Edited by T Leung; submitted 07.05.24; peer-reviewed by A Gholamrezaei; comments to author 18.07.24; revised version received 08.08.24; accepted 01.10.24; published 17.04.25.

Please cite as:
Egan KL, Cox MJ, Helme DW, Jackson JT, Richman AR
Text Message Intervention to Facilitate Secure Storage and Disposal of Prescription Opioids to Prevent Diversion and Misuse: Protocol for a Randomized Controlled Trial
JMIR Res Protoc 2025;14:e60332
URL: https://www.researchprotocols.org/2025/1/e60332
doi:10.2196/60332
PMID:

Protocol

Evaluating the Effectiveness of a Multimodal Psychotherapy Training Program for Medical Students in China: Protocol for a Randomized Controlled Trial

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Related Article:

This is a corrected version. See correction statement: https://www.researchprotocols.org/2025/1/e71220

Abstract

Background: Psychotherapy is central to the treatment of mental disorders, highlighting the importance of medical students and residents developing competencies in this area. Chinese medical residents have expressed a strong need for psychotherapy training, yet they are generally dissatisfied with the current offerings. This paper presents the protocol for an evidence-based, well-structured psychotherapy teaching program aimed at medical students and residents.

Objective: This study involves a randomized controlled trial of a 2-day multimodal intensive educational intervention designed to evaluate the effectiveness of a new psychotherapy teaching program for medical students and residents in China. The primary outcomes include participants' knowledge and utilization of psychotherapy, training program acceptability, self-reported self-efficacy, and motivation to apply psychotherapy.

Methods: This 2-arm randomized controlled trial was conducted at Sir Run Run Shaw Hospital. The study aimed to recruit approximately 160 medical students and residents, with about 80 participants in the intervention group and 80 in the control group. Both groups completed a baseline survey before participation, reporting their psychotherapy knowledge, utilization of psychotherapy, self-efficacy, and self-motivation. The intervention group received a 2-day multimodal intensive educational intervention (supervision-based online teaching), while the waitlist control group did not receive any intervention during this period. Both groups were followed up for 8 weeks, completing the same survey administered at baseline. At the end of the study, the control group received the intervention. The primary outcome measure was the change in trainees' psychotherapy knowledge before and after the intervention training. Secondary outcome measures included changes in the trainees' utilization of psychotherapy, self-reported self-efficacy, and self-reported motivation for psychotherapy. Additionally, training program acceptability was assessed. Analysis of covariance was used to analyze the primary outcomes. Pearson correlations and regression analysis explored factors associated with the knowledge score at baseline. The secondary outcomes, including participants' psychotherapy utilization, confidence, and motivation, were analyzed using the same methods as for knowledge. All tests were 2-tailed, with a significance level set at $P<.05$.

Results: A total of 160 participants were recruited and randomized between January 4 and 12, 2024. Baseline assessments were conducted from January 28 to February 1, 2024. The psychotherapy training program for the intervention group took place on February 3 and 4, 2024. Posttraining assessments were conducted starting April 1, 2024. Due to withdrawals, incomplete surveys,

and data loss, we had a total of 113 participants: 57 in the intervention group and 56 in the control group. The amount of data varied across measures. The data analysis was finished in August 2024.

Conclusions: This study aims to evaluate the effectiveness of the multimodal psychotherapy training program for medical students in China. If this brief, cognitive behavioral therapy–based psychotherapy skill training proves effective, the potential mental health impact of its nationwide expansion could be significant.

Trial Registration: ClinicalTrials.gov NCT06258460; https://clinicaltrials.gov/ct2/show/NCT06258460

International Registered Report Identifier (IRRID): DERR1-10.2196/58037

(JMIR Res Protoc 2025;14:e58037) doi:10.2196/58037

KEYWORDS

multimodal teaching; psychotherapy training; Chinese medical students; randomized controlled trial

Introduction

Background

The delivery of psychosocial and psychotherapeutic interventions remains central to the treatment of many patients with psychiatric disorders (eg, obsessive-compulsive disorder, panic disorder, major depression, eating disorders, and addictive behaviors) and psychosomatic disorders (eg, hypertension, bronchial asthma, and rheumatoid arthritis) [1,2]. Cuijpers et al [3] conducted a large-scale network meta-analysis to examine the effects of various types of psychotherapies for adult depression, including cognitive behavioral therapy (CBT), interpersonal therapy, psychodynamic therapy, problem-solving therapy, behavioral activation, life-review therapy, and "third-wave" therapies, as well as nondirective supportive counseling. They found that all types of these therapies were more effective than care-as-usual and waiting list control conditions and that most therapies were more efficacious than placebo. Additionally, most therapies maintained significant effects at the 12-month follow-up compared with care-as-usual. A strong evidence base indicated that several psychotherapy modalities were effective for most mental disorders, whether used alone or in combination, primarily including behavior therapy, CBT, and interpersonal psychotherapy [4,5]. According to a systematic review and meta-analysis, the emotional change processes and mechanisms of psychotherapy were most strongly associated with specific CBT methods, such as fear habituation, emotion regulation and experience, and the habitual reorganization of maladaptive emotional perceptions [6]. Today, CBT is recommended as a first-line intervention for both the acute treatment and relapse prevention of various mental illnesses, including major depressive disorder, and most patients prefer psychological treatment over pharmacologic options [5]. Therefore, medical students in clinical rotations and residents working in psychiatric and psychosomatic departments should be required to develop competencies in psychotherapy, particularly in CBT [7]. However, there remains a significant treatment gap for mental disorders in China [8]. Despite the high prevalence of mental disorders in the country, medical professionals in psychiatric or mental health departments often have a comparatively low capacity to provide adequate care and lack qualified training in psychotherapy. Learning basic psychotherapy skills would benefit medical students, residents, and other health care providers (HCPs), including doctors and nurses, across all departments. These skills can be applied in clinical practice to enhance doctor-patient relationships [9]. A study conducted in Beijing found that after participating in a 2-year psychotherapy training program, medical doctors reported improvements in diagnosing and treating mental illness, as well as in doctor-patient communication and the development of strong doctor-patient relationships. Patients also demonstrated significant improvements in levels of depression and anxiety, the severity of physical symptoms, quality of life, and the patient-rated therapeutic relationship [9]. Therefore, psychotherapy training for medical students, residents, and other HCPs requires greater emphasis.

A narrative review indicated that medical residents in psychiatry have a strong need for psychotherapy training to enhance their competence, yet they generally express dissatisfaction with the current training programs [10]. Therefore, providing evidence-based and well-designed psychotherapy training programs is essential for equipping medical students and residents with a foundational understanding of psychotherapy and the necessary skills for clinical practice [11]. Compared with traditional methods, psychotherapy teaching that emphasizes skill practice and role experience is more popular and effective. For instance, a single-day simulation training program has proven effective in psychiatry for medical students, enhancing their knowledge, communication and interview skills with patients, and confidence in treatment [12]. Despite the critical importance of learning psychotherapy skills during medical school and residency, there is a notable lack of formal evaluation of psychotherapy teaching methods and their efficacy. Given the lack of access to psychotherapy, medical and psychological educators, along with program directors, should design high-quality curricula to teach medical students, residents, and other HCPs the essential knowledge and skills in psychotherapy. These curricula should be evaluated through well-conducted, methodologically robust randomized controlled trials (RCTs) [13].

Aim and Hypotheses

To evaluate the effectiveness of the multimodal psychotherapy training program for medical students in China, well-designed RCTs of psychotherapy teaching programs are urgently needed. The primary aim of this proposed project is to assess the effectiveness of a new multimodal psychotherapy teaching program for medical students and residents in China, which is designed to enhance their psychotherapeutic skills and improve their performance in entry-level clinical settings. The primary

hypothesis was that, compared with a control intervention, the intervention group receiving the psychotherapy teaching program would acquire significantly more knowledge about psychotherapy after training. We also hypothesized that the program would lead to an increase in the utilization of psychotherapy and be associated with improved knowledge in this area. The third hypothesis posited that trainees' self-reported self-efficacy and motivation to apply psychotherapy in clinical practice would increase significantly.

Methods

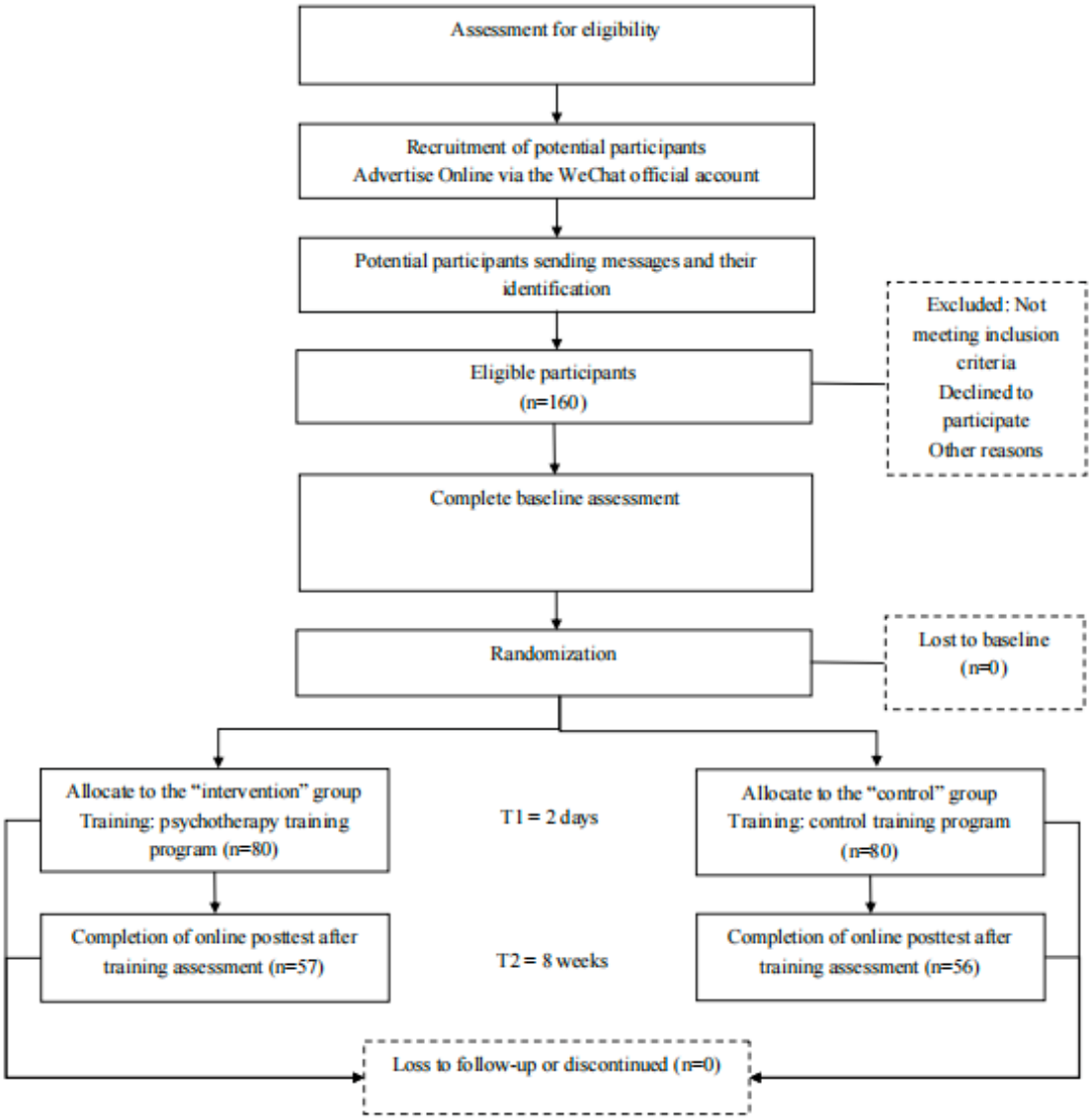
Patient and Public Involvement

Neither participants nor the public were involved in the trial's design, recruitment, or conduct of this study.

Study Design and Participants

This study was an RCT of a 2-day multimodal intensive educational intervention aimed at enhancing the clinical skills in psychotherapy of Chinese medical students and residents. The trial included a waitlist control group, with 8 weeks of follow-up for all participants. A detailed schedule of the study procedures is summarized in Figure 1.

Figure 1. Flowchart study design.



Study participants (n=160) primarily included medical students, residents, and a few other HCPs, such as doctors and nurses, in China. There were no specific restrictions for participants, although most were from Zhejiang University School of Medicine. An overview of participant eligibility criteria is provided in Textbox 1.

Textbox 1. Study inclusion criteria (participants who did not qualify for the criteria were not recruited to participate in this study).

- Medical students, residents, and other health care providers
- Aged 18 years or older
- Expressing an interest in psychotherapy
- Willing to receive randomization
- Willing to provide informed consent to participate in the study

Sample Size and Power Calculation

The sample size was calculated based on the primary outcome using G*Power [14] (version 3; Universität Düsseldorf). As the data were continuous variables and analysis of covariance (ANCOVA) would be used to compare differences between the 2 groups, an a priori analysis selecting ANCOVA as the statistical test was conducted to determine the required sample size. As only a few studies have examined the effectiveness of psychotherapy training for medical students, we were unable to reference effect size or other data as criteria. Therefore, a medium effect size for the primary outcome was estimated preliminarily. It was determined that 128 participants (64 in each group) would be required to achieve 80% power (effect size f=0.25; 1 – β=0.80; α=.05). To account for potential attrition, we aimed to recruit approximately 160 participants (80 in each group), ensuring that the proposed analysis would be sufficiently powered even if 25% of participants in each group were lost to attrition.

Randomization and Group Allocation

This study aimed to recruit approximately 160 participants, with about 80 in each group. The study coordinator randomized participants into the intervention and control groups using a random number generator in R software, maintaining a 1:1 ratio for allocation to the experimental and control conditions. Participants in the intervention group first received the experimental condition, which included the psychotherapy training program after the baseline assessment. The waitlist control group received the control condition, meaning they participated in the psychotherapy training program only at the end of the study. The timeline of the study was as follows: all participants underwent a baseline assessment, the intervention group received the training program, and the control group received a control training program. After 8 weeks, all participants were followed up, and finally, the control group received the intervention training program (Figure 1).

Recruitment

The researchers advertised the program online through the WeChat (Tencent Holdings Limited) official account of the Department of Psychiatry at Sir Run Run Shaw Hospital, Zhejiang University School of Medicine, to recruit potential participants. They encouraged sharing the program details with medical schools and hospitals. Interested individuals could register by sending messages and their identification to the research assistants (Zitang Zhou and Luyao Zou). Research assistants then contacted the respondents to assess their eligibility, explain the study to each participant, and inform them about the allocation to either the control or intervention groups, where they would receive the psychotherapy training program.

Baseline and Posttraining Data Collection

Before randomization, demographic information and self-reported questionnaires were collected from all participants at baseline. This information included participants' sex, age, identity (student, resident, or HCP), education level (undergraduate or graduate degree), department affiliation (psychiatric or nonpsychiatric), and years of psychotherapy-related work. Additionally, outcome measurements were gathered, including trainees' knowledge of psychotherapy, utilization of psychotherapy, self-reported self-efficacy, and self-reported motivation, among others. The questionnaires on psychotherapy knowledge, utilization, and self-efficacy and motivation to engage in psychotherapy were specifically designed based on our training program. Outcome measurements were assessed again 8 weeks after training (Table 1). Data were collected online using WenJuanXing (Questionnaire Star), a Chinese platform that provides professional online questionnaire surveys and data collection for RCTs [15]. The hospital's data monitoring committee oversaw the data collection process, and personal information was deidentified to ensure confidentiality.

Table 1. Schedule of enrollment and posttraining assessments.[a]

Schedule	Baseline	8 weeks after training
Initial approach	✓	N/A[b]
Informed consent	✓	N/A
Eligibility screen	✓	N/A
Randomization	✓	N/A
Intervention/control initiation	✓	N/A
Demographic characteristics	✓	N/A
Knowledge	✓	✓
Self-reported self-efficacy	✓	✓
Self-reported motivation	✓	✓
Utilization	✓	✓

[a]This table illustrates the schedule of enrollment and posttraining assessments. Initial approach, informed consent, eligibility screen, randomization, intervention/control initiation, and demographic characteristics were evaluated and collected only at the baseline timeline. Psychotherapy knowledge, self-reported self-efficacy, self-reported motivation, and utilization were both collected at the baseline and 8 weeks after the training.

[b]N/A: not applicable.

Development of the Psychotherapy Training Program

The psychotherapy training program was primarily developed by an experienced psychotherapist (Tao Pei) and an MD-level psychiatrist (Yanhui Liao), both of whom have approximately 20 years of relevant experience. The details of the 2-day psychotherapy training program are outlined in Multimedia Appendix 1. The program included 2 days of intensive training followed by 8 weeks of follow-up, with guidance on applying psychotherapy in clinical settings.

Intervention

Control Group

After providing consent, participants allocated to the waitlist control group received a message encouraging them to complete all questionnaires from baseline through to the final follow-up at 8 weeks. They were sent messages via WeChat to thank them for their participation and to remind them of the timeline for completing the study. Once they finished the posttraining measurement, a digital booklet of the psychotherapy training program was provided to them via WeChat or as a hard copy upon request. After the trial concluded, participants in the control group were offered the opportunity to receive the psychotherapy training program free of charge.

Intervention Group

All participants in the intervention group received the 2-day psychotherapy training program and were given a hard copy of the program booklet at recruitment. Additionally, supervision-based group meetings were held during the follow-ups at weeks 1, 2, 4, and 8, with each meeting lasting approximately 2 hours. During these follow-up meetings, instructors—including psychotherapists and psychiatrists—were available to answer any psychotherapy-related questions, encourage participants to practice psychological interventions, and provide further information to support the clinical application of psychotherapy.

Outcomes and Outcome Measures

Primary Outcome

Trainees' psychotherapy knowledge was assessed by participants using an 11-point scale (ranging from 0 to 10) before and after the 8-week period (Table 2). At baseline, 160 participants completed the self-reported psychotherapy knowledge questionnaire, and the results indicated a high internal consistency coefficient (Cronbach α) of 0.980 for the scores across the 17 items.

Table 2. Knowledge about psychotherapy.[a]

Variables	Measures (0-10)
Overview of psychotherapy	
Supportive psychotherapy techniques	
Overview of cognitive behavioral therapy	
Beck's cognitive therapy	
Identify automatic thinking and do cognitive conceptualization	
Cognitive conceptualization	
Evaluation of automatic thinking	
Reconstruction techniques for automated thinking1: Socratic questioning	
Reconstruction techniques for automated thinking2: pie charts, continuous spectrum, cost-benefit analysis, behavioral experiments	
Challenge automatic thinking	
Social skill training	
Problem-solving	
Behavioral therapy theory and behavioral conceptualization	
Behavioral activation	
Relaxation training	
Exposure therapy	
Competency structure of psychotherapists and the growth path of cognitive behavioral therapy therapists	

[a]This is the assessment of participants' knowledge about psychotherapy. Each item was rated on a 0-10 scale, where 10 means "knowing very well."

Secondary Outcomes

Training Program Acceptability

Program acceptability in the intervention group was measured using questions designed to assess acceptability, as detailed in Table 3.

Table 3. Questions for assessing the psychotherapy training program acceptability.[a]

Category and questions	Rating
General	
• Overall rating of the program	5=like very much; 4=like somewhat; 3=neutral; 2=dislike somewhat; 1=very dislike; 5=very likely
Appraisal	
• Appraisal of the program—the likelihood of applying the program for patients • Appraisal of the program—the likelihood of recommending the program to other medical students or other health care providers	5=very likely; 4=somewhat likely; 3=neutral; 2=unlikely; 1=not at all likely
Acceptability	
• I would have been able to help patients to deal with mental problems with the program • The program made it easier to communicate and help patients during clinical work • The program disrupted my daily schedule • The program is easy to understand	5=strongly agree; 4=agree; 3=neutral; 2=disagree; 1=strongly disagree
Frequency	
• Frequency of using psychotherapy	1=almost never; 2=sometimes; 3=always

[a]This is the rating of the training acceptability assessment. The last item, "Frequency of using psychotherapy," was rated on a 1-3 Likert scale, where 3 indicates "always."

Utilization of Psychotherapy

The utilization rate of psychotherapy interventions for patients during the 8 weeks of follow-up was assessed using items from Table 4.

Table 4. The utilization rate of psychotherapy.[a]

Variables	Measures (0-10)
Supportive psychotherapy techniques	
Social skill	
Problem-solving skill	
Behavioral activation	
Relaxation training	
Exposure therapy	

[a]This is the assessment of participants' utilization rate of psychotherapy. Each item was rated on a 0-10 scale, where 10 means maximum utilization and 0 means minimum utilization.

Self-Reported Self-Efficacy and Self-Reported Motivation

Self-efficacy and motivation were measured using a visual analog scale on a 10-cm line, representing a continuum from "no self-efficacy or motivation" to "the strongest self-efficacy or motivation" (Table 5).

Table 5. Self-reported self-efficacy and motivation of psychotherapy.[a]

Variables	Visual analog scale
Self-reported self-efficacy	
Confidence in practicing psychotherapy	
Confidence in practicing supportive psychotherapy	
Confidence in practicing cognitive behavioral therapy	
Self-reported m otivation	
Willingness or motivation to practice psychotherapy	
Willingness or motivation to practice supportive psychotherapy	
Willingness or motivation to practice cognitive behavioral therapy	

[a]This is the assessment of participants' self-reported self-efficacy and self-reported motivation. Each item was measured by the visual analog scale on a 10-cm line that represents a continuum between "no self-efficacy or motivation" and "the strongest self-efficacy or motivation.

All secondary outcomes were reported as mean values. According to the baseline measurements of our study, 160 participants evaluated their psychotherapy utilization, confidence, and motivation using self-reported questionnaires. The internal consistency coefficients (Cronbach α) for these 3 questionnaires were 0.950, 0.961, and 0.936, respectively.

Procedures

Figure 1 and Table 1 summarize the schedule for enrollment and posttraining assessments. Participants were evaluated at baseline (0 weeks), before and after receiving the intervention training, and at 8 weeks after training. They were also asked to maintain a daily log of their utilization of the psychotherapy training program, which included activities such as providing emotional support and teaching patients breathing techniques for stress relief. Reminders were sent to participants who did not complete the 8-week posttraining questionnaires.

Withdrawal From the Program

All participants were free to withdraw from the trial at any time without needing to provide a reason. Following the intention-to-treat principle [15], participants who did not respond to the 8-week posttraining assessment were retained in the analysis according to the group to which they were randomized, regardless of whether they received the intervention. Participants who withdrew were excluded from the analysis, and their reasons for withdrawal were recorded. A complete case analysis was conducted, excluding any participants who withdrew at the posttraining assessment point.

Data Analysis

All data were automatically collected via WenJuanXing through a WeChat-based link. The data were downloaded from the WenJuanXing database into a user-specific Excel file. This study did not include interim analyses; data were analyzed only after all had been collected. The trial statistician blinded the intervention assignment in the data using R software (R Foundation for Statistical Computing) and SPSS (2013 release; IBM Corp.).

The primary hypothesis was that, compared with the control intervention, the intervention group receiving the psychotherapy teaching program would significantly gain more knowledge about psychotherapy after training. We also hypothesized that the program would lead to increased utilization of psychotherapy and be associated with improvements in knowledge. The third hypothesis posited that trainees' self-reported self-efficacy and motivation to apply psychotherapy in clinical practice would increase significantly.

Descriptive statistics were used to assess demographic and psychotherapy-related characteristics at baseline. Following normality and homogeneity of variance tests, ANCOVA was used to analyze the primary outcomes. In the ANCOVA model, the dependent variable was the change in the knowledge score. The fixed factor was the group (intervention group or control group), while the covariates included the mean score of psychotherapy knowledge at baseline and years of psychotherapy experience. Pearson correlations and regression analysis (both linear and binary regression models) were used to explore factors associated with the knowledge score at baseline and to assess the increase in psychotherapy utilization in both the intervention and control groups. The secondary outcomes—participants' psychotherapy utilization, confidence, and motivation—will also be analyzed in the same manner as knowledge.

A complete case analysis was performed, excluding any participants with missing information on the posttraining assessment. Additionally, a sensitivity analysis of the missing data was conducted to determine whether the missingness is random. Demographic information and scores for psychotherapy knowledge, utilization, confidence, and motivation at baseline were compared between the complete data group and the missing data group. All tests were 2-tailed, with a significance level set at $P<.05$.

Safety and Adverse Events

Throughout the psychotherapy training program, adverse events were closely monitored. Participants were encouraged to communicate any psychotherapy-related issues or adverse events encountered during their clinical work. We prompted each participant to report any adverse events experienced at each group meeting, and they could also report them at any time. If participants experienced severe adverse events, they were encouraged to seek support from a psychologist or psychiatrist.

We did not anticipate any training-related serious adverse events (SAEs), such as life-threatening incidents, during this trial. However, if any adverse events occur, we will document the SAE, record it on the SAE form, and submit it to the ethics committee of Sir Run Run Shaw Hospital (the principal investigator's affiliation) within 24 hours.

Ethics Approval and Consent to Participate

This study was approved by the ethics committee of Sir Run Run Shaw Hospital, an affiliate of Zhejiang University School of Medicine (2024 Ethics Approval File No. 2024-0066). The trial was conducted in accordance with the Declaration of Helsinki. Participants were provided with informed consent before the baseline assessment. After thoroughly reading and understanding the content of the consent, they received a link to electronically sign their name at the end of the informed consent form and submit it via WeChat. Each participant was informed about the study's purpose, procedures, measurements, potential risks, and benefits before recruitment. Informed consent was then obtained from each participant. Participation was entirely voluntary, and participants could withdraw from the study at any time. Coordinating researchers' contact information was provided to all participants for any inquiries or concerns.

Data Security

The authors utilized the professional version of WenJuanXing, which features high-level security management, alongside an applet on WeChat that ensures the secure and confidential protection of participants' data.

Results

This study recruited 160 participants from January 4 to January 12, 2024. The 2-day training program took place on February 3 and February 4, 2024, and the posttraining assessment was completed on April 1, 2024. Due to withdrawals, incomplete surveys, and data loss, we had a total of 113 participants: 57 in the intervention group and 56 in the control group. The amount of data varies for each measure. Data analysis was completed in August 2024. The results will be published in peer-reviewed journals. If found to be effective, the psychotherapy training program and the accompanying program booklet will be made freely available to the public by the end of the trial.

Discussion

To our knowledge, this will be the first RCT to evaluate the efficacy of a multimodal psychotherapy training program for medical students in China.

The strength of this study lies in its theoretical framework, primarily guided by cognitive behavioral theory. With a large sample size, this RCT evaluates the efficacy of the psychotherapy training program using multimodal teaching methods in China. If effective, this multimodal psychotherapy training program could be applied nationwide, significantly enhancing its potential impact on public health. Its expansion could help HCPs acquire the necessary psychotherapy skills to effectively manage patients' psychological issues.

There are several limitations to this study. First, the effectiveness of teaching and the quality of learning can be influenced by various factors, such as opportunities to implement psychotherapy practice, the intensity of clinical work during the follow-up period (including the impact of holidays), and the availability of continuing education resources. These factors cannot be adequately controlled in this study. Second, the 2-day training will take place at Sir Run Run Shaw Hospital, which may deter participants from other regions of China from attending the program. Third, there are only 2 main instructors (Psychiatrist YL and Psychologist TP) involved in this training program. While both have nearly 20 years of teaching and clinical experience, their individual teaching styles and characteristics may still influence the overall effectiveness of the program. Fourth, although this 8-week training program aims to enhance the acquisition of therapeutic skills, developing proficiency in psychotherapy is likely to be a more prolonged process. Fifth, all measures rely on participants' subjective assessments, which may be influenced by personal biases and expectations of improvement following the intervention training. Lastly, we submitted this protocol to the journal during the recruitment process.

In conclusion, this is the first RCT to evaluate the efficacy of a multimodal psychotherapy training program for medical students in China. If this educational program, which offers brief and short-term psychotherapy skills training, proves effective, its nationwide expansion could have a significant health impact. It provides evidence-based psychotherapy training—primarily in CBT—for medical students, and its dissemination will equip HCPs to better manage mental health issues, such as stress and depression. Therefore, it is crucial to develop effective psychotherapy training that emphasizes basic psychotherapy skills. The results of this training's effectiveness can offer valuable insights for the future development of training programs, enabling them to better meet the learning needs of medical professionals and enhance doctor-patient relationships.

Acknowledgments

The research is supported by the China Medical Board (CMB) Open Competition Program (grant 22-485), the STI 2030-Major Projects of China (grant 2022ZD0211200), and the National Natural Science Foundation of China (grant U22A20302 to YH Liao). The funders had no role in the study design, data collection and analysis, the decision to write the report, or the submission of the paper for publication. We appreciate Dan Han's work as she contributed to manuscript discussion at the beginning stage of manuscript writing.

Availability of Data and Materials

Data sets from this study and the corresponding analysis code will be made publicly available at the conclusion of the study's analyses.

Declaration of Artificial Intelligence Use

Generative artificial intelligence was not used in any portion of the manuscript writing.

Authors' Contributions

YL designed the study, while YL and TP developed the program. YD verified the analytical methods. JT supervised the design of the work and revised the manuscript. All authors discussed and approved the final version of the manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
The details of the 2-day psychotherapy training program.
[DOCX File , 26 KB - resprot_v14i1e58037_app1.docx]

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Abbreviations

ANCOVA: analysis of covariance
CBT: cognitive behavioral therapy
HCP: health care provider
RCT: randomized controlled trial
SAE: serious adverse event

Edited by A Mavragani; submitted 04.03.24; peer-reviewed by A Hassan, S Hartmann; comments to author 04.07.24; revised version received 25.07.24; accepted 26.09.24; published 03.01.25.

Please cite as:
Pei T, Ding Y, Tang J, Liao Y
Evaluating the Effectiveness of a Multimodal Psychotherapy Training Program for Medical Students in China: Protocol for a Randomized Controlled Trial
JMIR Res Protoc 2025;14:e58037
URL: https://www.researchprotocols.org/2025/1/e58037
doi:10.2196/58037
PMID:39752191

Protocol

Impact of the Mediterranean Diet on Patients With Psoriasis: Protocol for a Randomized Controlled Trial

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Abstract

Background: Psoriasis is an inflammatory disease primarily treated through molecular-targeted therapies. However, emerging evidence suggests that dietary interventions may also play a role in managing inflammation associated with this condition. The Mediterranean diet (MedDiet), prevalent in southern European countries, has been widely recognized for its ability to reduce cardiovascular mortality, largely due to its anti-inflammatory properties. This anti-inflammatory potential has prompted interest in exploring the MedDiet's role in immune-mediated diseases, including psoriasis. Observational studies have indicated potential benefits, such as reductions in the Psoriasis Area and Severity Index. However, there is a need for well-designed clinical trials to address the methodological limitations of these studies and to establish specific dietary recommendations for psoriasis.

Objective: This study aims to evaluate the impact of an intensive dietary intervention based on the MedDiet in patients with psoriasis. The study will assess the effects of this intervention on skin involvement, metabolic parameters, and inflammatory cytokines. In addition, the emotional well-being and quality of life of participants will be evaluated using validated questionnaires. A methodological analysis will also be conducted to enhance the design of future large-scale clinical trials.

Methods: An open-label, single-blinded (evaluator) randomized controlled trial was designed to assess the impact of a high-intensity MedDiet intervention in patients with mild-to-moderate psoriasis. A total of 38 patients will be randomly assigned into 2 groups—an intervention group receiving the MedDiet intervention and a control group receiving standard care. The intervention group will participate in dietary education sessions aimed at adopting the MedDiet over 4 months, with monthly monitoring by experienced nutritionists. Participants will receive 500 mL of extra virgin olive oil per week, along with informative materials, recipes, and weekly menus. In contrast, the control group will receive standard low-fat diet recommendations without nutritionist monitoring. All participants will undergo a baseline visit, a 2-month follow-up visit, and a final visit at 4 months.

Blood tests will be conducted at the beginning and end of the study. This study protocol was approved by the Institutional Review Board of the Hospital Ramón y Cajal (Madrid) in July 2023.

Results: Enrollment concluded in October 2024, with data collection set to finish by February 2025. The findings will be presented at national and international conferences and published in peer-reviewed journals.

Conclusions: This protocol outlines the design of a clinical trial that implements the MedDiet in patients with psoriasis to evaluate its benefits on skin involvement, systemic inflammation, and quality of life.

Trial Registration: ClinicalTrials.gov NCT06257641; https://clinicaltrials.gov/study/NCT06257641

International Registered Report Identifier (IRRID): DERR1-10.2196/64277

(JMIR Res Protoc 2025;14:e64277) doi:10.2196/64277

KEYWORDS

psoriasis; Mediterranean diet; MedDiet; nutritional intervention; olive oil; inflammatory disease; Impact of the Mediterranean Diet on Patients with Psoriasis; MEDIPSO; dietary intervention; methodological analysis; randomized controlled trial; RCT; clinical trial; nutrition; diet; Europe

Introduction

Psoriasis is a common skin disease, affecting between 2% and 4% of the population [1,2]. Its pathogenesis involves a complex interplay between innate and adaptive immunity, with the interleukin (IL)-17/IL-23 axis playing a crucial role. While not all underlying molecular mechanisms have been fully elucidated, current medical treatments primarily target proinflammatory cytokines [3]. In today's era of media, nutrition has become a significant topic of interest among patients with psoriasis. A survey conducted by the National Psoriasis Foundation involving 1206 patients revealed that 89% (n=1073) believed it was important to discuss the role of diet in their disease with their physician, and 86% (n=1037) had attempted dietary modifications. Despite this, only 31% (374/1206) of patients had actually discussed dietary changes with a health care provider [4]. In fact, nutritional approaches play a very important role in the prevention and treatment process of chronic diseases such as inflammatory diseases, autoimmune diseases, cardiovascular diseases, and even mental diseases [5,6].

There is well-established evidence supporting the beneficial effect of weight loss in patients with psoriasis [7]. Dietary interventions that promote weight loss are recognized as valuable therapeutic strategies for reducing inflammation, particularly in obese patients with psoriasis [8]. In addition, the nutrigenomic effects of certain food components have been documented [9]. However, the only firm dietary recommendations currently reflected in most psoriasis guidelines and expert consensus are weight loss for patients who are overweight and obese and a gluten-free diet for those with positive celiac disease serology [10]. Therefore, there remains a need for dietary guidance that offers benefits beyond weight loss, applicable to patients of any body weight.

The Mediterranean diet (MedDiet) refers to the eating patterns typical of the olive-growing regions around the Mediterranean Sea. This dietary approach emphasizes the consumption of fruits, whole grains, vegetables, nuts, seeds, legumes, and olive oil—the hallmark of the MedDiet. It also includes a moderate intake of red wine with meals, seafood, poultry, and fermented dairy products, while limiting red and processed meats, sweets, and other ultraprocessed foods [11]. Growing evidence suggests that the MedDiet may influence the progression and severity of psoriasis [12,13]. In a 2018 cross-sectional study by Phan et al [14], which included 35,735 participants from the NutriNet-Santé cohort, 3557 participants had psoriasis, with 878 classified as severe cases. The multivariate analysis, adjusted for factors such as age, sex, weight, and cardiovascular risk, showed a significantly lower percentage of severe psoriasis cases among those with greater adherence to the MedDiet [14].

Several research groups have designed large-scale dietary interventions to implement the MedDiet in large patient cohorts. The PREDIMED (Prevention with Mediterranean Diet) study [15], which included 7447 patients at high risk of cardiovascular disease, randomly assigned participants into 3 groups—2 groups received Mediterranean dietary advice supplemented with extra virgin olive oil (EVOO) or a mixture of nuts, while the third group followed low-fat dietary recommendations. All groups were closely monitored by nutritionists. The PREDIMED study demonstrated the positive role of the MedDiet in preventing cardiovascular events. Subsequent satellite studies, such as the PREDIMAR (Prevention of Recurrent Arrhythmias with Mediterranean Diet) study [16], which used an entirely online dietary intervention, further underscored the MedDiet's benefits and the feasibility of achieving high adherence to this dietary pattern through a dietary intervention.

The MEDIPSO (Impact of the Mediterranean Diet on Patients with Psoriasis) study, detailed in this paper, was conceived to address the need for more evidence on the relationship between psoriasis and the MedDiet. This proof-of-concept randomized controlled trial, inspired by the PREDIMED study, involves a high-intensity MedDiet intervention in patients with psoriasis. The primary objective is to evaluate the impact of this dietary pattern on psoriasis skin involvement, inflammatory cytokines, and quality of life.

Methods

Study Design

The MEDIPSO study is an open-label, single-blinded (evaluator) randomized controlled trial. This experimental study involves patients with mild-to-moderate psoriasis who are on stable topical treatment, which will be randomly assigned to either a

control group or an intervention group. Patients in the intervention group will receive dietary education focused on adopting the MedDiet, with monthly monitoring by nutritionists experienced in the PREDIMED clinical trial. In contrast, the control group will not receive any active dietary modification interventions.

Both groups will undergo blood tests to assess metabolic parameters before and after the study period, and data on anthropometric characteristics and quality of life will be collected. The study aims to evaluate the effects of the MedDiet on skin involvement, metabolic parameters, and inflammatory cytokines, as well as its impact on emotional well-being and quality of life. In addition, a methodological analysis will be conducted to refine the design for future large-scale clinical trials.

Participants

In total, 38 patients with mild-to-moderate plaque psoriasis and no systemic treatment will be included. Participants for this study will be recruited from among patients who regularly attend dermatology consultations at Hospital Universitario Ramón y Cajal. The inclusion criteria and exclusion criteria are stated in Textbox 1.

Textbox 1. Inclusion and exclusion criteria for the participation in the Impact of the Mediterranean Diet on Patients with Psoriasis study.

Inclusion criteria:

- Psoriasis clinically diagnosed by an experienced dermatologist
- Predominantly psoriasis vulgaris
- Psoriasis Area and Severity Index ≥2 and ≤10 at the time of recruitment
- Stable weight (<5% weight loss or gain) in the last 3 months
- Treated exclusively with topical treatment for psoriasis at enrollment and throughout the study
- Willing and able to follow the study procedure, attend all scheduled visits during the study period, and provide blood samples as indicated in the procedure
- Able to give informed consent
- Willing to implement pregnancy prevention measures throughout the study period

Exclusion criteria:

- Type 1 or 2 diabetes mellitus
- Good adherence to the Mediterranean diet at the time of screening (energy-restricted Mediterranean Diet Adherence Screener score ≥8)
- Language barrier (patients not fluent in Spanish or English) or conditions that make telephone communication difficult (eg, severe hearing loss)
- History of cardiac disease
- Comorbidities that may compromise the implementation of the intervention (eg, cancer, digestive diseases, and so on) or limit survival to less than 6 months
- History or current eating disorder (anorexia, bulimia, etc; screening will be carried out using the Diagnostic and Statistical Manual of Mental Disorders, fifth edition, if indicated)
- Malnourished patients (screening using the Malnutrition Universal Screening Tool, if indicated)
- BMI greater than 40 kg/m^2
- Presenting gout
- Pregnant, planning pregnancy, or breastfeeding
- Use of diuretics at the time of sampling
- Difficulty or inconvenience in changing dietary habits and following the Mediterranean diet (allergies, food intolerances, and special diets)
- Participation in a clinical trial with drugs or dietary intervention in the year prior to inclusion in this study

Sample Size

There are no previous studies specifically evaluating the impact of MedDiet on skin involvement in patients with psoriasis. The only dietary intervention study in psoriasis to date is by Castaldo et al [8], which reported a decrease in Psoriasis Area and Severity Index (PASI) of 7.2 (95% CI –8.7 to –5.6) in a sample of 37 patients. However, this study differs significantly from MEDIPSO in design; it involved a single group without a control group, used a highly aggressive intervention including prolonged fasting periods, targeted only patients with obesity who have severe psoriasis, and excluded other adjuvant treatments, with a longer follow-up period.

In contrast, our study includes a control group, applies a less aggressive dietary intervention, and focuses on patients with mild-to-moderate psoriasis who are allowed to continue their stable topical treatments. Consequently, we anticipate the SD in PASI reduction at week 16 to be much lower, around 1. To

detect a difference of 1 unit on the PASI scale, with an α risk of 0.05 and a β risk of less than 0.2 in a bilateral contrast, we estimate that 19 participants per group (intervention and control) are needed. We assume a common SD of 1 and estimate a loss-to-follow-up rate of 15%.

Randomization

After signing the informed consent, all participants will be enrolled and randomly assigned into either the MedDiet intervention group or the standard-of-care group using closed envelopes. Randomization will be conducted using a computer-generated list created by an independent statistician, who is blinded to the trial and not involved in participant recruitment. The allocation will follow a 1:1 ratio. The recruiter will only open the envelope and learn of each patient's group assignment after the informed consent form has been signed by the patient.

Blinding

The study is single-blinded, as only the investigator evaluating the PASI is blinded. Both the patient, the nutritionists responsible for carrying out the intervention, and the person in charge of follow-up and nonsubjective data collection are aware of the group to which the patient has been assigned.

Roles

The entire dermatology department will be involved in patient recruitment. The principal investigator will oversee initial screening, follow-up, data collection, and the evaluation of side effects. Randomization will be conducted using a sealed-envelope system, with the principal investigator opening the envelopes only after the patient has been enrolled in the study and the informed consent has been signed. This investigator will not be blinded.

The nutritional intervention was fully designed by nutritionists from the University of Navarra, who will implement the intervention with the support of the principal investigator. The nutritionists will also not be blinded.

Evaluation of nonobjective parameters, such as PASI, and data analysis will be conducted by coinvestigators who are blinded to the group assignments.

The Nutritional Intervention

The objective of the nutritional intervention in the MEDIPSO study is to enhance adherence to the MedDiet. A hybrid approach combining remote and face-to-face interactions will be implemented. During the initial visit, when the first blood sample is taken and the patient's data are collected, initial dietary recommendations will be provided along with supportive materials, including instructions on the MedDiet, infographics, sample menus, and recipes. Following this, dietitian-nutritionists with experience from previous MedDiet intervention studies, such as PREDIMED, will conduct monthly telephone consultations with each participant.

During these consultations, the dietitian-nutritionists will assess adherence to the MedDiet and set individualized goals for improvement based on the participant's needs. In addition to the printed materials provided at the first visit, participants will have the opportunity to discuss any questions or concerns with the research team.

Participants in the intervention group will receive 500 mL of EVOO each week, distributed during clinic visits. The goal is to encourage participants to consume at least 4 tablespoons of EVOO daily, using it as the primary culinary fat in their homes as part of the MedDiet.

The dietary recommendations for the intervention will align with the habits defined in the MedDiet according to the Energy-Restricted Mediterranean Diet Adherence Screener (er-MEDAS) scale (Table 1) [17]. Participants will be instructed to follow specific guidelines, including consuming 4 or more tablespoons of EVOO daily for cooking and seasoning; 2 or more servings (200 g per serving) of vegetables per day (with at least 1 serving being raw); 3 or more servings (125 g per serving) of fruits per day (including natural juices); 3 or more servings (60-80 g per serving) of legumes per week; 3 or more servings (150 g per serving) of fish or seafood per week (including at least 1 serving of oily fish); and 3 or more servings (30 g per serving) of nuts per week. Participants will be advised to choose white meats (eg, skinless poultry and rabbit) over red meat (eg, beef and pork) or processed meats (eg, sausages and hamburgers). Regular use of sofrito (a sauce made with chopped tomato, garlic, and onion simmered in olive oil) for cooking, at least twice per week, will also be encouraged. In addition, whole grains (eg, bread, pasta, and rice) should be chosen over refined cereals. The dietary plan will recommend eliminating or limiting the consumption of cream, butter, margarine, carbonated and sugary drinks, baked goods (eg, sweet desserts, cakes, pastries, and cookies), and ultraprocessed foods. The nutritional intervention will not prescribe a specific caloric intake or macronutrient distribution.

Table 1. Energy-Restricted Mediterranean Diet Adherence Screener scale score (the maximum possible score is 17; this was the scale used to assess the adherence to the Mediterranean diet during the study; a score ≤7 was considered to be poor adherence to Mediterranean diet).

Question to be asked to the patient	Criterion to score 1 point; otherwise, 0 is recorded
Do you use extra virgin olive oil as the principal source of fat for cooking?	Yes
How many servings of vegetables do you consume per day? Count garnish and side servings as half a serving; a full serving is 200 g.	≥2
How many pieces of fruit (including fresh-squeezed juice) do you consume per day?	≥3
How many servings of red meat, hamburger, or sausages do you consume per week? A full serving is 100-150 g.	≤1
How many servings (12 g) of butter, margarine, or cream do you consume per week?	<1
How many carbonated and sugar-sweetened beverages do you consume per week?	<1
How many servings (150 g) of pulses do you consume per week?	≥3
How many servings of fish and seafood do you consume per week? (100-150 g of fish, 4-5 pieces, or 200 g of seafood)	≥3
How many times do you consume pastry such as cookies, cake, or sweets per week?	<3
How many times do you consume nuts per week? (1 serving=30 g) per week?	≥3
Do you prefer to eat chicken, turkey, or rabbit instead of beef, pork, hamburgers, or sausages?	Yes
How many times a week do you eat cooked vegetables, pasta, rice, or other dishes dressed with sofrito (a tomato, garlic, onion, or leek sauce simmered with olive oil)?	≥2
Do you add sugar to your beverages (coffee, tea)?	No
How many servings of white bread do you consume per day (1 serving=75 g)?	<1
How many servings of whole-grain bread, pasta, or rice do you consume per week?	≥5
How many servings of refined bread, rice, and pasta do you consume per week?	<3
Do you drink wine? How much do you consume per week? (1 cup=100 mL)	Male 14-21 cups; female 7-14 cups

Study Protocol

The intervention period will last 16 weeks, comprising 3 face-to-face visits for all participants and 2 additional telephone visits for those in the intervention group.

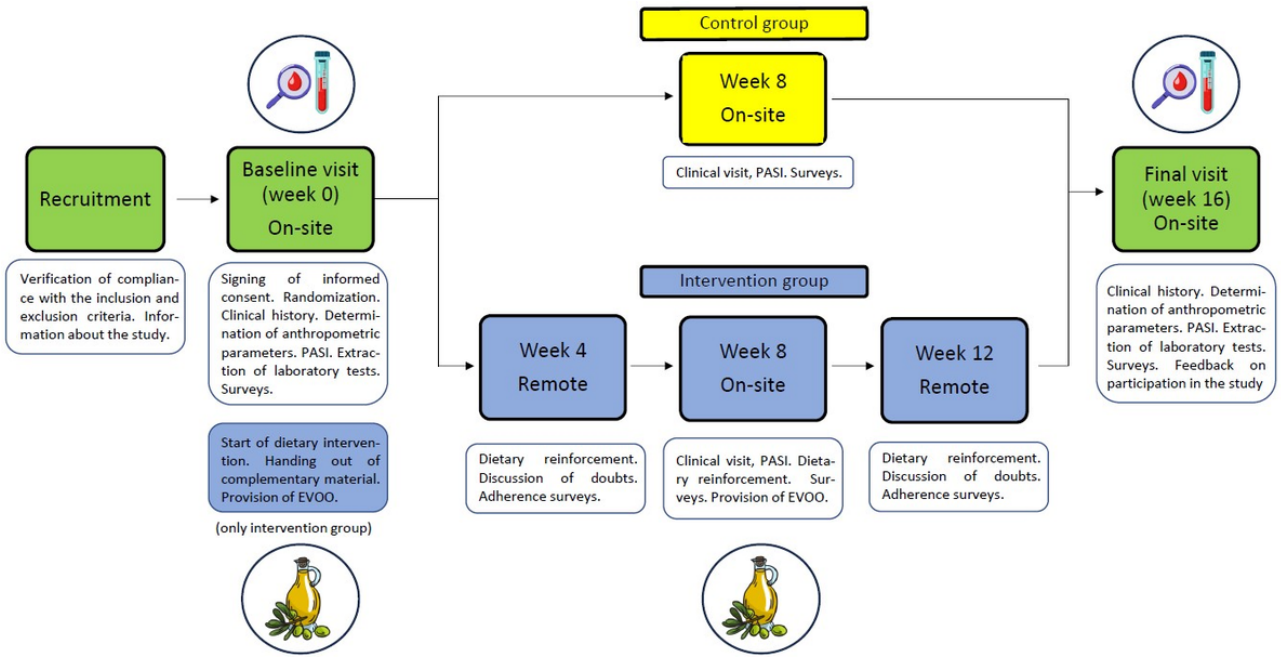
During the baseline visit (visit 1), patients will sign the informed consent, undergo randomization, and have clinical information collected. A complete physical examination will be conducted, and blood samples will be obtained. For patients randomized to the intervention group, this visit will also include the provision of informational materials, the distribution of EVOO, and the initiation of the nutritional intervention.

At week 8, a face-to-face visit (visit 2) will be conducted. The primary objective of this visit is to perform a clinical evaluation to determine if the patient has experienced any clinical worsening that would necessitate the initiation of systemic treatment. If systemic treatment is deemed necessary, the corresponding analytical tests and vaccination protocol will be initiated. This visit at week 8 ensures that participation in the study does not delay the start of systemic treatment if required.

During the final visit (visit 3), clinical information will once again be collected, a complete physical examination will be performed, and final blood samples will be drawn. In addition, feedback will be gathered from the patient regarding their experience in the study, any challenges encountered, and suggestions for improvement. This feedback will be collected through an anonymous, free-response online survey, as well as a brief interview in which the patient can discuss any issues identified during the study with the investigator.

The study protocol is summarized in Figure 1.

Figure 1. Comprehensive overview of the study protocol. As shown, patients in the control group will attend 3 on-site study visits. In contrast, patients in the Mediterranean diet intervention group will attend 3 on-site visits as well as 2 additional remote visits. Participants in the intervention group will receive 4 L of EVOO at weeks 0 and 8 (500 mL per week). Blood tests will be conducted at week 0 and week 16 in both groups. EVOO: extra virgin olive oil; PASI: Psoriasis Area and Severity Index.



Outcomes

The primary outcome is the change from baseline in the PASI at week 16. PASI is the most widely used scale for assessing psoriasis severity and informing therapeutic decisions, with scores ranging from 0 (no lesions) to 72 (severe lesions across the entire body surface) [18].

The secondary outcomes include:

1. Change from baseline in adherence to the MedDiet at week 16: Adherence will be assessed using the validated er-MEDAS questionnaire, which scores from 0 to 17, with higher scores indicating better adherence [17].
2. Change from baseline in anthropometric parameters at week 16: This includes weight, BMI, and abdominal circumference, measured before and after the intervention.
3. Change from baseline in serum inflammatory interleukins at week 16: Levels of various ILs and cytokines will be assessed, including granulocyte-macrophage colony-stimulating factor, interferon gamma (IFNγ), IL-1β, IL 2, IL 4, IL 5, IL 6, IL 9, IL 10, IL 12 (p70), IL 13, IL 15, IL 17A/CTLA8, IL-17E/ IL-25, IL 17F, IL 21, IL 22, IL 23, IL 27, IL 28A/IFNλ2, IL 31, IL 33/NF HEV (mature), MIP-3α/CCL20, tumoral necrosis factor alpha (TNFα), and TNFβ/Lymphotoxin-α (LTA).
4. Change from baseline in metabolic blood parameters at week 16: changes in serum cholesterol, low-density lipoproteins, high-density lipoproteins, lipoprotein A, apolipoprotein A1, apolipoprotein B, fasting serum insulin, hemoglobin, A_{1c} and C-reactive protein (CRP) will be measured.
5. Change from baseline in the impact of the disease on patient's life at week 16: quality of life will be assessed using the validated questionnaire Dermatology Life Quality Index [18]. Change in sleep quality will be evaluated using the Insomnia Severity Index [19] and emotional state changes will be measured using the Hospital Anxiety and Depression Scale [20].

Data Analysis

Once data collection is complete, statistical analysis will be performed using StataIC 17 (Stata Corp). A descriptive analysis of the baseline demographic and clinical characteristics of the patients included in the trial will be conducted. Normality will be assessed using skewness, kurtosis, and histogram plots. Parametric variables will be reported as mean (SD), nonparametric variables as median (IQR), and categorical variables as n (%).

To evaluate differences between the intervention groups, statistical significance will be assessed using the Student *t* test for comparing 2 groups and the ANOVA test for comparisons involving multiple groups, for parametric variables. For nonparametric variables, the Wilcoxon rank-sum test and Kruskal-Wallis test will be applied. Pearson chi-square test will be used for categorical variables. An intention-to-treat analysis will be performed.

Linear mixed-effects models will be used to assess changes in nutritional variables from baseline to follow-up visits. Statistical significance will be determined using a 2-tailed level of significance, with *P* values less than .05 considered significant.

Ethical Considerations

The study protocol (version 2.0; July 10, 2023) was approved by the Institutional Review Board of the Hospital Ramón y Cajal (Madrid) in July 2023 (170/23).

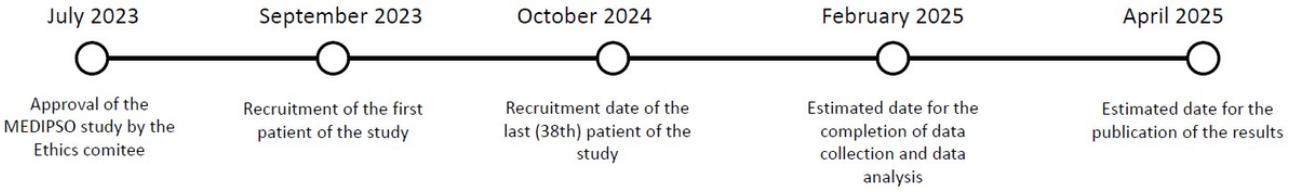
All personal and clinical information of potential and enrolled participants will be coded and used exclusively for clinical trial

purposes. This information will be securely stored in the BioeBank 3.01.0.R26 storage system. Access to this data will be restricted to the investigators involved in this study. No monetary compensation was provided to the participants.

Results

Enrollment concluded in October 2024, with data collection set to finish by February 2025. The findings will be presented at national and international conferences and published in peer-reviewed journals. The estimated study timeline is illustrated in Figure 2.

Figure 2. Estimated study timeline. MEDIPSO: Impact of the Mediterranean Diet on Patients with Psoriasis.



Discussion

Expected Findings

The relationship between psoriasis and the MedDiet has been explored in several cross-sectional studies. Barrea et al [21] conducted a case-control study involving 62 patients with untreated moderate-to-severe psoriasis and 62 healthy controls matched for age, sex, and BMI. This study found that patients with psoriasis were less adherent to the MedDiet than healthy controls. In addition, the consumption of EVOO and fish were identified as predictors of a lower PASI [21]. Similarly, Korovesi et al [22], in a study with a comparable design, reached analogous conclusions and also highlighted the beneficial effect of legume consumption on PASI reduction. Furthermore, Molina-Leyva et al [23] observed a lower severity of psoriasis in patients with greater adherence to the MedDiet, along with a reduction in CRP, a marker of systemic inflammation.

Despite the growing evidence suggesting the potential benefits of the MedDiet in psoriasis, the current evidence remains weak, primarily limited to nonexperimental studies [10]. In an attempt to provide more robust data, Castaldo et al [8] designed an experimental study where an aggressive weight loss was induced through a ketogenic diet followed by a hypocaloric Mediterranean-type diet. Significant reductions in skin involvement were observed, as measured by PASI. Interestingly, no linear correlation was found between weight loss and PASI, suggesting that ketone bodies and other dietary components from both dietary patterns may contribute to the observed anti-inflammatory effects [8]. However, the study's design lacked a control group, making it difficult to attribute the anti-inflammatory effects solely to the dietary intervention. In addition, the study only included obese patients, leaving unanswered the critical question of whether these potential benefits of the MedDiet could also be observed in patients with normal weight.

The molecular mechanisms underlying the potential benefits of the MedDiet on psoriasis severity are not yet well characterized. Beyond psoriasis, greater adherence to the MedDiet has been shown to reduce the severity of other immune-mediated diseases, such as rheumatoid arthritis [24] and inflammatory bowel disease [25]. This observation has shifted attention toward the MedDiet's potential systemic anti-inflammatory effects. Olive oil, a key component of the MedDiet, is rich in monounsaturated fatty acids. Virgin olive oil, in particular, retains all the lipophilic components of the olive, as well as α-tocopherol and phenolic compounds—molecules with strong antioxidant properties—whereas refined olive oil loses most of its antioxidants during the refining process [26]. Supporting this hypothesis, Mena et al [27] conducted a clinical trial demonstrating that patients who followed a MedDiet supplemented with EVOO exhibited a down-regulation of proinflammatory biomarkers associated with atherogenesis, including serum IL-6, soluble intercellular adhesion molecule-1, and CRP [27].

Our study's prospective and longitudinal design offers a valuable opportunity to assess how different inflammatory molecules vary following a dietary intervention specifically in psoriasis, potentially illuminating the molecular mechanisms by which the MedDiet exerts its effects in immune-mediated diseases. A key strength and distinguishing factor of this study compared with previous research is the inclusion of a control group, which enhances the ability to attribute observed changes directly to the dietary intervention. This is particularly important given the frequent use of topical treatments in psoriasis patients, regardless of systemic therapy, and the episodic nature of psoriasis, where spontaneous improvements in severity can occur. In addition, maintaining close contact with a small cohort of patients will enable a thorough evaluation of logistical challenges, which will be crucial for planning future larger-scale multicenter trials.

Several limitations of the study design should be noted. First, this is a unicentric clinical trial, which may limit the external validity of the results. In addition, the interventional nature of the study—characterized by close follow-up and the free provision of EVOO—may mean that the findings are not generalizable to all patients with psoriasis. Furthermore, the MedDiet intervention and follow-up period is limited to 4 months, and the sample size is relatively small, potentially resulting in insufficient statistical power for some analyses. However, these limitations should be viewed in the context of the study's proof-of-concept nature.

Strengths and Limitations of This Study

First, there are no firm dietary recommendations that can be provided to patients with psoriasis. This study is a pioneering effort in implementing the MedDiet in this patient population,

drawing on the expertise of epidemiologists and nutritionists who have specialized in MedDiet interventions, particularly in prestigious studies like the PREDIMED clinical trial.

Second, multiple outcomes resulting from the intervention such as psoriasis severity, cardiometabolic parameters, inflammatory cytokines, and quality of life will be evaluated. In addition, this clinical trial is designed to pave the way for a larger study, involving more patients, multiple centers, and extended follow-up periods.

Third, a possible limitation of this study is the relatively small sample size and the intervention duration of only 4 months, which reflects the proof-of-concept nature of the study.

Finally, the results of the nutritional intervention may not be generalizable to all patients with psoriasis for 2 reasons. First, the study population consists of patients with mild-to-moderate psoriasis who attend dermatology clinics, potentially indicating a higher level of health engagement than the general population. Second, while the provision of EVOO is a strength of the study, it may present a barrier in real-world situations due to the high cost of this product.

In conclusion, the MEDIPSO study was designed to generate high-quality evidence on the relationship between the MedDiet and psoriasis. Through this clinical trial, we aim to explore the anti-inflammatory effects of the MedDiet and their manifestation at both the clinical and molecular levels. In addition, this study is intended to lay the groundwork for future research in this area.

Acknowledgments

This work was supported by the grant conceded by Francisco de Vitoria University (Call for Research Project Grants 2024) and by the Research Grant 2023 conceded by the Psoriasis Group of the Spanish Academy of Dermatology and Venereology. All investigators who contributed to the design or execution of the clinical trial will be recognized as authors. No professional writers will be involved in the preparation of the manuscripts.

Data Availability

Access to the full protocol, participant-level dataset, and statistical code can be granted upon reasonable request to the investigative team.

Authors' Contributions

JP-B, AG-C, and MAM-G conceived and designed the study. JP-B, LG, EB-R, and CA-JdA will perform the study. JP-B and EB-R will collect and analyze all experimental data. JP-B provided the first version of the manuscript. EB-R, CA-JdA, RC-M, AB-M, and PJ-O provided critical comments on the original manuscript. JP-B and AG-C revised and finalized the manuscript. All authors read and approved the final version of the manuscript.

Conflicts of Interest

NM is a full-time US government employee. All the authors have no conflicts of interest to declare that are relevant to the content of this paper.

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Abbreviations

CRP: C-reactive protein
er-MEDAS: Energy-Restricted Mediterranean Diet Adherence Screener
EVOO: extra virgin olive oil
IFNγ: interferon gamma

IL: interleukin
MedDiet: Mediterranean diet
MEDIPSO: Impact of the Mediterranean Diet on Patients with Psoriasis
PASI: Psoriasis Area and Severity Index
PREDIMAR: Prevention of Recurrent Arrhythmias with Mediterranean Diet
PREDIMED: Prevention with Mediterranean Diet

Edited by A Schwartz; submitted 13.07.24; peer-reviewed by AR Moravejolahkami, M Rahimlou; comments to author 16.08.24; revised version received 29.08.24; accepted 25.11.24; published 29.01.25.

Please cite as:
Perez-Bootello J, Berna-Rico E, Abbad-Jaime de Aragon C, Cova-Martin R, Goni L, Ballester-Martinez A, Jaen-Olasolo P, Mehta N, Gelfand JM, Martinez-Gonzalez MA, Gonzalez-Cantero A
Impact of the Mediterranean Diet on Patients With Psoriasis: Protocol for a Randomized Controlled Trial
JMIR Res Protoc 2025;14:e64277
URL: https://www.researchprotocols.org/2025/1/e64277
doi:10.2196/64277
PMID:

Protocol

Efficacy and Safety of Murivenna Anal Infiltration Compared to Diltiazem Topical Application in Chronic Anal Fissure: Protocol for a Prospective, Randomized, Open-Label Clinical Trial

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Abstract

Background: Anal fissure is a common proctologic condition that causes significant pain and anguish to patients, significantly impacting their quality of life and well-being. There are various treatment options for anal fissure, ranging from pharmacological agents that reduce anal sphincter tone to surgical interventions for cases resistant to medical management. Ayurvedic treatments have shown potential for the therapeutic management of anal fissure.

Objective: This clinical study aims to analyze the efficacy and safety of murivenna anal infiltration compared to diltiazem topical application in chronic anal fissure.

Methods: This is an open-labeled, randomized, controlled parallel group clinical trial with a sample size of 66 participants to be randomized and allocated in a 1:1 ratio to 2 groups. The intervention group will be treated with murivenna anal infiltration, and the control group will be treated with topical application of diltiazem for a period of 4 weeks. The primary outcome will be the proportion of participants demonstrating complete healing after 4 weeks of treatment. The secondary outcomes will be the proportion of participants demonstrating complete healing after 7 days and 14 days of treatment, change in pain at or after defecation, cessation of bleeding, and any recurrence during the study period. Any adverse events will also be recorded during the trial period.

Results: The project was funded in July 2023, and the study period is 24 months. Participant recruitment started in December 2023. As of August 2024, we have enrolled 50 participants. The data analysis will be complete by June 2025, and the results are expected to be published by August 2025.

Conclusions: High recurrence rates, adverse effects, incomplete healing, and the negative impact on patients' daily activities and quality of life underscore the need for alternative therapeutic options. Ayurveda offers potential for more sustainable relief with fewer adverse effects. Murivenna oil is a time-tested medicated oil effectively used by Ayurvedic physicians for various ulcers of traumatic and pathological origin. This study will provide scientific evidence on the efficacy and safety of murivenna anal infiltration; further, it can be incorporated into the cost-effective management of chronic anal fissure.

Trial Registration: Clinical Trials Registry India CTRI/2023/09/057330; https://tinyurl.com/y4ut9e8p

International Registered Report Identifier (IRRID): DERR1-10.2196/63063

(JMIR Res Protoc 2025;14:e63063) doi:10.2196/63063

KEYWORDS

chronic anal fissure; murivenna anal infiltration; Ayurveda; efficacy; anal infiltration; murivenna; diltiazem; app; chronic; study protocol; randomized clinical trial; proctologic condition; proctologic; pain; quality of life; well-being; surgical intervention; defecation; cessation of bleeding; treatment

Introduction

Anal fissure is a painful tear or split in the distal anal canal. It is a common proctologic condition characterized by intense, prolonged anal pain after defecation, bleeding, and a significant deterioration in the patient's quality of life. The symptoms of anal fissure are a cause of considerable morbidity to the patient. The condition presents with symptoms including severe pain on defecation, which lasts from a few minutes to several hours, bleeding from the rectum, anal discharge, and swelling. If acute, there may be severe pain; the intensity will be comparatively less in the chronic phase. Spontaneous healing of anal fissures is rare due to the reactive spastic contraction of the internal anal sphincter, which diminishes blood flow to the affected area. This constriction impedes the natural healing process, prolonging the duration of symptoms such as pain and bleeding. Therapeutic intervention is often required to alleviate discomfort and promote healing. Various treatment modalities aim to relax the anal sphincter, increase blood flow, and facilitate tissue repair, thereby addressing the underlying cause and promoting resolution of the fissure. Conservative management includes, among other approaches, bulk agents, stool softeners, warm sitz baths, botulinum toxin injections, or topical application of ointments like diltiazem and glyceryl nitrate [1]. New treatment options, such as hyperbaric oxygen therapy to increase tissue oxygenation and induce wound healing, are now being studied [2]. Considerable drawbacks are reported, such as recurrences, toxicity, headaches, and giddiness, while using these external ointments [3]. Surgical treatment is adopted for those cases in which nonsurgical treatment for more than 6 to 8 weeks does not produce desirable results or when there is a recurrence of anal fissure. Surgical treatments include Lord dilatation, lateral internal sphincterotomy, advancement flaps, and fissurectomy [4,5]. Complications of surgical treatments include incontinence to flatus and feces, nonhealing external wounds, abscess, and fistula formation [6]. Miscellaneous novel therapies such as sacral nerve stimulation, autologous adipose tissue transplantation, and posterior tibial nerve stimulation are now being examined as alternatives to lateral sphincterotomy and reliable procedures to avoid fecal incontinence [7]. However, pharmacological modalities are more preferred for treatment of anal fissure, as they are well tolerated, with minimal to no side effects. *Susrutha Samhitha*, a comprehensive Ayurvedic textbook on surgical and parasurgical practices of ancient India, mentions anal fissures as being iatrogenic, and mentions a condition called *parikartika* ("cutting pain in the anus") in the context of *vaidya nimitha bastivyapat* ("indiscretion of the clinician while administering a medicated enema") and *gudakshata* ("ulceration/injury in the anus") in *bastinetravyapat* ("complications due to the enema pipe"). The book further says that this condition should be treated in the same way as traumatic wounds [8]. The *Susrutha* advocates oil irrigation or infiltration to pacify *pitta dosa* (metabolic and biochemical processes that generate heat), which is considered pivotal in the pathology of inflammation and wound formation. [8] *Murivenna* oil is a time-tested medicated oil that treats various exogenous and endogenous ulcers. The drugs used for the preparation of murivenna oil, namely *Aloe vera*, *Pongamia glabra*, *Borreria hispida*, *Asparagus racemosus*, and *Moringa oleifera* are *pittasamaka* (pacifying *pitta*) and *vranavasadana* (ie, they reduce the hypergranulation of wounds). Further, they have been proven to have analgesic and anti-inflammatory properties [9]. Murivenna can potentially help to lessen pain and spasm and promote healing of anal fissures. Further, the anal infiltration process enables the medicine to be retained in the anal canal for an extended period, which can help in reducing increased sphincter tone and associated symptoms.

Hence, this clinical study will compare the effect of murivenna anal infiltration against diltiazem topical application in the treatment of chronic anal fissures. The primary objective of the study is to determine the efficacy of murivenna anal infiltration for healing of anal fissures in comparison with a topical application of 2% diltiazem. The secondary objectives are to determine the safety and efficacy of murivenna anal infiltration for the reduction of pain and bleeding and the prevention of recurrences of anal fissure in comparison with the topical application of 2% diltiazem.

Methods

Study Design and Setting

The study is an open-label, randomized, controlled, parallel group clinical trial conducted at the National Ayurveda Research Institute for Panchakarma (NARIP), Cheruthuruthy, Thrissur District, Kerala, India. The schedule of enrollment, intervention, assessments, and follow-up visits for the study participants is given in Table 1.

Table 1. Schedule of screening, enrollment, intervention assessments, and follow-up in the clinical trial.

Content	Screening	Intervention period					Follow-up period				
		Day 1 (baseline)	Day 8	Day 15	Day 22	Day 30 (treatment end)	Day 60	Day 90	Telephonic follow-up		
									Month 1	Month 2	Month 3
Eligibility evaluation	✓										
Provision of participant information sheet	✓										
Informed consent	✓										
Medical history and demographic profile		✓									
Clinical examination		✓	✓	✓	✓	✓	✓	✓			
Assessment of subjective parameters		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Laboratory test	✓					✓					
Drug compliance assessment			✓	✓	✓	✓					
Rescue medication assessment			✓	✓	✓	✓	✓	✓	✓	✓	✓
Adverse events assessment			✓	✓	✓	✓					
Recurrence of disease							✓	✓	✓	✓	✓

Study Participants

Inclusion Criteria

Participants of either sex will be included if they are in the age group of 16-65 years, have a chronic anal fissure persisting for more than 6 weeks, are capable of and freely willing to provide written informed consent prior to participation in the study, and comply with the study protocol requirements.

Exclusion Criteria

Individuals with comorbidities, including uncontrolled diabetes mellitus, hypertension, anemia, malnourishment caused by systemic disease, fistula in ano, hemorrhoids, perianal abscess, clinically evident fecal incontinence and anal stenosis/fibrosis, inflammatory bowel disease, tuberculous ulcer, malignancies, HIV, clinically significant renal disease, hepatic disease and cardiovascular disease, psychological disease (eg, anxiety and depression), and active substance abuse will be excluded; participants using medications hampering wound healing will also be excluded. Patients with fissures associated with abscess, drug-induced fissures, fissures resulting from external trauma, fissures located at lateral locations, and multiple fissures will be excluded. Participants using oral calcium channel blockers, having sensitivity to the intervention drugs or calcium channel blockers, with frequent history of headaches, or using drugs such as steroids or nonsteroidal anti-inflammatory drugs, either for fissure or any other unrelated disease or condition, will be excluded from the study. Pregnant and lactating women and participants who have used either of the trial interventions within 30 days prior to the trial's randomization will be excluded from the trial.

Study Intervention

Participants in the intervention group will be treated with anal infiltration of murivenna oil for 4 weeks. The medical team will administer the oil through the anal canal using sterilized rubber tubes attached to syringes at baseline. Either the participant or the attendee will receive education on the procedure and will be asked to perform the procedure on subsequent days until the next visit. The participant should lie down for 15 minutes after completing the procedure. In the first week, the patients will receive anal infiltration of 30 ml of murivenna oil once daily, and for the remaining 3 weeks, they will receive anal infiltration of 20 ml of murivenna oil once daily. During the trial period, participants in the intervention group will receive *triphala choornam* (another Ayurvedic medicine; 10 g) at bedtime as a mild laxative, and the participants will be further advised to perform a sitz bath with triphala kashayam once a day. Participants in the control group will be treated with 2% diltiazem gel for 4 weeks. They will be instructed to apply the gel at least 1.5 cm to 2 cm into the anus in the morning and at night after the sitz bath. During the trial period, participants in the control group will receive lactulose syrup (15 ml) at bedtime as a laxative. Participants in both groups will be advised to consume foods rich in dietary fiber and avoid activities that could cause microtrauma to the anus, such as prolonged sitting or traveling on a bicycle or motorcycle.

The murivenna oil was manufactured at the Good Manufacturing Practices (GMP)–certified pharmacy at NARIP, and the triphala choornam was manufactured by a GMP-certified pharmacy at the Central Ayurveda Research Institute, Jhansi, India, as per the respective standards available in the Ayurvedic

Pharmacopoeia of India [10]. Table 2 lists the ingredients of murivenna oil.

Table 2. Ingredients of murivenna oil.

Serial number	Ingredient	Sanskrit name	Quantity	Part used
1	*Pongamia glabra* Vent	Karanja	384 g	Bark
2	*Piper betle* L	Tambuli	384 g	Leaf
3	*Aloe vera* L	Ghritakumar	384 g	Leaf
4	*Erythrina indica* Lam	Mura	384 g	Leaf
5	*Allium cepa* L	Palandu	384 g	Bulb
6	*Moringa oleifera* Lam	Sobhanjana	384 g	Leaf
7	*Borreria hispida* (L) Schum	Madanaghanti	384 g	Whole Plant
8	*Asparagus racemosus* Wild	Shatavari	192 g	Rhizome
9	Coconut oil	__[a]	768 ml	Oil

[a]Not applicable.

Outcome Measures

The primary outcome will be the proportion of participants who undergo complete healing after 4 weeks of treatment. The secondary outcome measures will include the proportion of participants with complete healing after 7 days and 14 days of treatment, respectively. In the present context, we define healing of the fissures as the disappearance of symptoms and the evidence of fissure re-epithelization, which the investigators will record based on an examination. The investigators will categorize the healing as follows at each follow-up visit: none, partial, or complete.

Another secondary outcome measure will be the mean change in pain intensity during or after defecation. The investigators will ask the participants to record their pain intensity during or after defecation over the last 24 hours using a 100-mm visual analog scale at each follow-up. The investigators will also record how long it takes for participants to experience an improvement in pain intensity and cessation of bleeding, as well as how many participants require analgesics for pain relief. The investigators will advise the participants to log their pain intensity, bleeding status, and any need for analgesics in diary log sheets. The team will issue these sheets on the baseline day, as well as on the 8th, 15th, and 22nd days. Investigators will educate the participants on how to fill out the sheets. The participants will be followed up for 5 months after the intervention period to record any recurrence of anal fissure.

Safety Outcomes

Participant-reported adverse events (AEs) during the trial period will be recorded on every scheduled follow-up visit in a structured format. All AEs during the study will be monitored and appropriate care will be provided. There have been no past reported AEs for murivenna anal infiltration [11]. The predictable AEs for triphala choornam include loose stools, obstipation, change in the sense of taste, nausea, skin lesions, and tiredness [12]. Dizziness, headache, weakness, nausea, or swelling of the hands or feet may rarely occur with the use of diltiazem ointment [13]. Diarrhea, bloating, nausea, vomiting, and stomach pain are reported side effects of lactulose syrup. Rarely reported serious AEs include weakness and irregular heartbeat [14].

Withdrawal Criteria

Participants not willing to continue or who are noncompliant with the study procedures (a minimum 80% compliance is essential to continue in the study) will be withdrawn from the study. Participants developing life-threatening complications or any other severe illness because of another pathology that requires urgent treatment will also be withdrawn from the study. Participants developing serious AEs or treatment-induced AEs requiring hospitalization will be withdrawn from the study. It will be ensured that these participants receive appropriate incidental care or are referred to a higher medical facility if required. The reasons for withdrawal will be recorded in the participant's case record form (CRF). The sponsor and the ethics committee will be informed within 2 working days, and will be provided with proper justification.

Sample Size

The sample size was calculated based on the previous differences in the proportion of participants having complete healing of anal fissures between study groups. In a previously published study, 25% of participants had complete healing of anal fissure by the fourth week of treatment with 2% diltiazem gel, and based on the results of another previously published observational study, we assumed that fissures would heal in nearly 60% of participants treated with the trial intervention [11,15]. A sample size of 30 per group is needed to achieve 80% power with a 95% CI. Adding an attrition rate of 10% results in a sample size per group of 33. Therefore, a total of 66 participants will be enrolled in the trial.

Recruitment

Participants from the outpatient department of NARIP diagnosed with chronic anal fissure will be screened for their eligibility to participate in the clinical trial. Informed consent will be obtained from the participants before screening. Participants eligible as per the inclusion and exclusion criteria will be allocated to one of the study groups based on the randomization schedule.

Randomization and Allocation Concealment

A computer-generated randomization number sequence with block randomization will be created by the study statistician independently of the investigators undertaking recruitment and subsequent visits. The statistician will use Stata (version 16; StataCorp) to generate a random sequence, ensuring that each participant is randomly assigned to one of the study arms in a 1:1 ratio. The assignments will be enclosed in sequentially numbered, opaque, sealed envelopes, which will be opened by the participants at the time of enrollment.

Compliance

Compliance with the prescribed medicines will be monitored through a compliance assessment form issued to the participants on each visit. The participants will be instructed to complete the assessment form after each medicine intake or administration. In addition, compliance will be evaluated by counting the number of containers and tubes returned and the approximate quantity of medications used by each participant. A minimum of 80% compliance is essential for the participant to continue the study.

Concomitant and Rescue Medication

The participants will be instructed to inform the investigators before taking any type of medication apart from the trial drugs. The investigators will record the details of the medications and the reason for taking them in the CRF. If there is any medical emergency, the use of any rescue medication will be permitted, and this medication will be recorded in the relevant section of the CRF.

Data Collection and Documentation

Before conducting this clinical study, the investigators and research team will be uniformly trained on Good Clinical Practice (GCP) protocols, trial-specific processes, and documentation. The research team will collect the information and fill in the details in the CRF (Table 1 provides details) for each visit. All documented data will be checked regularly by the principal investigator (PI) to avoid mistakes and omissions. Any modifications made will be clearly visible, and the corrections will be signed and dated by the PI. The data will subsequently be recorded in an e-format and verified as required; the original CRFs will be archived in order with a search catalog.

Statistical Analysis

All statistical data analyses will be performed using SPSS (version 26.0; IBM Corp). Categorical data will be presented as numbers (percentages) and will be compared using the χ^2 test or Fisher exact test. Continuous variables will be described with either means and SDs for data with a normal distribution or median and IQR for nonnormally distributed data. The within-group analysis will be done using a 2-tailed paired sample *t* test for normal data, whereas the Wilcoxon signed-rank test will be used to compare nonnormal data. Comparisons between the experimental and control groups at each time point will be done using an independent sample 2-tailed unpaired *t* test or Mann-Whitney test for normal and nonnormal data, respectively. $P \leq .05$ will be considered statistically significant.

Monitoring

The monitoring committee set up by the sponsor will conduct on-site or virtual monitoring to ensure adherence to the trial protocol and compliance to GCP and the Central Council for Research in Ayurvedic Sciences Research Policy.

Trial Audit

The regulatory authorities, the institutional ethics committee (IEC), or the funding agency will audit the trial, and the investigators will ensure access to all the documents related to the study for the on-site audit.

Ethical Considerations

The study has been approved by the IEC of NARIP (8/16/23/NARIP/Tech meeting/2511; March 31, 2023) and has been registered prospectively at Clinical Trials Registry - India (CTRI) (CTRI/2023/09/057330). The study will be conducted in accordance with the Indian Council for Medical Research National Ethical Guidelines for Biomedical and Health Research on Human Participants (2017). Written informed consent (in English and Malayalam) will be obtained from the eligible participants before screening. All protocol modifications will be communicated to the IEC and funding agency and corrected accordingly in the CTRI. The CRFs will be stored in a secure area, and the participants' data will be coded to ensure confidentiality. The study participants will be given routine medical care, if required, after the completion of the study period. The study participants will be compensated for any financial losses (eg, loss of wages) with an incidental support of Rs 300 (US $3.49) for each visit.

Results

The project was funded in July 2023, and the study period is 24 months. The participant recruitment was started on December 2023. As of August 2024, we have enrolled 50 participants. The data analysis will be complete by June 2025, and the results are expected to be published by August 2025. The study outcomes will be disseminated through research articles in peer-reviewed scientific journals and presentations at national conferences.

Discussion

This randomized, open-label clinical trial is expected to assess the effect of murivenna anal infiltration compared to topical application of diltiazem in the treatment of chronic anal fissure.

Strength

This is the first randomized clinical trial to evaluate the efficacy of murivenna anal infiltration for chronic anal fissure. The quantitative outcome measures included in this trial will yield valid data for clinical use of murivenna for the treatment of anal fissure.

Limitations

The study is being conducted at a single center, and hence participants from only a single area are included in the trial. The study will apply to countries where Ayurveda is practiced. However, the procedure can be performed by trained persons of other countries provided they have regulatory permission to

use murivenna and triphala choornam. Further, single-pack administrations with a fixed dose of murivenna may be considered for better patient adherence.

Conclusion

If this clinical trial proves effective, medical professionals can consider murivenna anal infiltration as a potential alternative therapeutic option, which may further be incorporated into cost-effective management for chronic anal fissure.

Acknowledgments

The Central Council for Research in Ayurvedic Sciences, Ministry of Ayush, government of India, is funding this study. The funding agency also provided technical support for study design and development of the study protocol. We thank the director and assistant directors of the National Ayurveda Research Institute for Panchakarma, Cheruthuruthy, for their immense support and guidance. We would also like to thank Dr Rabinarayan Acharya, director general of the Central Council for Research in Ayurvedic Sciences, for the support.

Authors' Contributions

Conceptualization and writing (original draft): PSKM
Methodological support: IPP, PB, AKR, AA
Writing (review and editing): SJ
Protocol review and administrative support: BCSR, NS, RA

Conflicts of Interest

None declared.

Multimedia Appendix 1
SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) checklist.
[DOCX File , 24 KB - resprot_v14i1e63063_app1.docx]

Multimedia Appendix 2
Consent form and patient information sheet.
[DOCX File , 28 KB - resprot_v14i1e63063_app2.docx]

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Abbreviations

AE: adverse event
CRF: case record form
CTRI: Clinical Trial Registry - India
GCP: Good Clinical Practice
GMP: Good Manufacturing Practices
IEC: institutional ethics committee
NARIP: National Ayurveda Research Institute for Panchakarma
PI: principal investigator

Edited by A Schwartz; submitted 15.06.24; peer-reviewed by S Kulkarni, M Masoodi; comments to author 03.09.24; revised version received 29.09.24; accepted 06.11.24; published 03.02.25.

Please cite as:
Shankar KM P, Puthan Purayil I, Binitha P, Rai AK, Jameela S, Ahmad A, Bhogavalli CSR, Srikanth N, Acharya R
Efficacy and Safety of Murivenna Anal Infiltration Compared to Diltiazem Topical Application in Chronic Anal Fissure: Protocol for a Prospective, Randomized, Open-Label Clinical Trial
JMIR Res Protoc 2025;14:e63063
URL: https://www.researchprotocols.org/2025/1/e63063
doi:10.2196/63063
PMID:

Protocol

ChatGPT-4 Performance on German Continuing Medical Education—Friend or Foe (Trick or Treat)? Protocol for a Randomized Controlled Trial

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Abstract

Background: The increasing development and spread of artificial and assistive intelligence is opening up new areas of application not only in applied medicine but also in related fields such as continuing medical education (CME), which is part of the mandatory training program for medical doctors in Germany. This study aimed to determine whether medical laypersons can successfully conduct training courses specifically for physicians with the help of a large language model (LLM) such as ChatGPT-4. This study aims to qualitatively and quantitatively investigate the impact of using artificial intelligence (AI; specifically ChatGPT) on the acquisition of credit points in German postgraduate medical education.

Objective: Using this approach, we wanted to test further possible applications of AI in the postgraduate medical education setting and obtain results for practical use. Depending on the results, the potential influence of LLMs such as ChatGPT-4 on CME will be discussed, for example, as part of a SWOT (strengths, weaknesses, opportunities, threats) analysis.

Methods: We designed a randomized controlled trial, in which adult high school students attempt to solve CME tests across six medical specialties in three study arms in total with 18 CME training courses per study arm under different interventional conditions with varying amounts of permitted use of ChatGPT-4. Sample size calculation was performed including guess probability (20% correct answers, SD=40%; confidence level of 1–α=.95/α=.05; test power of 1–β=.95; $P<.05$). The study was registered at open scientific framework.

Results: As of October 2024, the acquisition of data and students to participate in the trial is ongoing. Upon analysis of our acquired data, we predict our findings to be ready for publication as soon as early 2025.

Conclusions: We aim to prove that the advances in AI, especially LLMs such as ChatGPT-4 have considerable effects on medical laypersons' ability to successfully pass CME tests. The implications that this holds on how the concept of continuous medical education requires reevaluation are yet to be contemplated.

Trial Registration: OSF Registries 10.17605/OSF.IO/MZNUF; https://osf.io/mznuf

International Registered Report Identifier (IRRID): PRR1-10.2196/63887

(JMIR Res Protoc 2025;14:e63887) doi:10.2196/63887

KEYWORDS

ChatGPT; artificial intelligence; large language model; postgraduate education; continuing medical education; self-assessment program

Introduction

ChatGPT-4 is the latest development in the large language model (LLM) family from ChatGPT. It is said to be trained on more than one trillion parameters, making it one of the most advanced LLMs currently available for generating conversation-style responses to user input. The parameters are the numerical values that determine how a neural network processes input data and produces output data. They are learned from data during the training process, encoding the model's knowledge and skills [1].

Since its launch by OpenAI, the ChatGPT family has stimulated widespread conversation and momentum across different specialties in medicine, as demonstrated by more than 3300 publications related to ChatGPT (or Chat-GPT) indexed in PubMed as of mid-May 2024. Generally, LLMs enable humans to interact and discuss a broad range of topics with artificial intelligence (AI) chatbots. New features of ChatGPT-4 include the acceptance of images as input and the generation of captions, classifications, and analyses, which were not available in earlier versions. Compared to its predecessors, ChatGPT-4 is 82% less likely to respond to inappropriate content requests and 40% more likely to provide factual answers than GPT-3 in internal evaluations [2].

After its success in passing the United States Medical Licensing Examination, performing at a level comparable to that of a third-year medical student [3], these results have been largely confirmed across various medical specialties. Comparisons with different ChatGPT versions and other LLM providers, such as Google, support these findings [3-13]. There are currently two reviews on this topic [14,15], and recent data specific to Germany have been published [16].

In conclusion, there is now a range of data on the use of LLMs in undergraduate education and teaching but less on postgraduate education, such as continuing medical education (CME) [17] or self-assessment programs [4]. Table 1 shows a selection of studies on this topic.

In Germany, CME, which is mandatory for medical specialists, requires earning 250 training points over five years. These CME points can be acquired through further specialization, attending congresses and conferences, and studying medical literature with consecutive answers to specific questions in the text. This approach essentially "credits" the self-study time spent attentively reading a text and then answering questions.

For this study, we decided to use ChatGPT-4 because of its extensive database and ability to enter texts directly. Additionally, the input and operation of ChatGPT are carried out by adult high school students without any prior medical training. This was to differentiate as clearly as possible whether and to what extent LLMs can offer support today. This study aims to provide further insight into whether AI, in the form of LLMs, can support various levels of medical education by correctly answering CME-relevant questions, allowing participants to generate CME credits independently of existing medical knowledge.

Table 1. Data on ChatGPT and postgraduate medical education (continuing medical education or self-assessment programs).

First author	Year	Study	Comparator	Major findings	Conclusions
Sherazi and Canes [4]	2023	Comparative trial	ChatGPT-3.5 versus ChatGPT-4	GPT-4 scored significantly higher than GPT-3.5 on the AUA[a] SASP[b] examinations in overall performance, across all test years, and in various urology topic areas.	Results suggest improvement in evolving AI[c] LLM[d] in answering clinical urology questions. Certain aspects of medical knowledge and clinical reasoning remain challenging for LLM.
Riedel et al [16]	2023	Comparative trial	Performance of ChatGPT on OB/GYN[e] course examinations versus questions from the German medical state licensing examinations	ChatGPT demonstrated consistent and comparable performance across both datasets, providing correct responses at a rate comparable with that of medical students.	ChatGPT has promise as a supplementary tool in medical education and clinical practice, providing efficient and personalized learning experiences and assistance for health care providers.
Noda et al [18]	2024	Comparative trial	ChatGPT-3.5 versus ChatGPT-4 versus Bard (Gemini)	GPT-3.5 and Bard performed similarly while being significantly surpassed by GPT-4. GPT-4's performance was between third- and fourth-year nephrology residents.	GPT-4 outperformed GPT-3.5 and Bard, meeting the Nephrology Board renewal standards in specific years, albeit marginally. The results highlight LLMs potential and limitations.
Ali et al [6]	2023	Comparative trial	ChatGPT-3.5 versus ChatGPT-4 versus user average	GPT-4 significantly outperformed question bank users and GPT-3.5. Increased word count and higher-order problem-solving were associated with lower accuracy for GPT-3.5 not however for GPT-4.	LLMs achieved passing scores on a mock 500-question neurosurgical written board examination, with GPT-4 significantly outperforming ChatGPT.
Watari et al [13]	2023	Comparison study	Chat GPT-4 versus Japanese Residents' performance on GM-ITE[f]	Of 137 GM-ITE questions in Japanese, GPT-4 scores were significantly higher than the mean scores of residents.	GPT-4 demonstrated a tendency to score higher on difficult questions. However, GPT-4 scored comparatively lower on questions testing attitudes toward patients and professionalism requiring an understanding of context and communication.
Guerra et al [5]	2023	Comparative trial	ChatGPT-4 versus ChatGPT, SANS[g] users, medical students, and neurosurgery residents	GPT-4 outperformed ChatGPT exceeding the performances of medical students, neurosurgery residents, and the national average of SANS users across all categories.	GPT-4 significantly outperformed medical students, neurosurgery residents, and the national average of SANS users.

[a]AUA: American Urological Association.

[b]SASP: self-assessment study program.

[c]AI: artificial intelligence.

[d]LLM: large language model.

[e]OB/GYN: obstetrics and gynecology.

[f]GM-ITE: General Medicine In-Training Examination.

[g]SANS: self-assessment in neurosurgery examination.

Methods

Study Design

This is a randomized controlled trial that will be undertaken following the Declaration of Helsinki principles and after approval by the local Ethics Committee of Witten/Herdecke University (S-108/2024, date of approval May 15, 2024) and after registration in a study register (open scientific framework). To obtain representative, comprehensive, and meaningful data, three large German publishing houses (Deutscher Ärzteverlag GmbH, Cologne; Georg Thieme Verlag KG, Stuttgart; and Springer Medizin Verlag, Heidelberg) that offer journals with CME will be evaluated for one volume each of already expired journals (ie, without the possibility of earning credit points) from the fields of internal medicine, surgery, gynecology, pediatrics, neurology, and anesthesiology. The CME tests provided by the publishing houses needed no further adaptation for utilization in the study.

Ethical Considerations

The study protocol which was submitted to and accepted by the Ethics Committee of University Witten/Herdecke (S-108/2024, date of approval May 15, 2024) stated decisively that no monetary or other compensation was to occur. The participant's information was depersonalized by means of not collecting any personal information to begin with, as they were deemed insignificant to the study's results leading to participants enrolling entirely voluntarily. Furthermore, to participate in the study, the students were required to provide a signed informed consent form which all students were given the opportunity to voice concerns and questions and were informed about their ability to revoke their consent without having to provide a reason, while not having to expect any repercussions.

Study Participants

To minimize any influence from prior medical knowledge on the results, adult high school students from North Rhine-Westphalia who are willing to participate will be randomized into three study arms. As high school students can be assumed to be void of relevant medical prior education, the choice to include this group as participants is based on its ability to represent the approximate level of medical knowledge of the general population. The inclusion and exclusion criteria are shown in Textbox 1. It should be emphasized that it is not the high school students who are the participants of the study but the CME course tests to which the methods of the three study arms are applied. Careful considerations were put into the selection of the CME tests screening for images of diseases that students may have deemed disturbing. Such CMEs were excluded. The students were encouraged to voice concerns if the contents of the CME tests resulted in uneasiness. Furthermore, ample opportunity was provided for discussing the students' experiences if deemed necessary by the participants. All these measures aided in minimizing the potential psychological impact of participation in the study. The experience of the participants while attempting to solve the CME tests is not represented in the study's results as they were deemed to exceed the scope of the study. The student's proficiency in the German language was required in the hope of avoiding skewed results based on linguistic incomprehension of the provided literature. The students act purely as "tools," preferably without any medical knowledge of their own.

Textbox 1. Inclusion and exclusion criteria.

Inclusion criteria

- Aged 18 years or older
- Voluntary participation
- No financial compensation
- German as a native language or at a native speaker level
- Ability to operate ChatGPT or other required software

Exclusion criteria

- Being underage
- Refusal to participate
- Insufficient German language skills
- Inability to operate ChatGPT or other required software

Interventions

This trial is designed as a three-armed randomized controlled trial, including one control arm.

Intervention Group 1: "All-In"

In this group, CME-subject-specific text is entered into ChatGPT-4 first, and then, the questions are answered by ChatGPT based on that input.

Intervention Group 2: "Just Answers"

In this group, questions are answered using only the knowledge available in the ChatGPT-4 database at that time, without entering any subject-specific text first.

Control Group 3: "Search and Find"

Participants in this group were asked to answer the questions using only keywords and common sense without any AI support. As the CME were viewed as digital files, the use of "find in text" of the respective document viewing software was permitted.

The approach to having the CME test questions answered in three study arms aims to uncover significant differences in ChatGPT-4's ability to solve the CME tests, as well as assess the varying time required in the individual study arms.

Data Analysis

Sample size calculation was performed for the hypothesis that CME test results will improve from guess probability (20% correct answers, SD= 40%) to pass level (70% correct answers) with a confidence level of $1–\alpha=.95$, that is, $\alpha=.05$, and a test power of $1–\beta=.95$. Therefore, for an independent-samples, two-sided study, a sample size of at least 18 CME training courses per study arm is needed. Nonetheless, since the CME courses, as our study subjects, can be processed repeatedly using different methods without altering them or the methods, a paired-sample study is possible and preferable. This allows the same CME courses to be used in the three study arms. Although a sample size of 9 for a single-sided paired-sample study would be sufficient (only an improvement in CME test results is expected and desired by applying the study arm methods), we decided to take a conservative route and will work with 18 CME tests that will be run through all three study arms. The CME tests treated were randomly chosen from a large number of available tests. Care was taken to ensure that every high school student completed the same number of tests in each arm of the study so that confounding variables in the students were evenly distributed across the three groups. In addition, none of them would work on a single CME test twice using different methods to avoid learning effects. Together with the reuse of the CME tests in the three study arms (paired study, see above), these measures prevent any bias arising from the high school students

as performing tools or the CME tests themselves as study participants. The AI-supported arms would run through within the shortest possible time and in the correct order so that unwanted training of the AI or the students during the process could be ruled out as much as possible. Statistical data analysis will be performed using the open-source software "R" (R Core Team; 2023). The data is presented as mean ± SD. Since the aim of the study is to identify differences in the percentage test results due to the different approaches in the three study arms, the Student *t* test (1-tailed) or the Mann-Whitney *U* test will be used for the pairwise comparison of means between groups, depending on the normality of the datasets. The Shapiro-Wilk test will be used to check normality. Fisher's exact test was used to assess the independence of categorical variables. Benjamini-Hochberg adjustments of *P* values will be applied in multiple comparisons. Values of $P<.05$ were considered statistically significant.

Results

As of October 2024, we have tested five out of the six students we deemed necessary to examine the 18 CME tests across the three study arms. We are set to terminate the data acquisition by November 2024. The ensuing data analysis is predicted to end in December 2024, enabling us to present our results as early as early 2025.

Discussion

Principal Findings

To present the influence of AI as objectively as possible, we deliberately refrained from using medically trained test participants. This allowed us to identify the pure influence of AI. Depending on the degree of success, it was necessary to determine to what extent AI can be permissible in CME training courses and what conditions or protective measures were to be imposed.

Since its launch in 2023, not only the development of ChatGPT but also its integration into the medical context increased rapidly, as shown by the ever more extensive database versions and the steadily growing number of medical publications [3-6,19-23]. However, as the capabilities of AI increase, so does the responsibility of actual intelligence to use it in the best possible way for the benefit of all without causing harm ("primum nihil nocere"). Even if the use of AI to solve examinations, whether student or specialist examinations, has already been investigated several times, there is still a knowledge gap in postgraduate teaching and its effects. Ethical, social, and above all, legal aspects, also need to be clarified.

AI has the potential to revolutionize various aspects of our lives. In medicine, its strength lies in its wide range of possible applications. However, the use of AI in education, training, and specialization must be clearly labeled, as it presents not only opportunities but also weaknesses and threats, particularly with the use of LLMs such as ChatGPT and related programs [1]. The correct use of AI in postgraduate medical education, especially LLMs, still needs to be explored and discussed.

This study aims to show that medical training tests can be successfully completed by medical laypersons using AI, which raises questions about the continued usefulness of current training programs, potential regulations to prevent misuse, and opportunities to harness AI capabilities in this context. Currently, self-study to obtain CME credits is an integral part of German postgraduate medical education. This study's results may have the potential to influence this practice significantly.

The decision to examine ChatGPT's results in three study arms was based on the hope of being able to compare the results obtained while gaining insight into whether the literature backgrounds of the CME were required to generate significantly superior results.

The rationale behind the choice of medical specialties whose CME tests were analyzed in the study results from ChatGPT-4's ability to merely process text. All the medical specialties we chose to include do not predominantly diagnose based on visual symptoms. However, a new investigation on newer ChatGPT versions, which possess the ability to obtain information from images is underway.

Limitations

This study has several limitations. First, only German CMEs are evaluated. Second, only a minority of specialties were chosen. Finally, we completely dispensed CME with image content, as is usual in radiology, dermatology, or pathology, for example, to avoid changing the selectivity.

How potential biases that result from the data that was used in training the AI tools impacted the results of the study is not derivable, as ChatGPT does not possess knowledge in the classical sense. It is rather the case that lexical data is produced based on prior training.

If knowledge acquired through AI-generated literature is retained differently than medically conventionally attained knowledge is yet to be assessed in future research.

Conclusions

The impact on current on future CME programs should be considered as the certified means of personalizing one's medical education remains scarce. AI could play a role in tailoring continuous education to personalized needs and, for example, adapting the modules based on prior results to target potential individual shortcomings. The role AI could play in medical education provided by university faculties, as well as personalized learning programs surely merits further investigation [24-26].

Acknowledgments

This research received no external funding.

Data Availability

The datasets generated during or analyzed during this study are not yet publicly available as they are yet to be analyzed but can be made available from the corresponding author upon reasonable request.

Authors' Contributions

The conceptualization was a result of cooperation by TS, DG, AB, and CB; the formal analysis was performed by CB, AB, DG, and TS; funding acquisition was accomplished by DG; our methodology was developed by TS, FB, and JE; project administration was supervised by TS and DG; the original draft was written by CB and AB, and it was then rewritten, edited, and reviewed by TS, JE CB, AB, FB, SCT, and DG. All authors have read and agreed to the published version of the manuscript.

Conflicts of Interest

None declared.

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Abbreviations

AI: artificial intelligence
CME: continuing medical education
LLM: large language model

Edited by A Schwartz; submitted 02.07.24; peer-reviewed by CN Hang, X Liu, B McGowan; comments to author 09.10.24; revised version received 02.12.24; accepted 27.12.24; published 06.02.25.

Please cite as:
Burisch C, Bellary A, Breuckmann F, Ehlers J, Thal SC, Sellmann T, Gödde D
ChatGPT-4 Performance on German Continuing Medical Education—Friend or Foe (Trick or Treat)? Protocol for a Randomized Controlled Trial
JMIR Res Protoc 2025;14:e63887
URL: https://www.researchprotocols.org/2025/1/e63887
doi:10.2196/63887
PMID:

Protocol

Proposal and Strategy for Nursing-Led Research: Protocol for an Unfunded Clinical Trial

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Abstract

Background: Clinical trials are known to provide cause-and-effect results and data with low levels of bias. However, a lack of funding for clinical trials, which are considered expensive, means that academic sponsors are rarely able to conduct them. Academic trials are considered highly relevant for the valuable results they provide for clinical questions. This is why initiatives to conduct unfunded clinical trials have been identified as an important issue to pay attention to in future studies. Therefore, we present our initiative through Rogers' theory, which is highlighted in the literature for diffusing innovative change across organizations.

Objective: The purpose of this paper was to describe our case regarding management for conducting a nonfunded nurse-led clinical trial based on our previous low-interventional clinical trial across a specific health organization and with nurses.

Methods: We conducted a low-intervention, nonexternally funded clinical trial using the human and material resources available on site. We managed our trial in a clinical trial unit where there were staff, sources, and ongoing commercial clinical trials. We conducted our trial based on an ongoing commercial trial, and, to do so, we needed behavioral changes. We relied on Rogers' theory, and we identified strengths and barriers to change by analyzing actors' characteristics, perceptions of the situation, motivation, and information. Afterward, we divided the staff according to their characteristics related to innovation and change into permanent staff (research staff with a culture of change) and nonpermanent staff (nursing staff with occasional attendance and resistance to change). First, we preselected only those nurses who were more aware of change (innovators and pioneers) to participate in our trial to avoid a massive rejection, and later, we asked others to join (late adopters). We followed Rogers' phases. For research staff who were aware of the funding, we focused on the "persuasion phase," while for nursing staff, we mixed the "knowledge and persuasion phases" and used pioneers and early adopters as a positive example for other nurses as well as nonfinancial incentives (persuasion). Our trial consisted of different methods of vein cannulation, which was performed in the ongoing commercial trial. Thus, the entire development of our low-interventional clinical trial was conducted without interfering at any point with the parallel commercial clinical trial.

Results: Our management allowed effective conduct of our study, and we met our aims without external funding and without ethical impact during the commercial clinical trial. Costs remained low, primarily because the major expenses were covered by the commercial clinical trial as an inherent part of its design.

Conclusions: Our initiative to conduct a low-intervention clinical trial with no or limited funding was cost-effective. This initiative can be used by researchers with valuable academic research questions who do not have the external funding to conduct studies.

Trial Registration: ClinicalTrials.gov NCT04027218; https://clinicaltrials.gov/study/NCT04027218

International Registered Report Identifier (IRRID): RR1-10.2196/56062

(JMIR Res Protoc 2025;14:e56062) doi:10.2196/56062

KEYWORDS

clinical trial; academic trial; nonfunded; commercial; nurse-led; low intervention; health product; peripheral venous cannulation; PVC; protocol; randomized controlled trial; RCT; adults; healthy adults; funding; academic sponsors; cause-effect results; insurance

Introduction

Background

Clinical trials are known to provide cause-and-effect results and usually yield high-quality data due to low levels of bias [1]. In addition, clinical trials not only provide the best context for advancing clinical research and health care but also create opportunities to reduce health care costs [2]. Moreover, clinical trials involve key personnel, such as nurses, who can be recruited and trained to carry out a protocol [3]. In the case of clinical research nurses, their ability to work independently has been recognized, but they face practical, ethical, and resource challenges [4]. In particular, the lack of funding for clinical trials, which are considered expensive and involve additional effort (especially investigator-led clinical trials), leads to voluntary activities [5]. It should also be noted that academic sponsors are rarely able to conduct trials without external funding [6]. Therefore, it has become clear that there is a need for increased coordination to ensure that robust research is conducted and to adopt adaptive trial design strategies to respond to the rapidly evolving evidence landscape [7].

Nevertheless, academic trials (ie, trials in which the comparator is usually standard clinical practice [1]) are considered highly relevant due to the valuable results they provide when investigating clinical questions [8]. Academic trials enable comparative data and may lead to changes in practice [5], but researchers in such trials face multilevel challenges, most notably applying for grants and managing funds to pay for participation or study-related injuries [9].

In Europe, between 10% and 30% of clinical trials are conducted by academic or noncommercial sponsors [8], and only a limited number of nurses receive support through funding mechanisms [10] despite evidence showing that trials led by a nurse or physician have noninferior results [11].

Therefore, although our trial is registered at ClinicalTrials.gov (NCT04027218) and our results are published [12], initiatives to conduct nonfunded clinical trials, such as low-interventional clinical trials, have been identified as a major issue to be targeted in future studies [8]. However, implementing initiatives, new ideas, or innovative processes across an organization is challenging. The literature suggests the use of Rogers' curve or Rogers' diffusion of innovation theory to introduce innovation because it applies within and across organizations [13], such as in schools and for teachers [14,15] as well as in health care organizations [16].

Objective

The purpose of this paper was to describe our case of managing the conduct of a nonfunded, nurse-led clinical trial across a specific health organization and with nurses.

Methods

The Field and Study Context

The aim of our initiative was to conduct a phase 4 low-interventional clinical trial without external funding that resulted in low bias, was of high quality, and used available onsite human and material resources.

Thus, we managed our trial in a clinical trial unit where staff and sources were already available. However, up until our trial, almost all clinical trials in this unit evaluated drugs, were financed by the pharmaceutical industry, and involved procedures, particularly venipuncture by nurses, that were performed in the same way.

In other words, the nurses and other research staff in the unit did not participate in a culture of conducting different clinical trials, such as our clinical trial involving medical devices and that proposed changing "the assembly line." In our case, a clinical trial was conducted with different forms of venipuncture, which had previously always been performed using the same technique. This involved changing certain positioning and behavioral barriers.

In the clinical trials unit, there were fixed staff (researchers) and variable staff (nurses). The variable staff consisted of a pool of 20 to 25 nurses who came on occasional days to support the clinical trials but whose main activity was in other hospital departments.

Management and Sampling Access

Rogers' 5 stages of innovation decision-making consist of knowledge, persuasion, decision, implementation, and confirmation information [16]. There are different roles to implementing change. His theory shows that the following roles exist in certain proportions: innovators (2.5%), early adopters (13.5%), adopters (34%), late adopters (34%), and nonadopters (16%). He also considered the minimum threshold for change to be the sum of innovators and early adopters.

Thus, we contemplated the "knowledge phase" for the fixed and variable staff. In the case of workers in the fixed staff component, they were already aware of the problem of obtaining funding to pay employees, so we only focused on the "persuasion phase" as we aimed on getting approval from the director of the unit, who introduced our clinical trial to the fixed and variable staff members.

Another exception had to be made at this stage regarding the expert in blood sample analysis (research staff), as we needed him to analyze our indicators in addition to those that were requested for the unit's trials. Persuasion consisted of suggesting authorship in publications given his interest in his scientific career and the potential for indirect income.

For the variable staff (nurses), we mixed the "knowledge and persuasion phases." We chose to invite only nurses who had the most knowledge or awareness of the change (knowledge) to participate in our clinical trial. In other words, we preselected the nurses (innovators and early adopters) to avoid mass rejection of the trial and to try to allow other nurses to see that a few nurses (innovators and early adopters) had seen this change as a positive step (persuasion). We did not conduct a survey to classify the nurses according to Rogers' roles because we knew the pool of our nurses well and we already knew their positions.

Specifically, to carry out the research, the nurse in charge of this study could not offer any direct payment. We offered to thank the staff in publications, and if anyone wanted to play a more active role in writing manuscripts about this study, they would be positively considered for authorship of articles resulting from the study. The publications are considered professional merit in our country and serve to increase the salary in one's professional career.

Nurse innovators and early adopters agreed to appear in acknowledgements (they did not want to have a more active role) and contribute to the culture and advancement of innovation and research in the nursing profession for colleagues who did not have this insight (late adopters mainly).

In the implementation phase, some nurses (adopters) asked the nurse in charge of the study about the new technique being performed by some collaborating nurses in this study. Therefore, we took advantage of this interest to invite more than one-half of the pool of nurses (adopters and late adopters) to participate in our study. We had a small group of nurses who we knew would not be interested in participating (nonadopters), and they were the last to be invited to participate and declined.

In relation to the fixed staff (research staff), we only focused on the "getting to know" and "confirmation" phases, as they already had knowledge of the project. They were observers, and we only gave them a 20- to 30-minute training on how the study was going to be developed in the unit at the same time a phase 1 clinical trial was being conducted (which was the routine work of the unit) and sought their confirmation to be aligned with the project.

Trial Design

Although our clinical trial protocol was already registered at ClinicalTrials.gov and is freely accessible, we deemed it necessary to provide a brief summary of our trial design so that our management of the field and study context were fully understood.

Study Sample and Eligibility Criteria

Our participants were recruited from the population of individuals who provided written informed consent for the primary clinical trial at the unit (phase 1 bioequivalence study). As shown in Table 1, on the night of first admission (visit 2 in phase 1), participants in the phase 1 bioequivalence study were invited to enroll in our phase 4 clinical trial. They signed the informed consent at that time. Participation in our phase 4 clinical trial was voluntary. We informed participants that this study was a nonfunded study and that no incentive would be provided beyond the payment they received from the phase 1 trial. We also communicated that the potential benefit for them was the expected effective interventions hypothesized in our phase 4 trial (Table 2).

The inclusion and exclusion criteria were the same as those for the bioequivalence trial. In addition, we added 3 criteria for our phase 4 clinical trial that were also compatible with the criteria for the phase 1 trial. These 3 criteria were 6 hours to 8 hours of fasting before vein cannulation, fluid intake limited to ≤500 mL 6 hours to 8 hours before venous cannulation [17], and having been a former participant in a bioequivalence clinical trial at our hospital.

Table 1. Procedures of the phase 1 clinical trial.

Procedures	Visits												
	0	1. Screening[a]	2. Day 1 of first entry[b]	3. Day 2 of first entry[c]	4. Day 3 of first entry[d]	5. Day 4 of first entry[e]	6. Day 4 of first entry[f]	Washout[g]	7. Day 1 of second entry[h]	8. Day 2 of second entry[i]	9. Day 3 of second entry[j]	10. Day 4 of first entry[k]	11. Day 4 of first entry[l]
Informed consent	✓	—[m]	For the phase 4 trial	—	—	—	—	—	—	—	—	—	—
Inclusion and exclusion	✓	✓	✓	✓	—	—	—	—	—	—	✓	✓	—
Concomitant medications	—	✓	✓	✓	✓	✓	✓	—	✓	✓	✓	✓	✓
Blood and urine analysis	—	✓	—	—	—	—	—	—	—	—	—	—	—
Medical history	—	✓	—	—	—	—	—	—	—	—	—	—	—
Physical examination	—	✓	—	✓	—	—	—	—	—	✓	—	—	—
Height	—	✓	—	—	—	—	—	—	—	—	—	—	—
Weight	—	✓	—	✓	—	—	—	—	—	✓	—	—	—
Electrocardiogram	—	✓	—	✓	—	—	—	—	—	✓	—	—	—
Vital signs (HR[n], BP[o])	—	✓	—	✓	—	—	—	—	—	✓	—	—	—
Tympanic temperature	—	✓	—	✓	—	—	—	—	—	✓	—	—	—
Peripheral vein catheterization	—	—	—	✓	—	—	—	—	—	✓	—	—	—
Pharmacokinetic blood basal sample	—	—	—	✓	—	—	—	—	—	✓	—	—	—
Drug administration	—	—	—	✓	—	—	—	—	—	✓	—	—	—
Pharmacokinetic blood samples	—	—	—	✓	✓	✓	✓	—	—	✓	✓	✓	✓
Venepuncture	—	—	—	—	✓	✓	✓	—	—	—	✓	✓	✓
Adverse events record	—	—	✓	✓	✓	✓	✓	—	✓	✓	✓	✓	✓

[a]Up to 3 days after visit 0.

[b]1 week after screening.

[c]10 hours after visit 2.

[d]24 hours after visit 3.

[e]48 hours after visit 4.

[f]72 hours after visit 5.

[g]1 week after visit 6.

[h]Up to 24 hours after washout.

[i]10 hours after visit 7.

[j]24 hours after visit 8.

[k]48 hours after visit 9.

[l]72 hours after visit 10.

[m]Not applicable.

[n]HR: heart rate.

[o]BP: blood pressure.

Table 2. Procedures of the phase 4 clinical trial.

Procedures	Visits										
	0	1	2	3	4	Washout	5	6	7	8	9
Informed consent	✓	—[a]	—	—	—	—	—	—	—	—	—
Inclusion and exclusion	—	✓	—	—	—	—	—	✓	—	—	—
Vein perception	—	✓	—	—	—	—	—	✓	—	—	—
Sequence allocation	✓	—	—	—	—	—	—	—	—	—	—
Intervention or comparator	—	✓	—	—	—	—	—	✓	—	—	—
Pain assessment	—	✓	—	—	—	—	—	✓	—	—	—
Hemolysis	—	✓	—	—	—	—	—	✓	—	—	—
Skin type assessment	—	✓	—	—	—	—	—	—	—	—	—

[a]Not applicable.

Randomization, Allocation, and Sample Size

Participants were randomized to 1 of 3 interventions and one of the sequences of applying those interventions within 2 periods. Thus, we allocated sequences of 1 intervention and a comparator (1 sequence for each participant).

As Figure 1 shows, randomization was performed at visit 0 of the phase 1 clinical trial after informed consent form was obtained and before participants were screened for inclusion and exclusion criteria for both the phase 4 and 1 trials. As shown in Table 3, we designed 6 sequences.

The study was carried out in the clinical trial unit at our hospital, where bioequivalence clinical trials (phase 1) were performed with groups of 12 participants. Accordingly, we duplicated the 6 sequences used for each group of participants.

Figure 1. Combined fieldwork of the phase 1 and 4 clinical trials. Pk: pharmacokinetics; v: visit.

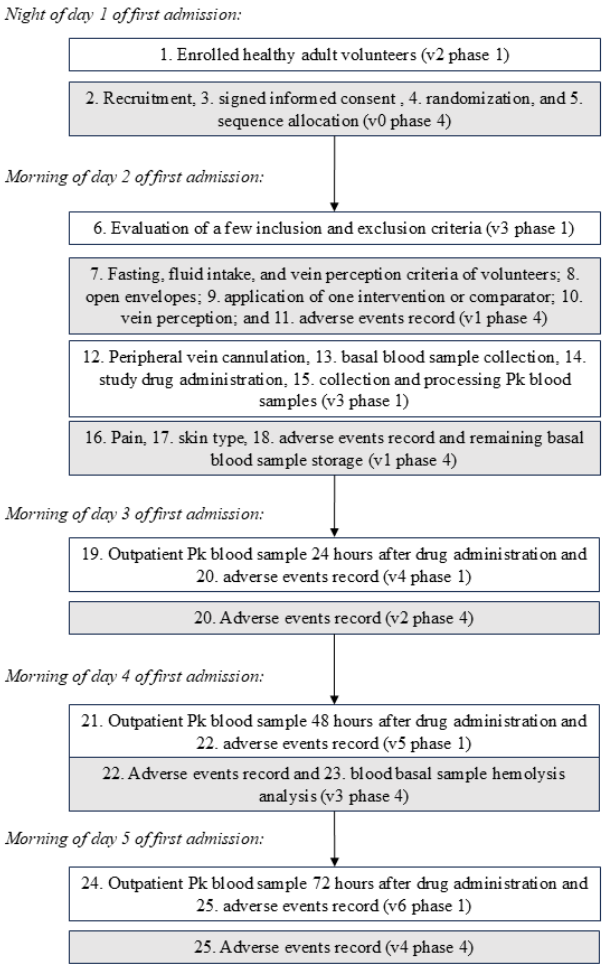

Table 3. Description of the sequences.

No	Sequence	First period	Second period
1	Dry topical heat, comparator	Dry topical heat	Comparator
2	High pressure, comparator	High pressure	Comparator
3	Dry topical heat and high pressure, comparator	Dry topical heat and high pressure	Comparator
4	Comparator, dry topical heat	Comparator	Dry topical heat
5	Comparator, high pressure	Comparator	High pressure
6	Comparator, dry topical heat and high pressure	Comparator	Dry topical heat and high pressure

Interventions and the Comparator

Our interventions, given that we designed the additional eligibility criteria, were compatible with the interventions planned in the bioequivalence clinical trial. In the bioequivalence clinical trial, venous cannulation is always performed to obtain blood samples, and we established the following interventions and comparator to avoid interfering with those in the phase 1 trial. First, to apply dry topical heat, 2 bags were heated and placed on each participant's forearm for 7 minutes while an elastic compressor was applied [18]. Second, high pressure was applied via a sphygmomanometer cuff set at 100 mm Hg [19]. Third, for the combined intervention, dry heat was applied followed by pressure per interventions 1 and 2. The 3 interventions had a common comparator (ie, the elastic compressor), which was provided by the hospital and used according to CLSI GP41-A6 guidelines [20], as was performed in the phase 1 clinical trial.

Measures

Vein perception was assessed using the Venous International Assessment scale, which is a validated scale [21]. Vein cannulation was performed using a 20-gauge diameter catheter, and an EDTA K2 blood sample was collected using a Vacutainer blood collection tube (Becton, Dickinson and Company). Pain was assessed using the visual analogue scale, which is validated for acute pain [22]. Skin type was assessed using the Fitzpatrick scale, which has been previously validated [23]. Adverse events were assessed with a severe causality algorithm from the World Health Organization (WHO) [24].

The aforementioned materials are routinely used by nurses in the clinical trial unit and in clinical practice at our hospital. The nurses were familiar with the scales except for the Venous International Assessment scale, Fitzpatrick scale, and WHO algorithm. Therefore, collaborative nurses were trained to administer these tools. We also measured hemolysis in our blood samples, which was performed by an expert who routinely used a NanoDrop 2000 Spectrophotometer (ThermoFisher Scientific) at the unit. Again, we used human and material resources already available in the unit.

Adherence and Monitoring

Our phase 4 clinical trial involved the use of nonharmful interventions. Our interventions delayed vein cannulation by only 7 minutes (heat application), and the data collection did not require extra visits or blood draws. Because our phase 4 clinical trial was a nonfunded study, economic incentives for participants came only from the phase 1 commercial clinical trial. Therefore, the phase 1 trial guaranteed a low dropout rate and adherence to our clinical trial.

According to the low-interventional clinical trial regulations [25], an external monitor was not provided, and the nurse principal investigator conducted the study.

Ethical and Financial Considerations

The research protocol and methodology were approved by the Ethics Committee of the Hospital de La Princesa (Madrid, Spain) under code ECYPVEN-H/17 and registration number 3113.

This was considered a low-interventional clinical trial because "the intervention poses only very limited additional risk to the subject compared to normal clinical practice." We performed our clinical trial based on a phase 1 clinical trial that involved a vein cannulation procedure to ensure participant safety in relation to the same procedure in other clinical trials. Thus, we did not require specific insurance for any potential injury to participants; they were covered by the phase 1 insurance or health system insurance. Data from participants in the phase 1 clinical trial were coded for our study to ensure privacy [25].

Both clinical trial protocols and informed consent forms were in accordance with the Declaration of Helsinki [26]. Specifically, as our clinical trial was concerned with nursing, announcements and information about this trial were made by the nurse who was the principal investigator.

The participants did not receive any remuneration for participation in the low-intervention trial or any other type of compensation.

Furthermore, none of the information appearing in this article allows the identification of data or images of the participants.

We calculated that less than €200 (US $209.50) would be sufficient to cover the overall costs of our phase 4 study, including materials required for our interventions and comparators: 6 pairs of carob seed bags for heat application (4 pairs for use and 2 pairs for backup), 5 sphygmomanometers for pressure application (4 for use and 1 for backup), and 4 timers.

The aforementioned cost overrun was mainly for materials, as the rest of the costs were covered because we used resources from the clinical trials unit where the phase 1 study was conducted.

Blinding

This open study was justified by the complexity of masking interventions (heat or pressure) and operators, as proposed by the CONSORT (Consolidated Standards of Reporting Trials) Statement for Randomized Trials of Nonpharmacologic Treatments [27]. Only the biologist who analyzed plasma sample absorbance was blinded [27].

Results

Our management was effective for conducting a low-intervention study, and we met our objectives without external funding. We conducted a clinical trial in the clinical trial unit of Hospital Universitario de La Princesa (Madrid) during the months of June 2017 and July 2017 with 59 healthy adults who were randomly allocated to 1 of 3 interventions: (1) using dry topical heat for 7 minutes produced by 2 hot seed bags (n=21), (2) applying controlled pressure from a sphygmomanometer inflated to 100 mm Hg (n=18), and (3) combining heat and pressure (n=20). We found that the pressure intervention (n=18) was the most effective for relieving pain, followed by heat (n=21) and the combined intervention (n=20). Furthermore, hemolysis was not significantly affected by any of our interventions, and no serious adverse events occurred [12]. None of the participants dropped out of the study, and a total of 10 nurses who had at least 1 year of experience in the clinical trial unit contributed to the fieldwork of the trial.

Discussion

Main Findings

Our strategy was effective for carrying out a low-intervention, academic clinical trial, as claimed by previous studies. Therefore, we were able to provide an answer to a problem detected in the scientific literature [8].

Our results [12] were consistent with those of previous parallel clinical trials that were funded by (1) a foundation and involved a specific device provided by a manufacturer [18] and (2) a grant [28].

Comparison With Prior Work

Similar to our study sample of 59 participants [8], additional studies have been conducted using 68 participants per group [18] and 36 and 34 participants in 2 groups [28]. In contrast, our study was a crossover, nonfunded study [12]. Although a previous study stated that noncommercial clinical trials recruit fewer participants than commercial trials [1], presumably due to the lack of financial compensation, we could not confirm that statement based on our results.

In addition to the clinical benefits, our results supported our strategy and showed how nurses, who receive relatively little funding (39.4% of total National Institutes of Health funding), can benefit from research funding [29] and lead a high-quality clinical trial without funding. Nurses in a variety of positions are involved in clinical trials, including clinical research nurses (69.7%), research nurse coordinators (17.9%), nurse practitioners (4.4%), and clinical and administrative or program support staff (8%) [30], even if they are not principal investigators [3]. Many are involved in oncology clinical trials [30]. In contrast, our study was conducted with a nurse as the principal investigator [12].

Our trial management was in accordance with the standard framework of Core Competency Domains by the Joint Task Force for Clinical Trial Competency, which consists of 8 domains [31]. Specifically, our study met domains 1 (research design) and 5 (study and site management), which describe a cost-effective, low-interventional clinical trial design and a commercial clinical trial design, respectively. Additionally, domain 7 (leadership and professionalism) [31] was met because our principal investigator was a nurse scientist with a PhD, which the literature highly recommends for research management [3,32].

According to the Rogers' management curve or theory, contextual factors are crucial and, although we were in a suitable environment (clinical trial unit), both the variable and fixed staff had standardized working procedures to reduce variables. Therefore, paradoxically, we agree with other studies [16] that negotiations (persuasion) for the diffusion of innovation are the biggest complication in those environments where there is no routine development of innovative concepts. However, the fixed staff members were easier to persuade due to their professional profile and career and the possibility of authorship in publications or other merits. Furthermore, unlike the aforementioned study, we did not apply the 5 stages of this theory to all variable and fixed professionals, as the latter had a more advanced research and innovation culture.

We also agree with Lundblad [13], as we were able to establish this theory across the health care organization and in a field where work is dedicated to improving research but the traditional theoretical basis does not include diffusion innovation, as in the variable nursing staff. For this reason, we consider our work to be groundbreaking in a collective that is resistant to change [33]; therefore, we could be introducing an innovative initiative according to Rogers' curve.

We also agree with the previous study that less complex innovations (such as our research procedure of vein cannulation) are adopted more quickly than those where the adopter must develop new skills and understanding [16].

Unlike the previous study, we did not conduct an interview to categorize staff profiles according to Rogers' theory, because we believed we knew our pool of nurses (variable staff) and research staff (fixed staff) well and did not need to obtain more information for profile categorization.

We consider that we used the theory adequately, as we were able to conduct our clinical trial and conclude with published results. Furthermore, we agree that this theory is very social, and it depends mainly on two important factors: interpersonal communication relationships and similar actors [13,16]. These were nurse to nurse in our study, rather than doctor or employer to nurse. In our study, the nurses in the pool had very strong rapport and even had a WhatsApp group. Because they asked each other questions through the chat group, they were able to diffuse this innovation. As recommended by Afraz et al [16],

we used the innovators as a factor for promoting diffusion, and we demonstrated that it was effective.

A total of 36.5% of registered clinical trial protocols are sponsored by universities, hospitals, and other academic and nonprofit agencies worldwide [34], although the rate is lower in Spain (ie, 10%-30%) [8]. Noncommercial registered protocols are mainly for phase 4 studies and unmasked, controlled clinical trials. Additionally, only 39.4% of noncommercial protocols registered in ClinicalTrials.gov were published in peer-reviewed scientific journals [8]. However, our nonfunded study was an open phase 4 clinical trial registered in a database and published in a peer-reviewed scientific journal [12].

Additionally, we believe that our nonfunded management benefited from industry-sponsored clinical trials in study design, site selection, quality recruitment support, clinical coordinator centers, and access to study databanks, as Laterre and François [35] proposed that academic and industry trials should be constructive and not opposed.

Controversial statements declare that, compared with commercial studies, academic clinical trials are less restrictive with regards to inclusion and exclusion criteria, have less complex protocols, and have higher external validity than internal validity [1]. Others have reported that methodology clinical trials are as valid as commercial and noncommercial clinical trials; however, blinded and multicontinental trials that are usually conducted by major pharmaceutical companies are still considered superior [34]. Conversely, we believe that academic trials could be as restrictive as commercial trials if they are designed like commercial trials, given that our results were in line with such funded studies [18,28].

Our findings also agree with those of Fuentes Camps et al [8], who highlighted the scarcity of economic resources and suggested that initiatives such as low-interventional clinical trials could fill the void. Our low-interventional management optimizes scientific research by conducting a clinical trial at a cost of approximately €153 (US $186) and without ethical concerns or injury to the participants of the commercial clinical trial.

Clinical trials require specific insurance to cover the potential risks; thus, funding is required [36]. However, clinical trials funded by grants, public institutions [5], or associations [36] usually do not have all their costs met [36]. Therefore, our strategy for a low-interventional trial could be a solution when little or no funding is available. Commercial clinical trials could assume 15% to 22% and 11% to 29% of total costs for clinical procedures and administrative concerns, respectively [5].

Additionally, project management was identified as having a high impact on the total costs of a clinical trial [5] and is usually performed by a coordinator [26]. We agree with the proposal by Bevans et al [30] that a principal investigator who coordinates a single-center clinical trial reduces costs without assuming extra effort.

Contrary to our management, a previous study proposed that a better choice to decrease research costs would be to add a hospital employee to the research team instead of modifying the study design [37]. Although the research question guides the study design [37], we consider that, sometimes, a modified study design could contribute superior benefits from a nonfunded clinical trial for the original or similar research purposes compared with foregoing the study altogether.

As a reflection, if the proposed low-intervention study were to be developed in tandem with a nonfunded study, we consider that, obviously, the benefits of funding and use of resources would be lost. Therefore, when considering the possibility of such studies, one of the main criteria is likely to be that the context or the study on which it is based is funded or standard practice, as is the example of the study proposed here.

It may not be so much a question of whether to obtain funding but rather of making existing funding more efficient and taking advantage of the sometimes scarce resources available for research. We believe that rigorous, relevant, pertinent, and original research can be carried out, even without funding, if creative solutions are devised, such as the one that this article aimed to provide: taking advantage of existing resources to carry out low-intervention but rigorous studies from an experimental point of view. In this sense, would higher quality research be possible if funding was available? It seems obvious that the answer is yes but not in the sense of being rigorous or methodologically robust (which is mandatory when it comes to research). Rather, the answer is related to the sense of opportunity, of deciding what I want to investigate, and when and where I am going to do it. For the rest, we believe that it is even an obligation in the use of resources.

Most of the literature consists of partnership sponsors [10], budgeting [1,5], qualifications of research staff [31], or data contributions from registries [34]. However, a description of a nonfunded, low-interventional clinical trial and its corresponding results was identified for analysis in future research [8]; thus, no comparison is possible in the current article. Therefore, we suggest that our management description can be used for other researchers to conduct a clinical trial without funding or with limited funding.

Strengths and Barriers of the Field and Study Context

According to Rogers' theory, the adoption process depends on the characteristics of actors (such as values, skills, status), situational perception (such as norms, economical aspects), motivation, and information [16]. Thus, adoption depends not only on the individual position, which is conditioned by the collective one, but also on other environmental factors. In our specific noneconomic health care environment, we found strengths and barriers to change.

Regarding strengths, of all the nurses in the hospital, the nurses (variable staff) working in the unit were the most aware of research and innovation. However, the fixed research staff were aware and accepted that additional things were conducted, but they did not collaborate actively; they were only observers.

Regarding barriers, we cannot forget that the nursing profession is one of the least sensitive to innovation and only collaborates with economic incentives. Moreover, the fact that it is a variable component makes constancy difficult, both in the introduction of a new procedure and in the acceptance of changes. Although

they were offered recognition in publications or similar, the big barrier was the lack of a direct financial incentive.

Limitations

Our case is not applicable to all commercial trial designs, but it enables the creation of an option of management that can be adjusted according to the study field and commercial trial. Although our strategy could not guarantee the optimum design for ambitious aims, the proposed strategy could make it possible to conduct a nearly optimal study design and, therefore, provide results for research progress.

This article provides a strategy for conducting noncommercial or nonfunded clinical trials by including similar procedures in a funded study in order to reduce budget, personnel, and the cost of providing participants with extra conveniences.

Consequently, another limitation could be that knowledge about research methodology along with change theories or strategies is required. In this study, there was a research nurse with knowledge about change theories for innovation; therefore, we suggest this innovative management to help anyone who has to face a similar challenge.

Conclusion

Our strategy is a cost-effective means of conducting a low-interventional clinical trial with no funding or with limited funding. Furthermore, this strategy can be used by nurse researchers or other researchers to facilitate clinical trial design and site management to provide high-quality results without ethical concerns. Ideally, nurses engaged in care themselves should be able to pose research questions like research nurses, develop them as such, and not be figures with necessarily distinct roles.

Data Availability

The data sets generated and analyzed during this study are not publicly available but are available from the corresponding author on reasonable request.

Conflicts of Interest

None declared.

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Abbreviations

CONSORT: Consolidated Standards of Reporting Trials
WHO: World Health Organization

Edited by A Mavragani; submitted 04.01.24; peer-reviewed by D Moralejo; comments to author 15.07.24; revised version received 22.07.24; accepted 01.12.24; published 10.02.25.

Please cite as:
Simón-López LC, Ortuño-Soriano I, Luengo-González R, Posada-Moreno P, Zaragoza-García I, Sánchez-Gómez R
Proposal and Strategy for Nursing-Led Research: Protocol for an Unfunded Clinical Trial
JMIR Res Protoc 2025;14:e56062
URL: https://www.researchprotocols.org/2025/1/e56062
doi:10.2196/56062
PMID:39927682

Protocol

Effectiveness of Adaptation of a Resilience-Building Intervention Among Individuals With Adverse Childhood Experience: Protocol for a Randomized Controlled Trial

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Abstract

Background: The impact of adverse childhood experiences (ACEs) has been the focus of most studies for the past decade. There is an indication that developing resilience can help youth overcome these ACEs.

Objective: This article presents a study protocol for a randomized controlled trial (RCT) to investigate the effects of a resilience-building intervention on psychological well-being, coping strategies, stress, quality of life, resilience, resource finding, and resilience among individuals affected with ACEs in Malaysia.

Methods: The is a 2-armed, single-blind, RCT, whereby 50 participants (25 in each group) with ACEs will be randomly assigned to intervention and control groups. The former will be exposed to a resilience-building program (R2), which entails a multisystemic approach to resilience and recognizes the importance of rugged qualities and access to resources among individuals affected with ACEs. The intervention will be delivered via internet-based by a facilitator and broadly divided into 5 sessions, focusing on self-exploration and social support, coping techniques and coping skills, resource finding, spirituality, and resilience building. Meanwhile, the control group participants will not receive any form of intervention. Saliva samples will also be collected from both groups and assessed for salivary cortisol levels. Outcome measures will be assessed during baseline and postintervention using validated instruments. Another follow-up measurement will be conducted 4 weeks later.

Results: The clinical trial has been registered with the Australia New Zealand Clinical Trials Registry. Ethical approval was obtained from the Research Ethics Board at the National University of Malaysia (UKM PPI/111/8/JEP-2021-894). A total of 28 participants have been recruited to the RCT Participant recruitment will be completed by January 2025. The final analysis will be conducted by March 2025.

Conclusions: This is among the first studies to provide evidence in the context of RCTs for resilience-building intervention that combines self-report and physiological measures (ie, saliva and heart blood pressure) among individuals with ACEs. The findings will assist relevant authorities in the health and policy sectors to develop effective strategies for addressing the negative impacts of ACEs on the vulnerable population in Malaysia.

Trial Registration: ACTRN12622000604707; https://www.anzctr.org.au/Trial/Result/DataSharingStatement.aspx?id=383614

International Registered Report Identifier (IRRID): DERR1-10.2196/56826

(JMIR Res Protoc 2025;14:e56826) doi:10.2196/56826

KEYWORDS

adverse childhood experience; resilience; resilience-building intervention; young adults; stress; psychological well-being

Introduction

Background

Adverse childhood experiences (ACEs) are stressful or traumatic events faced by individuals that could have a pervasive impact throughout the developmental stages of their lives through psychological and physiological mechanisms, particularly when the consequences are neglected [1]. ACE can have profound effects on individuals of all ages [2,3]. These experiences may culminate in disrupted development of brain areas that are stress-sensitive [4,5], which are reflected in behavioral alterations.

For example, individuals with ACEs may face challenges with emotion regulation, thereby leading to diverse negative consequences such as difficulties with interpersonal relationships, alcohol, and smoking habits [6,7]. Overall, these events are associated with obesity, depression, suicide, anxiety, heart attack, chronic health problems, chronic obstructive pulmonary disease, asthma, stroke, cancer, and unemployment [8,9]. Apart from emotion regulation, ACE survivors' experience deficits in several domains of executive functions [10], which impact their well-being and psychological health [11]. Evidence suggests that individuals with ACEs, particularly children and young adults, are disadvantaged in terms of coping with increased stress relative to their peers without such bad experiences [12]. Since young adults are still experiencing biological and psychosocial development, the consequential impacts of ACE can be profound during adolescence and young adulthood [12].

Mental health problems are common among children and adults, which are predominantly presented as depression or anxiety and are characterized by frequent comorbidities [13]. Studies have demonstrated that ACEs represent an important predictor of emotional problems [14]. Previous research has documented several underlying events for the association between emotional problems and early ACEs among young children and adults [13,14]. For instance, individuals with a history of early ACEs were more accurate in recognizing threatening stimuli [15], constituting an adaptive response in harmful conditions. Nevertheless, it can heighten the risk of mental health disorders over time [16]. While individuals with ACEs are more likely to adopt maladaptive emotional regulation skills such as disengagement, expressive suppression, and rumination, they are less likely to perform successful activities such as cognitive appraisal [15], thereby leading to early emotional anomalies [16].

Specifically, ACEs also constitute a significant barrier to an individual's capacity for resilience. Resilience depicts the resources, capability, and processes available to a system or an individual to adapt successfully in the face of challenges or adversities [17-19]. Resilience encompasses the factors that facilitate positive adaptation and navigation toward resources to sustain well-being in the context of adversity [16]. Therefore, researchers have developed an interest in resilience intervention as a potential approach to addressing the negative impacts of ACEs [19]. For instance, cognitive behavioral therapy (CBT) has been used in resilience interventions in ameliorating health problems, particularly among adults with a history of ACEs [19-21]. Hence, building resilience in individuals with adversity in the context of psychological intervention offers a new approach to managing individuals with ACEs.

Adverse Childhood Experiences and Negative Consequences Among Children and Adults in Malaysia

ACEs refer to neglect, abuse, and dysfunctional households that may be deleterious to a person's health and well-being. Research conducted in Malaysia has depicted an increasing frequency of child abuse and neglect cases, which are typical examples of ACEs that may impact negatively on physical and mental health [22]. ACEs also contribute to the growing health care expenditure, as the health consequences of ACEs reportedly accounted for 2% of the gross domestic product [23].

Nevertheless, information on the prevalence and negative impacts of ACEs among children and adults in Asia, specifically Malaysia, is scarce due to limited research. A recent study revealed a high prevalence of various ACEs among university students in northeast Malaysia, with a report of emotional abuse, emotional neglect, physical abuse, and sexual abuse occurring in 30.2%, 29.2%, 28.7% and 9.1% of the studied population [22]. High-risk behaviors (HRBs), particularly physical inactivity and community violence were recorded among 39.3% and 54.5% of the students, respectively [22].

Apart from HRBs, depression has been identified as a consistent outcome of ACEs among young adults in Malaysia [24,25]. Young individuals from Shah Alam, Malaysia, exhibited a high level of depression and ostracism, which was associated with ACEs. Early psychological mistreatment such as parental neglect of a child's needs can lead to poor mental well-being [25], externalizing and internalizing problems, as well as anxious and avoidant attachment styles, making it challenging for children to develop a sense of belonging and feeling ostracized [26,27]. Therefore, early life traumatic events and ignorance appear to have strong influences on psychological well-being among this vulnerable population.

Besides the younger population, older adults in Malaysia have also been shown to be affected by ACEs, which may ultimately transit into elder abuse [28]. Furthermore, the risk of elder abuse increased with the cumulative number of ACEs. The results depict how early life adversities play an important role in older adults' victimization. Recognizing the possibility that vulnerability to maltreatment can persist throughout the life course of elderly individuals is critical when attempting to address the problem through emotional and social support.

Resilience-Building Interventions for Individuals With Adverse Childhood Experiences

Resilience is considered to be pertinent in the association between emotional problems and ACEs. Studies have depicted that resilience is a protective factor that can propel an individual to successfully address adverse experiences [29]. Thus, resilience is regarded as playing a protective role in the relationship between emotional disorders and ACE [29-31].

ACEs constitute a public health crisis that requires a wide range of interventions due to their high prevalence and impact on health disparities [31,32]. Resilience interventions are typical examples of CBT that are effective in ameliorating mental health disorders faced by individuals with ACEs [15]. According to Iniguez and Stankowski [33], ACE research has yielded strong evidence to support claims that "resilience resources and well-timed interventions to promote resilience can ameliorate the negative effects of ACEs" [33].

Chandler et al [21] demonstrated the feasibility and efficacy of an empower resilience intervention to enhance resilience and health behaviors among young adults with a history of ACEs. By using a 2-arm pre-post repeated measures design, young adults in the intervention group recorded significantly higher scores for building strengths, creating support connections, and reframing resilience. Meanwhile, a face self-help app designed by Brodbeck et al [34] and based on cognitive-behavioral principles, is currently being tested for its efficacy in promoting resilience and well-being in emerging adults with a history of ACE. MacIsaac et al [35] also evaluated the effects of an innovative, smartphone app-based resilience intervention on first-year university students' self-regulatory skills (ie, emotion regulation and executive functioning), and the mediating role of emotion regulation. After 4 weeks of using the app, students' emotion regulation and depressive symptoms improved significantly, with a faster rate of change in emotion regulation among those with more ACEs. Thus, evidence suggests that app-based resilience intervention can assist young adults with ACE by improving their emotion regulation skills and mitigating depression.

Systematic review findings depict that most interventions for addressing ACEs focused on psychological interventions and mental health outcomes, and cognitive-behavioral therapy has been consistently found to be effective in mitigating the negative impacts of abuse [36]. On the other hand, findings from interventions involving psychological therapies, specific support such as parent training, and broad support interventions are generally inconclusive despite some promising results [36]. In summary, significant gaps exist in the available evidence on interventions for ACEs, with most research focusing on individual psychological effects while neglecting the social pathways which may indirectly influence the negative impacts of ACEs. Several areas such as social relationships, life circumstances and health behaviors are examples of several negative impacts of ACEs that are still under investigation in most intervention research [34-36].

Building upon the global view on ACE research and resilience-building interventions, the Malaysian context must be taken into account in order to develop an effective intervention to address the problem of ACEs among children and young adults. Literature findings from the studies conducted in Malaysia have shown that ACE is a multifactorial problem that requires a multidimensional approach, rather than focusing on one individual aspect [22,23]. Such an approach is well-described in the multisystemic model of resilience developed by Ungar [8], highlighting the capacity of biopsychosocial and social-ecological systems to support external and internal conditions for well-being, as well as improving diverse populations' quality of life. Thus, resilience encompasses the process whereby individuals harness the resources that are necessary for them to function optimally and seek resources to be provided using meaningful approaches, either contextually or culturally [8].

Interventions that emphasize individual change without considering the environmental domain may yield short-term benefits [37]. Hence, intervention should have a dual focus, encompassing personal and environmental change. For instance, a child's resilience is a product of both their capacity to cope effectively under stress and the capacity of their physical and social environments to facilitate positive development. Under conditions of normal stress, individual ruggedness may be sufficient to support well-being; nevertheless, resources become more important and required as the individual experiences greater barriers to functioning. These 2 broad aspects form the foundation of the multisystemic perspective of resilience "R2," which was coined to affirm the need to mitigate both the rugged qualities of individuals and their access to resources) [38].

Research has shown that individuals with more internal capacities such as problem-solving, self-regulation, and positive future orientation are more likely to harness opportunities for relationships and exploit such opportunities for academic or financial success [39,40]. Likewise, higher levels of motivation to execute life tasks and being more optimistic were observed among individuals with better access to external resources [41,42]. These findings reflect the dynamicity of resilience, whereby individuals interact with the world around them to make the best use of available resources despite exposure to adversity or atypical stress.

As highlighted in the reviewed resilience-building interventions for ACEs, while some target the public and common adversities like job burnout [43] and stress [44], others are aimed at specific groups, such as chronically diseased individuals [45], employees returning to work [46], and health care workers [47]. These interventions are delivered using diverse methods, ranging from phone apps to web-based tools or printed manuals, and duration may be as short as single-day workshops to weekly or monthly sessions. However, a recent meta-analysis revealed that such interventions have a small to moderate effect on improving resilience [44,47]. Existing resilience interventions also differ in terms of the targeted protective factors, such as self-efficacy, problem-solving skills, and cognitive flexibility, with most focusing on rugged factors. Only a few interventions consider resources that are external to individuals with ACEs [48]. Accumulated evidence suggests little to no data on interventions that explicitly target both coping strategies and ways of creating better-resourced environments around individuals with ACEs.

Hence, this study will modify and implement an R2 resilience program based on a resilience-building intervention designed with the principles of implementation science [38]. The multisystem aspect of the intervention allows it to focus on multiple systems for the individual's change process and adaptation process around life circumstances. It is a curriculum-based approach that integrates all the well-researched factors and presents equal emphasis on the surrounding environments to the individual [8,38]. Thereafter, the factors and aspects can be modified and implemented into the resilience-building intervention accordingly. This study aims to explore the effects of the resilience-building intervention on mental health, stress, resilience, and resource finding among individuals affected with ACEs in Malaysia.

Methods

Study Design and Setting

This is a 2-armed, single-blinded, randomized controlled trial (RCT) that will be conducted among Malaysian youths with ACEs at the Department of Clinical and Health Psychology, National University of Malaysia. Briefly, the intervention group includes an evidence-based curriculum and components such as emotion regulation, active coping and goal setting, cognitive flexibility, mindfulness-based stress reduction, social support, self-exploration, resources and navigation, and finally, spirituality and religion. Participants in the control group will not receive any form of intervention. The main outcome of this study is resilience among youths with ACE while the secondary outcomes include coping, psychological well-being, quality of life, subjective stress, perceived stress, personal resources, and adult resilience. These variables will be evaluated at baseline and postintervention. Intention-to-treat analysis will also be performed. This clinical trial has been registered with the Australia New Zealand Clinical Trials Registry (trial Id: ACTRN12622000604707).

Sample Size

Sample size calculation was performed using G*power 3.1 software (Heinrich-Heine-Universität Düsseldorf). By assuming a study power of 0.8, 95% CI (α=0.05), and a moderate effect size of 0.25 as recommended by Ferguson (2009), the *F*-test was selected alongside repeated measures ANOVA with in-between interaction, with 2 groups and the number of measurements. Thus, a total sample size of 36 was obtained, reflecting 18 participants per group. We considered a high drop-out rate of 50% as several individuals may be unwilling to participate given the adverse effects of ACEs and confidentiality in sharing experiences with the researchers. Therefore, the sample size was increased to 50, amounting to 25 participants per group.

Eligibility Criteria

The inclusion criteria entail participants aged 18 to 30 years old and an individual who scores more than 4 or higher levels of ACE. This age group spans the young adulthood phase of an individual, and it is considered a significant developmental stage characterized by exposure to unique challenges and opportunities [21]. Meanwhile, the exclusion criteria are individuals receiving any type of intervention, demonstrating any severe psychopathology or psychiatric illness that requires a psychopharmacological approach, and those who had received intervention or therapy consistently in the past. Individuals need to fulfil the criteria to be recruited as mentioned above. Individuals will be recruited through multiple centers and social media platforms

Participant Recruitment and Randomization

The participants for this study are Malaysian youths with ACE, particularly those visiting the Psychological Department at the National University of Malaysia Medical Centre. During the selection stage, participants will be approached by the researcher and seek their consent to participate in the study. Those providing affirmative responses will then be instructed to fill up the self-administered ACE questionnaire.

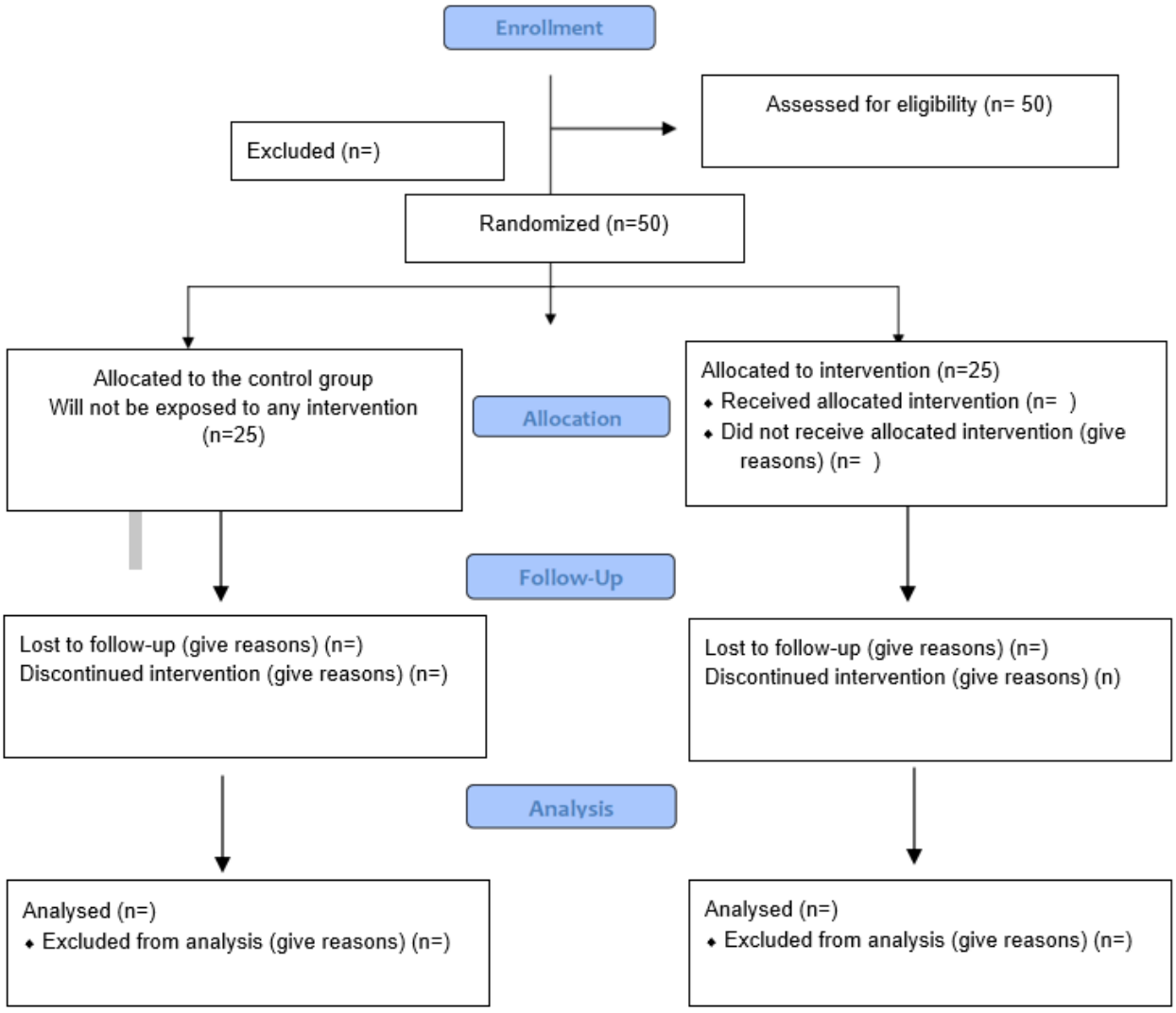
This assessment period is the screening stage to identify those that fulfil the inclusion criteria. Participants who score four or more of ACE will then be included in a pool of participants and assigned randomly to either the control group or intervention group. Random assignment procedure will be implemented by random allocation software, Research Randomiser [31], to generate numbers and assign participants to an intervention group or control group. Allocation concealment will be performed by a single blinding procedure, whereby the assessors of the outcome measures will be unaware of the specific group the participants belong to. In other words, only the investigator allocating participants to either the control or intervention group will be aware of this information while other assessors are blinded. Table 1 depicts the participant enrolment schedule, time points and assessments to be performed during the study period.

Table 1. SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) schedule of enrolment, interventions, and assessments.

	Study period			Close-up
	Enrolment	Allocation	Postintervention	Four-week follow-up
Timepoint	t_1	0	t_2	t3+4weeks
Enrolment	✓			
Screening	✓			
Eligibility screen	✓			
Informed consent	✓			
Allocation		✓		
Interventions				
Intervention A				
Control				
Assessments				
Brief Coping Orientation to Problem Experienced Scale - English and Malay version	✓		✓	✓
Ryff's Scale of Psychological Well-being (SPWB) - English and Malay version	✓		✓	✓
Quality of Life –WHOQL-BREF - English and Malay Version	✓		✓	✓
Subjective stress – Perceived Stress scale - English & Malay version	✓		✓	✓
Personal Resources Questionnaire 2000 - English and Malay version	✓		✓	✓
Adult Resilience Measure-Revised - English and Malay version	✓		✓	✓
Biomarker - measure changes in salivary cortisol	✓		✓	
Blood pressure (blood pressure measured with a sphygmomanometer	✓		✓	

Participants in the control group will receive no intervention, while those in the intervention group will receive five sessions of resilience-building intervention conducted by a trained facilitator. Hotlines, post session, and appropriate resources will be provided for those reporting distress after the intervention. Investigators will be blinded throughout the whole process of randomization and data collection as the whole process is handled by a research assistant (randomization), counsellor, and clinical psychologist (data collection). Under no circumstances will unbundling occur as a research assistant, counsellor, and clinical psychologist are briefed with the standard operating procedure to follow when an incident occurs. The flow diagram is presented in Figure 1.

Figure 1. Consolidated Standards of Reporting Trails 2010 flow diagram.



Contents and Delivery Method of the Intervention

The intervention will be adapted and modified according to the R2 Resilience building program designed by Ungar [20], which comprises 7 principles; help people to navigate, help people to negotiate, think about systems, coordinate services and supports, provide continuous support, be relevant to place and culture, and share responsibility for solutions. These principles will guide the process of modifying the intervention and the principles will be reflected in each session. The intervention will be delivered in 5 sessions.

Session 1 is divided into subsessions entitled “Self-exploration” and “Social support.” The first subsession focuses mainly on building rapport with the participants and helping them explore their coping skills, strengths, weaknesses, and talents. The second subsession emphasizes the importance of social support to enhance a sense of belonging and connection, as well as explore resources relating to social support. Both sessions will be delivered via internet-based with each lasting for 60 minutes.

The second session is also divided into 2 parts, coping technique including cognitive flexibility and grounding technique, and coping skills. The coping technique focuses on participants’ coping strategies and a deeper insight compared with the first session. This section also aims to provide cognitive exercise for preventing catastrophic thinking. As for coping skills, the strategies will be discussed in depth and practiced together with the facilitators. Participants will also be directed to work in pairs and assisted to identify their best coping strategies, either emotion-focused or solution-focused.

The third session comprises 2 parts to familiarize the participant with resource findings and explore their understanding of resilience. First, the facilitator will recap what the participant has learnt in the previous sessions and help identify where they can get help and access the available resources. Such assistance will be tailored for each participant to learn about resilience resources and harnessing them accordingly. In the second part, in-depth discussion will be held with each participant by focusing on past ACEs and how they were able to overcome the experiences, as well as their past resilience resources. Both

sessions will be delivered via internet-based with each lasting for 60 minutes.

The fourth session is also divided into 2 subsessions; (1) what is resilience to you (part II), and (2) spirituality. The first subsession is the continuation of the second part of the third session with the same components as shown in Table 2. Meanwhile, the second subsession entails learning from each other regarding the role of religion and spirituality in addressing past adversities. The last session is the "Resilience-building (wrap-up)," whereby all the intervention components will be reviewed and visualized in the form of a diagram. Each session of the intervention will last for 2 hours (60 minutes for each session, with 15-minute breaks between sessions). Each session will be conducted weekly, week 1 for the first session and week 5 for the fifth session respectively. All sessions of the intervention will be administered via internet-based to each participant by the facilitators.

Table 2. Components of the intervention.

Week	Session	Session	Duration	Mode of delivery	Focus
Week 1	1st session (1A)	Session 1A: Self-exploration	60 minutes	Internet-based	1. Build rapport among students with an ice-breaking activity 2. To help participants explore their coping skills, strengths, weaknesses, and talents
Week 1	1st session (1B)	Session 1B: social support	60 minutes	Internet-based	1. To talk about the importance of social support 2. To foster a sense of belonging and connection. 3. To explore resources regarding social support
Week 2	2nd session (2A)	Session 2A: coping techniques: cognitive flexibility and grounding technique	60 minutes	Internet-based	1. Explore participants' coping strategies (be mindful of labelling participants' strategies). Go deeper from session 1A 2. Cognitive exercise to prevent catastrophic thinking 3. How do you practice cognitive exercise? 4. What is fallacy thinking? 5. Introduce A-B-C and how to practice them
Week 2	2nd session (2B)	Session 2B: coping skills	60 minutes	Internet-based	1. Discuss the strategies in depth and practice them together. (Follow up from Session 2A) 2. Finding allies (participants form a pair and check in with each other) 3. Emotion-focused coping vs. solution-focused coping 4. During a crisis, how do these routines help? 5. Helping the body to feel safe
Week 3	3rd session (3A)	Session 3A: resource finding	60 minutes	Internet-based	1. Review and monitor from the previous session to recap what has been learned 2. To help participants know where to get help and the resources available 3. To help participants learn about their resilience resources and how to tap into them
Week 3	3rd session (3B)	Session 3B: what is resilience to you?	60 minutes	Internet-based	1. How do you survive? 2. What is the meaning of your stories? 3. What are your resilience resources in the past?
Week 4	4th session (4A)	Session 4A: what is resilience to you? part II	60 minutes	Internet-based	1. How do you survive? 2. What is the meaning of your stories? 3. What are your resilience resources in the past?
Week 4	4th session (4B)	Session 4B: spirituality	60 minutes	Internet-based	1. Review and monitor from the previous session to recap what has been learned 2. To learn from each other about the role of religion and spirituality
Week 5	5th session (5A)	Session 5B: eesilience-building (wrap-up)	120 minutes	Internet-based	1. To review and discuss all of the components 2. To draw a diagram with all of the components involved

Intervention Protocol and Fidelity

The intervention will be conducted in Malay or English. It aims to encompass both languages and will be provided according to the participant's native language. Therapists will be trained to follow the protocol and the manual. A recap will be conducted at the end of the session. Dynamic assessment will be used to track the learning progress. Participants will use journaling as a method to practice their skills. In addition, progress and practice will be discussed at the beginning of each session. As for intervention fidelity, journals and progress of group sessions will be collected from mental health professionals after each session to ensure they continue a similar structure for the intervention. The checklist will be prepared for the mental health professional.

Data Collection Instruments and Outcome Measures

Adverse Childhood Experience Questionnaire

The Adverse Childhood Experience Questionnaire (ACE-Q) is a 10-item measure to assess events of traumatic or adverse experiences that an individual experienced before the age of 18 years. The instrument evaluates the individual's exposure to childhood physical, psychological, or sexual abuse, as well as household dysfunction such as substance use, domestic violence, and incarceration. The ACE-10 has been validated among the Malaysian population with an acceptable internal consistency of 0.86 and internal validity ranging from 0.28-0.70 [49].

Patient Health Questionnaire-9

The English and Malay versions of the Patient Health Questionnaire-9 (PHQ-9) will be used in this study to assess depression among youths with ACEs. The instrument has been validated among the Malaysian population by Sherina et al [50] with a sensitivity of 87% (95% CI 71%-95%) and specificity of 82% (95% CI 74%-88%). It was also reportedly suitable as a case-finding instrument in Malaysian primary care clinics.

Brief Coping Orientation to Problem Experienced Scale

The brief coping orientation to problems experienced (COPE) instrument comprises 28 items with 14 broad coping strategies. The Malay version of the instrument was validated by Saiful [51] among secondary school adolescents and was found to be valid and reliable in identifying coping strategies. Specifically, the overall Cronbach α value was 0.83 with the majority of the coping strategies reflecting acceptable internal consistency.

Ryff's Scale of Psychological Well-Being and Quality of Life

The Ryff's Scale of Psychological Well-being (SPWB) and World Health Organization Quality of Life Assessment (WHOQL-BREF) will be used in this study to assess the psychological well-being and quality of life among adolescents with ACEs. These instruments have been validated among the Malaysian population with acceptable discriminant validity, construct validity, and test-retest reliability greater than the threshold value of 0.5 [52-54].

Personal Resources Questionnaire 2000

The personal resources and workability of the participants will be assessed using the Work Ability-Personal Radar (WA-PR) instrument, which has been previously translated into Malay and validated by Hamdan et al [55]. The instrument has adequate psychometric properties and has been validated with acceptable discriminant validity, construct validity, and test-retest reliability greater than the threshold value of 0.5, making it suitable to be used in investigating personal resources and workability levels in the Malaysian population [55].

The Perceived Stress Scale-10

The Perceived Stress Scale-10 (PSS-10) is generally used in assessing stress perception. The Malay version of the PSS-10 has been validated among diverse populations in Malaysia, with the latest being nurses from government hospitals [39]. The instrument revealed acceptable internal consistency with a Cronbach α value of 0.63 and intraclass correlation coefficient of 0.81 (95% CI 0.62-0.91) following a 7-day test-retest reliability analysis. Furthermore, previous studies found significant correlations between the stress component of Depression Anxiety and Stress Scale 21 and the total score and negative component of the PSS-10 (r=0.56-0.61). Therefore, the PSS-10 is considered valid and suitable for investigating stress perception among Malaysian youths, including adolescents [56].

Saliva Cortisol and Blood Pressure Assessment

Each participant will be instructed to provide approximately 2 mL of whole saliva by passive drool, which will be then split into multiple 100 uL aliquots and frozen immediately. One aliquot of each of the 50 participants' saliva will be transported overnight on dry ice to the institutional laboratory. Cortisol analysis will be performed using commercially available immunoassay according to the manufacturer's guidelines (Salimetrics). Meanwhile, participants' blood pressure will be measured objectively with a sphygmomanometer.

Time Points for the Primary Outcomes and Retention

Premeasurements will be conducted at baseline, whereas postmeasurements will be collected after the fifth session as shown in Figure 1. Participants will be given Ringgit Malaysia 50 after the third and fifth sessions of the intervention to ensure they do not drop out of the study. Another follow-up will be conducted 4 weeks after the Intervention.

Data Analysis

All data management and statistical analysis will be conducted using SPSS (version 26; IBM Corp). Data management will be performed by screening for missing data and checking for potential outliers. Descriptive statistics will be used to assess the data normality and to summarize the pre and postintervention scores for each group at different periods. Mean and SDs will be provided for normally distributed data, followed by mixed ANOVA with repeated measures to compare the pre and postintervention mean scores between and within the groups.

The assumptions of ANOVA include randomly collected and normally distributed data, sufficient sample size, homogeneity of variances, and absence of violation and outliers. Levene's test will be applied to test the homogeneity of variance. Mixed ANOVA benefits RCT design as it allows testing for 2 groups across 2-time points. Mixed ANOVA analysis aims to handle

response outcomes conducted on the same experimental unit at a different time or under different conditions [57]. The differential effects of the intervention components will be tested with interactions between the component and time. These analyses will model random slopes and intercepts for participants, explore the fixed effects of the condition, and test the repeated measures over time. This type of analysis is advantageous by accounting for missing values through the maximum likelihood estimation method [57]. Effect sizes will be computed based on Cohen *d*.

In addition, the intention-to-treat analysis will be applied to analyze the participants according to their assigned groups. This analysis includes all participants and ignores noncompliance, protocol deviation, and withdrawal. The intention-to-treat analysis is a complete trial strategy for the design, execution, and analysis of RCT, focusing on the consolidated standard of reporting trial guidelines. Thus, the number of participants in each assigned group will be analyzed by the intention-to-treat principle.

As for missing data, drop-out in this study refers to participants who withdraw actively from the intervention post randomization. All cases of dropouts will be considered in the intent-to-treat samples since they have been randomized and included in the analysis. The extent and pattern of missing data will be assessed, and depending on the results, missing values will be replaced by using multiple imputations. The impact of the imputation of missing values will be further explored by conducting sensitivity analyses.

Criteria for Discontinuing or Modifying Intervention

All the intervention modules were well understood by the participants enrolled in the pilot test; hence, no attempt has been made to review the intervention. Participants have the right to withdraw from the research at any given time if they do not feel comfortable continuing with the study. If the counselor or clinical psychologist reviews and discusses the harm of the participants continuing to participate in the research project, they will advise the participants to drop out of the study based on their professional judgment. A panel comprising counselors, and clinical psychologists will jointly review the case and make a consensus decision.

Data Auditing and Management

The team is required to submit first and second progressive reports to the Research Ethics committee, at the National University of Malaysia as part of the auditing process. Only group data will be reported. Data will be reported collectively; individual data will not be disclosed. Journal and progress of group sessions will be collected from mental health professionals after each session to ensure they continue a similar structure for the intervention. The checklist will be prepared for the mental health professionals.

As for data storage and management, the data will be entered digitally and stored in a Microsoft Excel sheet and Microsoft Word document by the investigator after being collected from mental health professionals. Each dataset will be assigned a code to protect the participants' identity. The encryption of the firewall will help secure and protect the data. A passcode will be generated to protect these documents. The data will be stored in the institution for 5 years, kept confidential and used only for educational purposes.

Standard Operating Procedure to Manage Harm

Counsellors and clinical psychologists will evaluate if any of the participants feel discomfort or express interest in withdrawing from the studies. This assessment will be carried out during the break intervals between each session of the intervention and the follow-up periods post intervention. Participants will be asked verbally if they still feel comfortable and willing to proceed with the intervention. Follow-up and proper redirecting to resources will be practiced with individuals who dropped out of the study.

Protocol Amendments

Any modification to the protocol, an update will be submitted to the Australia New Zealand Clinical Trials Registry and Research Ethics Board, The National University of Malaysia, and related journal publications.

Recordkeeping and Specimen

Consent will be obtained from participants to collect saliva. Data obtained through this study will only be published under group data. No individual data will be identified. The saliva samples obtained will not be kept and discarded right after the cortisol level measurement and analysis. All participants' data and information will be stored for this research as group data.

Ethical Considerations

Ethical approval was obtained from the Research Ethics Board at the National University of Malaysia (UKM PPI/111/8/JEP-2021-894; January 28, 2021). Detailed information on the intervention and recruitment process is provided in the next sections.

Results

This protocol, the informed consent and other relevant documents were reviewed and approved before the conduct of the research. Letters of extension and ethics approval were obtained from the Research Ethics Board at the National University of Malaysia. Amendments will be communicated to investigators, ethics review boards and publishing journals.

By January 2025, a total of 28 participants have been recruited into the study, comprising 14 in the intervention and 14 in the control group. Only 2 participants withdrew from the intervention group mainly due to a change in location and issues relating to data privacy and security. It is expected that participant recruitment will be completed by 30 January 2025. Preliminary analysis is ongoing, and the results suggest improvement in the investigated outcomes among participants in the intervention group across time. Final analysis will be conducted by March 2025, upon completing the data collection.

Discussion

Principal Findings

ACEs are relatively common, trigger substantial suffering and are well-documented as a risk factor for diverse physical and mental health conditions throughout life. While primary prevention is pertinent in reducing ACE, the deleterious short and long-term consequences of ACE can be mitigated by selective prevention.

This study adopted the multisystemic approach to resilience "R2," which recognizes the importance of rugged qualities and access to resources among individuals affected by ACEs. As discussed earlier, the multisystemic model of resilience emphasizes 2 broad aspects, encompassing personal and environmental change [37]. We considered these 2 aspects as pertinent in addressing the consequences of ACEs among young adults in Malaysia, aligning with recommendations from previous studies to approach the problem in a multidimensional manner [8,38]. This study will be the first attempt to adopt an evidence-informed intervention for resilience-building among Malaysians with ACEs. In addition, this research is among the few interventions that explicitly entail both coping strategies and creating better-resourced environments around individuals affected by ACEs.

It is anticipated that the resilience-building intervention will have moderate to strong effects by ameliorating mental health, and stress, and improving participants' resilience and resource finding compared with those in the control group. These expected findings are consistent with the report by Chandler et al [21], whereby a resilience intervention centered around 4 main components (ie, active coping, building strength, cognitive flexibility, and social support) was effective in mitigating the adverse effects of ACEs.

Our intervention is structured into 5 sessions, focusing on self-exploration and social support, coping techniques and coping skills, resource finding, spirituality, and resilience-building. These components are expected to enhance participants' internal capacities such as self-regulation and problem-solving, thereby harnessing opportunities to achieve success in life [39]. By educating them on how to identify and gain better access to external resources, they will be motivated to accomplish life tasks and be more optimistic [42]. These events will assist in building resilience, facilitating participants' interaction with the world around them, and using available resources effectively regardless of being exposed to adversities.

This intervention aims to focus on vital resilience components which are emotion regulation, active coping and goal setting, cognitive flexibility, physical health, mindfulness-based stress reduction, social support, self-exploration, resources and navigation, financial planning, and spirituality and religion. One of the weaknesses of this intervention is that these components will be monitored by informal assessment such as observation, tracking, and recap to ensure participants have learned and acquired the tools and knowledge. It is also difficult to ensure participants from the control group will not receive any form of therapy during the whole duration of the intervention. Hence, the therapist has to check in with the group from time to time to ensure their well-being is taken care of. If needed, the therapist will conduct a post-group counselling session with an individual who is distressed by the intervention. Given that the participants were selected from a pool of individuals obtaining a specific level of ACEs, the findings might not be generalized to the entire population of people with ACEs in the country.

Conclusion

This is the first full clinical trial study investigating resilience-building intervention for youths with ACEs in Malaysia. There are limited studies evaluating the effectiveness of resilience-building interventions combining mental health and physiological responses as outcome measures in Malaysia. Thus, this study conceptualizes resilience from a biopsychosocial-ecological perspective and adapts resilience-building intervention in the Malaysian context. This study aims to develop resilience-building intervention modules specifically for Malaysia, focusing on the process of adapting the modules and modifications according to the Malaysian culture. This will be one of the first studies to provide evidence in the context of RCTs for resilience-building intervention combining self-report and physiological measures (ie, saliva and heart blood pressure) among individuals with ACEs. The findings will assist relevant authorities in the health and policy sectors to develop effective strategies for addressing the negative impacts of ACEs on the vulnerable population in Malaysia.

Acknowledgments

The study has received financial grant support from grant research National University of Malaysia (GUP-2022-054). The grant sponsor is only required to submit a progressive report at the end of the project. It will not involve any of the research activities.

Data Availability and Dissemination Policy

Group data will be available on the Australia New Zealand Clinical Trials Registry. The public will have access to full protocol and group-level datasets. The investigator will publish trial results to participants and health care professionals through publication and data-sharing arrangements on the Australia New Zealand Clinical Trials Registry. The public will have access to the full protocol. Data will be available upon the study's completion.

Authors' Contributions

NJK, MA, CMHC, SZ, and MU contributed to conceptualization and methodology. NJK and MA handled project administration. NJK, MA, CMHC, SZ, MU, and PA/LS managed module refinement, data analysis, and supervision. NJK wrote the original draft. NJK, MA, CMHC, SZ, MU, PA/LS contributed to review and editing.

Conflicts of Interest

None declared.

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Abbreviations

ACE: adverse childhood experience
ACE-Q: Adverse Childhood Experience Questionnaire
CBT: cognitive behavioral therapy
COPE: Brief Coping Orientation to Problems Experienced Scale
HRB: high-risk behavior
PHQ-9: Patient Health Questionnaire-9
PSS-10: Perceived Stress Scale-10
RCT: randomized controlled trial
SPWB: Ryff's Scale of Psychological Well-being
WA-PR: Work Ability-Personal Radar
WHOQL-BREF: World Health Organization Quality of Life Assessment

Edited by T Leung; submitted 27.01.24; peer-reviewed by M Sadiq, J Brodbeck; comments to author 16.07.24; revised version received 27.08.24; accepted 29.10.24; published 12.02.25.

Please cite as:
Kiat J, Ahmad M, Mei Hsien Chan C, Zainalabidin S, Ungar M, Subramaniam P
Effectiveness of Adaptation of a Resilience-Building Intervention Among Individuals With Adverse Childhood Experience: Protocol for a Randomized Controlled Trial
JMIR Res Protoc 2025;14:e56826
URL: https://www.researchprotocols.org/2025/1/e56826
doi:10.2196/56826
PMID:

Protocol

Neural Mechanism of Cognitive Reserve in Acupuncture Stimulation: Protocol for a Randomized, Placebo-Controlled Functional Near-Infrared Spectroscopy Trial

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Abstract

Background: Dementia is a clinical syndrome characterized by a progressive decline in various cognitive domains. Since there is still no treatment for dementia, early diagnosis and prevention are the best approaches. In this context, the cognitive reserve (CR) concept has received considerable attention in dementia research with regard to prognosis. It originates from discrepancies between the degree of brain pathology and clinical manifestations. Acupuncture, as a complementary intervention, has long been widely applied in neurological diseases in East Asia. At the macroscale level, how acupuncture stimulation affects neural activity concerning CR in normal aging and dementia is largely unknown.

Objective: The aim of this study is to investigate the acute neural mechanisms of acupuncture stimulation concerning CR in the normal aging group and the group with cognitive impairment using neuroimaging methods.

Methods: This study is a randomized, placebo-controlled trial. Participants without (n=30) and with cognitive impairment (n=30) will be randomly assigned to the verum or sham acupuncture groups. The verum acupuncture group will receive acupuncture stimulation at acupoints related to cognitive function and gain deqi sensation. The sham acupuncture group will receive superficial needling at nonacupoints not related to cognitive function. Each group will undergo cognitive function tests, functional near-infrared spectroscopy imaging before and after acupuncture stimulation, and an assessment of CR. The primary outcomes will be differences in resting brain activities according to disease status, differences in resting brain connectivity before and after acupuncture stimulation between the 2 groups, and changes in brain activity in relation to the CR index. The secondary outcomes will be brain connectivity or network metrics associated with CR and differences in neural activity between the cognitive task and resting states.

Results: The recruitment began in August 2023; to date, there have been 50 participants, divided into 20 in the group with cognitive impairment and 30 in the unimpaired group. The recruitment process will continue until February 2025.

Conclusions: CR refers to the individual susceptibility to age-related brain changes and pathologies in cognitive impairment, and it is a factor affecting the trajectories of the disease. Although acupuncture is a widely used intervention for various neurological diseases, including dementia, its mechanism associated with CR at the macroscale has not been clearly identified. This study

could contribute to identifying the neural mechanisms of acupuncture stimulation associated with CR using neuroimaging methods and provide a basis for future longitudinal research.

Trial Registration: Clinical Research Information Service of the Republic of Korea KCT0008719; https://tinyurl.com/ydv5537n

International Registered Report Identifier (IRRID): DERR1-10.2196/66838

(JMIR Res Protoc 2025;14:e66838) doi:10.2196/66838

KEYWORDS

cognitive reserve; acupuncture; dementia; mild cognitive impairment; neuroimaging; fNIRS; brain connectivity; neural mechanism; RCT; randomized controlled trial

Introduction

Cognitive impairment refers to a generic term in which various cognitive functions, such as memory and executive function, are impaired, and the symptom severity ranges from mild to severe enough to interfere with daily life. Among them, dementia is a clinical syndrome preventing patients from leading a daily life due to the severe decline in several cognitive domains. Alzheimer disease (AD) is by far the most frequent cause of dementia and accounts for up to 80% of all dementia diagnoses [1]. AD symptoms typically begin with mild memory difficulties and gradually progress to severe memory impairment, inducing dysfunctions in daily life [2]. The prevalence and incidence of AD are increasing with an increase in life expectancy, leading to a socioeconomic burden worldwide [3,4].

The concept of cognitive reserve (CR) has received consistent attention in dementia-related research. CR refers to the adaptability of cognitive processes, which helps explain the individual vulnerability of cognitive abilities. It has also been suggested as an active model of the reserve, indicating that dynamic cognitive and functional processes counteract aging-related brain changes or damage [5]. This concept suggests that the brain actively attempts to cope with brain damage, allowing an individual with high CR to better deal with brain pathology. Many studies have shown that CR works differently depending on disease status. In the group without cognitive impairment, participants with high CR showed a slower decline in cognitive function; however, in the AD group, individuals with high CR showed more rapid cognitive deterioration than those with low CR [6,7]. Therefore, CR is considered a factor that modulates the relationship between the neuropathological burden of dementia and clinical symptoms [8,9]. Generally, CR has been measured through proxies, such as years of education, occupational complexity, and questionnaires covering various lifelong experiences.

Various neuroimaging techniques such as magnetic resonance imaging, functional magnetic resonance imaging (fMRI), positron emission tomography, and electroencephalography have been used for the early detection of AD [10]. Although fMRI is noninvasive and has good temporal and excellent spatial resolutions among functional neuroimaging methods, it has inherent limitations such as high cost, immobility due to heavy equipment, and vulnerability to head motion artifacts. In contrast, functional near-infrared spectroscopy (fNIRS) has been suggested as an alternative tool for functional neuroimaging. fNIRS is an optical neuroimaging technique that allows the measurement of changes in brain tissue concentrations of oxyhemoglobin (HbO_2), deoxyhemoglobin (HbR), and total hemoglobin (HbT) within the brain, achieved by irradiating the head with near-infrared (NIR) light [11,12]. This equipment has several practical advantages over conventional techniques represented by fMRI: It has a relatively higher temporal resolution, is noninvasive, cost-effective, lightweight, and easy to handle. It is applicable to cases difficult to fMRI scanning, such as agitated patients, individuals with claustrophobia, and those with pacemakers [13,14]. Moreover, it can be used on patients without moving from the hospital or laboratory, which can be critical for dementia patients with mobility difficulties. With these advantages, it allows us to monitor the alterations in brain function in patients with cognitive impairment in real time and explore neural responses induced by long-term or short-term interventions.

In a recent systematic review of dementia research using fNIRS, its diagnostic and investigative usefulness was evaluated while reviewing 88 studies in the field of dementia [15]. In summary, fNIRS could capture the aberrant hemodynamic responses and a lack of task-appropriate lateralization, often focused on frontal regions, in dementia. On the other hand, inconsistent results were found in prodromal stages. Cognitive decline accompanied by either reduced functional responses or hyperactivity was identified, the latter implying a compensatory response not represented at the dementia stage. However, there have been few fNIRS studies dealing with CR, one of the important factors in cognitive impairment.

Acupuncture has been practiced for thousands of years as an important treatment for a variety of diseases in East Asian medicine [16,17]. It is also being explored in AD research as a complementary and alternative therapy. In a meta-analysis, acupuncture treatment alone showed acceptable efficacy compared to conventional medicine for the management of AD. In addition, in a randomized controlled trial in patients with mild to moderate AD, acupuncture was found to be safe, well tolerated, and effective in improving cognitive function and global clinical status [18]. Specifically, acupuncture has been shown to regulate the release of central neurotransmitters, including acetylcholine and monoamine neurotransmitters [19]. Current neuroimaging studies of acupuncture cover a variety of diseases ranging from pain-related diseases such as chronic low back pain to peripheral and central nervous system disorders including carpal tunnel syndrome, stroke, Parkinson's disease, and dementia [20-24]. Through these, the analgesic mechanism and neuroprotective effect of acupuncture, which are distinct

from sham needling, are consistently elucidated. Among them, a systematic review dealing with 13 AD-related neuroimaging studies found that acupuncture may modulate the default mode network, the central executive, and the frontoparietal networks in the brains of AD patients [24]. However, on the macroscale, the acute neural mechanisms of acupuncture stimulation in relation to CR according to disease status are largely unknown. To identify the neural mechanisms of acupuncture stimulation associated with CR in healthy aging and cognitive impairment patients, rigorous clinical trials such as randomized, placebo-controlled trials with neuroimaging techniques are required.

In this study, our main hypothesis would be that brain networks and brain activations focused on frontal regions would be altered according to the disease status and CR level, and that brain connectivity in the frontal regions would change before and after acupuncture stimulation. Next, we aim to investigate the neural substrates of CR and cognitive function using network metrics. Herein, we present a protocol for a randomized, placebo-controlled, parallel-group clinical trial to explore the acute neural changes after acupuncture stimulation according to CR and elucidate the neural substrates of CR according to disease status by applying fNIRS.

Methods

Trial Design, Setting, and Aim

This study will be a single-center, block-randomized, placebo-controlled, parallel-group clinical trial. The study will be conducted at the College of Korean Medicine at Sangji University. This protocol complies with the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) guidelines [25]. The aim of this study is to investigate the acute neural mechanisms of acupuncture stimulation concerning CR and to identify the neural substrates of CR in the group without cognitive impairment and the group with cognitive impairment using fNIRS.

The participants will be divided into 2 equal groups: the verum acupuncture group (study group) and the sham acupuncture group (control group). After each group is confirmed to participate in the study through screening (visit 0), fNIRS scanning and acupuncture manipulation will be conducted at visit 1. Cognitive function assessments, including the Korean version of the Mini-Mental State Examination (MMSE-K) and Montreal Cognitive Assessment (K-MoCA), will be conducted during screening. At visit 1, each participant will be measured twice using fNIRS (first and second scan) before and after acupuncture stimulation. Finally, CR marker assessment, such as the Cognitive Reserve Index Questionnaire (CRIq), will be conducted through interviews in visit 1. The period between visit 0 and visit 1 will not exceed 1 week. Participant recruitment was initiated on August 22, 2023, and the study is scheduled to continue until February 2025. The flow chart is illustrated in Figure 1, and the overall procedure is presented in Table 1.

Figure 1. Flowchart of this study. K-MoCA: Montreal Cognitive Assessment (Korean version); MMSE-K: Mini-Mental State Examination (Korean version).

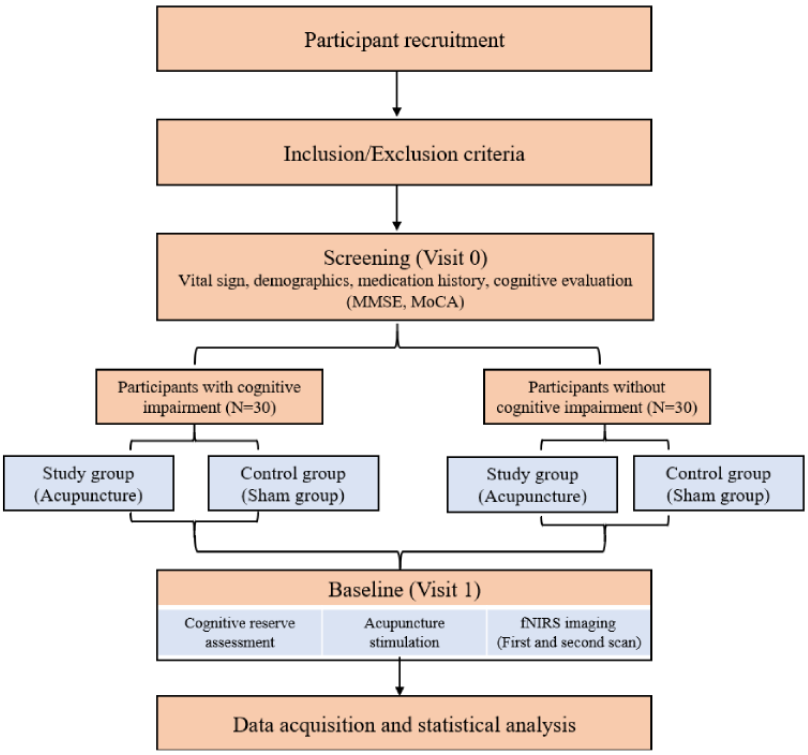


Table 1. Overall procedure of this study.

	Study period	
Time point	Visit 0 (screening)	Visit 1
Enrollment		
Eligibility screen	✓	
Informed consent	✓	
Randomization and allocation	✓	
Intervention		
Verum acupuncture group		✓
Sham acupuncture group		✓
Assessment		
Demographics	✓	
Medical history	✓	✓
MMSE-K[a]	✓	
K-MoCA[b]	✓	
CRIq[c]		✓
fNIRS scan[d]		✓
Safety		
Vital sign	✓	✓
Adverse events		✓

[a]MMSE-K: Mini-Mental State Examination (Korean version).

[b]K-MoCA: Montreal Cognitive Assessment (Korean version).

[c]CRIq: Cognitive Reserve Index Questionnaire.

[d]fNIRS: functional near-infrared spectroscopy.

Participants and Recruitment Strategy

Eligibility Criteria

The inclusion criteria for healthy controls (the group without cognitive impairment) are as follows: (1) males and females aged ≥19 years without cognitive impairment (MMSE-K≥24, K-MoCA≥23); (2) participants without severe neurological, organic dysfunction; and (3) participants or authorized surrogates who voluntarily sign the informed consent.

The inclusion criteria for the group with cognitive impairment are as follows: (1) males and females aged ≥60 years showing cognitive impairment (MMSE-K<24, K-MoCA<23) or diagnosed with mild cognitive impairment (MCI) or dementia with a clinical dementia rating<3; (2) participants or authorized surrogates who voluntarily sign the informed consent; and (3) participants who can complete this study.

The exclusion criteria for healthy controls (the group without cognitive impairment) are as follows: (1) participants with other brain disorders, alcoholism or drug abuse, neuropsychiatric disease, or taking psychiatric medicines, and severe organic dysfunctions inducing cognitive impairment; and (2) participants with any other reasons that may be considered inappropriate by the researcher.

The exclusion criteria for the group with cognitive impairment are as follows: (1) severe dementia patients with a clinical dementia rating of 3; (2) patients with other brain disorders such as cerebrovascular disease and epilepsy; (3) patients with cognitive impairment induced by another primary disease; (4) patients with severe organic dysfunctions; (5) patients presenting alcoholism or drug abuse, with neuropsychiatric disease or taking psychiatric medicines; and (6) patients with any other reasons that may be considered inappropriate by the researcher.

Enrollment, Randomization, and Blinding

Recruitment will be conducted through advertisements on websites and public announcements. Promotion through local communities is also under consideration. The recruitment of participants with cognitive impairment will be promoted through cooperation with community dementia care centers. In this study, in accordance with the recruitment of the participants, the effect of age on brain function will also be investigated; therefore, recruitment in the group without cognitive impairment will not be restricted to older adult participants.

Stratified block randomization will be performed according to sex. Both groups will be assigned in a 1:1 ratio to the study and control groups by applying a block size of 4. Randomization will be conducted using a computer-generated allocation list by an assigned researcher not involved in the assessment or intervention. Participants will be blinded to the type of

intervention used. The practitioner will not provide clues regarding allocating information to the participants during the study. Blinding will be maintained until the end of the study. Participants will be asked about their experience of blinding after the end of the study.

Sample Size

In this study, the number of participants has been determined statistically. In our hypothesis, the significance level (α) and power (1–β) will be set to 5% and 80%, respectively. Then, an effect size will be calculated using an estimated value of the variability in the MMSE-K and K-MoCA scores based on the literature [26]. As a result, the number of samples came out to be about 10-15 for each group (study or control group) to satisfy the criteria of the normal deviates of significance level and power in the healthy controls and patient groups. The anticipated dropout rate was set to 10%. A similar number of subjects (i.e., 10–15 subjects in each group) can be found in the previous neuroimaging studies [27-29].

Study Procedures

All participants will be subjected to measurement of vital signs (blood pressure, pulse rate, and temperature), demographic information, and medical history (past, present, and family). Cognitive function assessments (MMSE-K and K-MoCA) will also be performed during visit 0 (screening). Eligible participants who meet the inclusion and exclusion criteria will receive the schedule for visit 1.

At visit 1, the investigator will check the participant's vital signs and changes in medication, perform 2 fNIRS scans before and after acupuncture stimulation, and assess the level of CR using CRIq. For medications, the investigator will check for changes but will not specifically allow or restrict certain drugs. According to stratified randomization, the participants will be assigned to 2 acupuncture stimulation groups. Acupuncture stimulation will be performed by a Korean medicine doctor with >3 years of clinical experience. fNIRS scans consist largely of 2 main parts: a 5-minute resting state scan and a task scan of working memory.

Cognitive Function Assessment

The investigator will assess 2 cognitive function tests: the MMSE-K and K-MoCA. The MMSE-K is a 30-point questionnaire consisting of 12 questions that are widely used in clinical and research settings to measure cognitive impairment [30]. The K-MoCA is an extensively used 30-point cognitive assessment tool that effectively differentiates MCI [31]. The evaluation of each assessment will be conducted by an investigator blinded to the assigned group.

Measurement of Cognitive Reserve

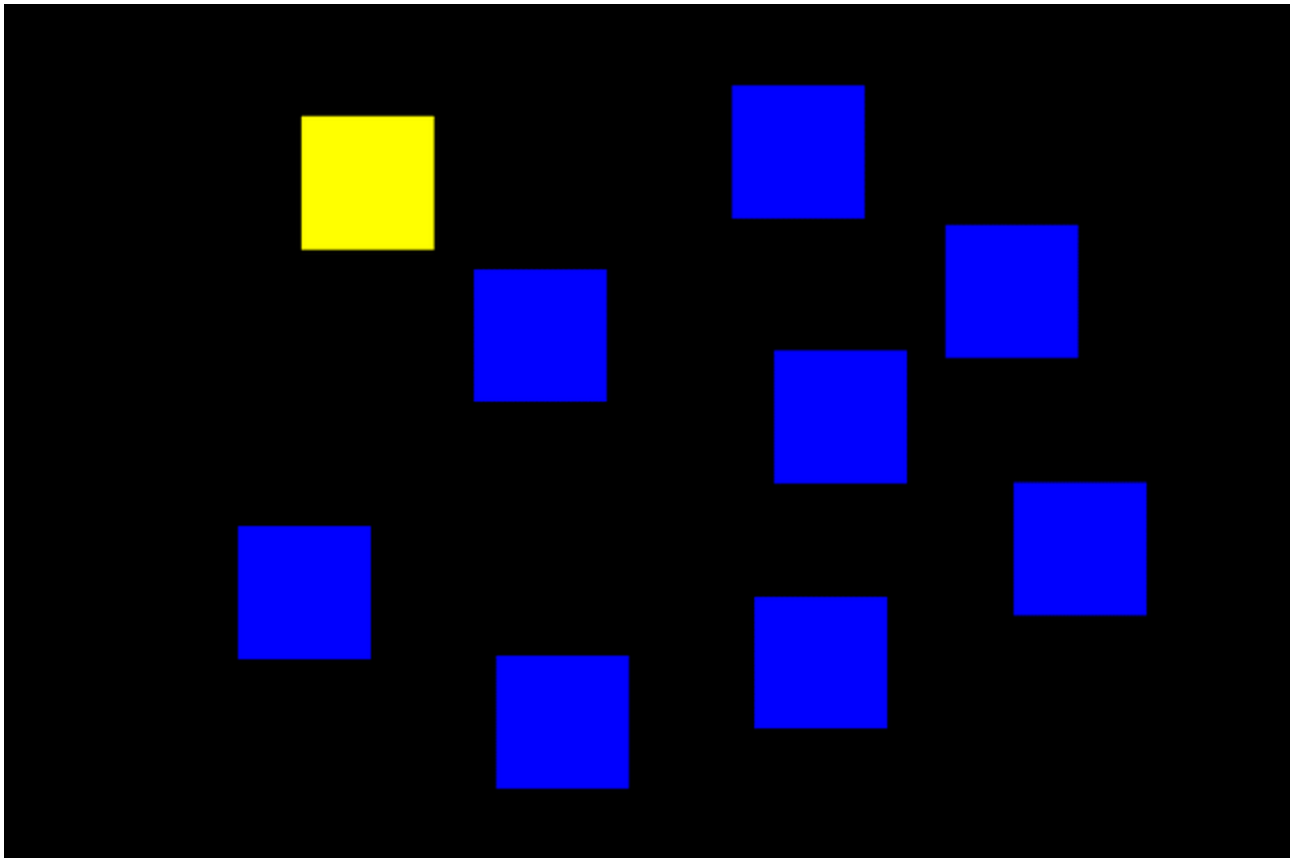
CR assessment will be conducted using the CRIq questionnaire [32]. It includes demographic data and items categorized into 3 sections: education, working activities, and leisure time; each item returns a subscore. It evaluates the CR of an individual by compiling the information associated with the individual's entire adult life. The quantification of CR will be calculated as the sum of all domains, and the subscore of each domain will also be applied in further correlation analysis. Depending on the mean value of CRIq, it will be dichotomized into the high CR and low CR groups. The investigator will also assess the participants' bilingualism. The evaluation of each assessment will be conducted by an investigator blinded to the assigned group.

fNIRS Imaging

For this experiment, fNIRS equipment (NIRSIT, OBELAB) will be used. fNIRS is a portable near-infrared neuroimaging device that measures hemodynamic variations in cerebral blood by irradiating the cerebral cortex with a near-infrared laser. The equipment irradiates the wavelengths of 780 and 850 nm of laser, which is harmless to humans. It contains 48 channels that can cover the frontal regions of the brain, allowing the quantification of ΔHbO_2, ΔHbR, and ΔHbT in that area. Based on this, the analysis applied in fMRI, such as graph theory analysis and general linear model analysis, can be used.

The fNIRS scans will be conducted before and after acupuncture. The scan consists of 2 parts: a resting state and working memory task scan. The resting-state fNIRS scan lasts for 5 minutes, during which the participant is asked to look at the monitor screen and remain comfortable. The task fNIRS scan is performed while conducting a Corsi block tapping task, a cognitive task related to working memory [33]. This experiment requires participants to tap a spatially separated sequence of up to 9 identical blocks in the same order in which they are presented. The sequences start simple, using 4 blocks, and become more complicated using a maximum of 6 blocks (Figure 2).

Figure 2. Presentation of Corsi block task.



Interventions

In the study group, verum acupuncture stimulation will be conducted for 15 minutes by stainless steel acupuncture (0.25 mm×40 mm, Dongbang acupuncture) on acupoints, which are known to be associated with cognitive functions in previous studies (Baihui [GV20], Sishencong [EX-HN1], Taixi [KI3], Zusanli [ST36], Hegu [LI4], and Taichong [LR3]), and deqi sensation will be induced [24,34,35]. The needle will be lifted and thrust approximately 30-50 mm and twisted and rotated at approximately a 90°-180° angle 60 times/minute (60 Hz). The manipulation will then be performed at 1-minute intervals to maintain the amount of stimulation and achieve deqi sensation. A questionnaire on deqi sensations will be implemented.

For the control group, superficial needling acupuncture (depth of needling: 1-2 mm per nonacupoint) will be performed for 15 minutes using stainless steel acupuncture (0.25 mm×40 mm, Dongbang acupuncture) on nonacupoints. Nonacupoints, which are not related to cognitive function, would be approximately 1 cm away from the acupoints of the study group. The needles for sham acupuncture will remain in place. In the case of superficial needling, manipulation techniques and induction of deqi sensation will not be achieved.

Superficial needling can be a subtype of minimal acupuncture [36]. We thought that the characteristics of acupoints, depth of acupuncture stimulation, intensity of the stimulation, and deqi sensation would all be determinants of acupuncture stimulation. Therefore, we selected minimal acupuncture that lacks these features as a sham control. This type of sham acupuncture has been applied in various studies, including Bell's palsy, migraine, and chronic musculoskeletal pain syndrome, for a long time [37-40].

Outcome Measures

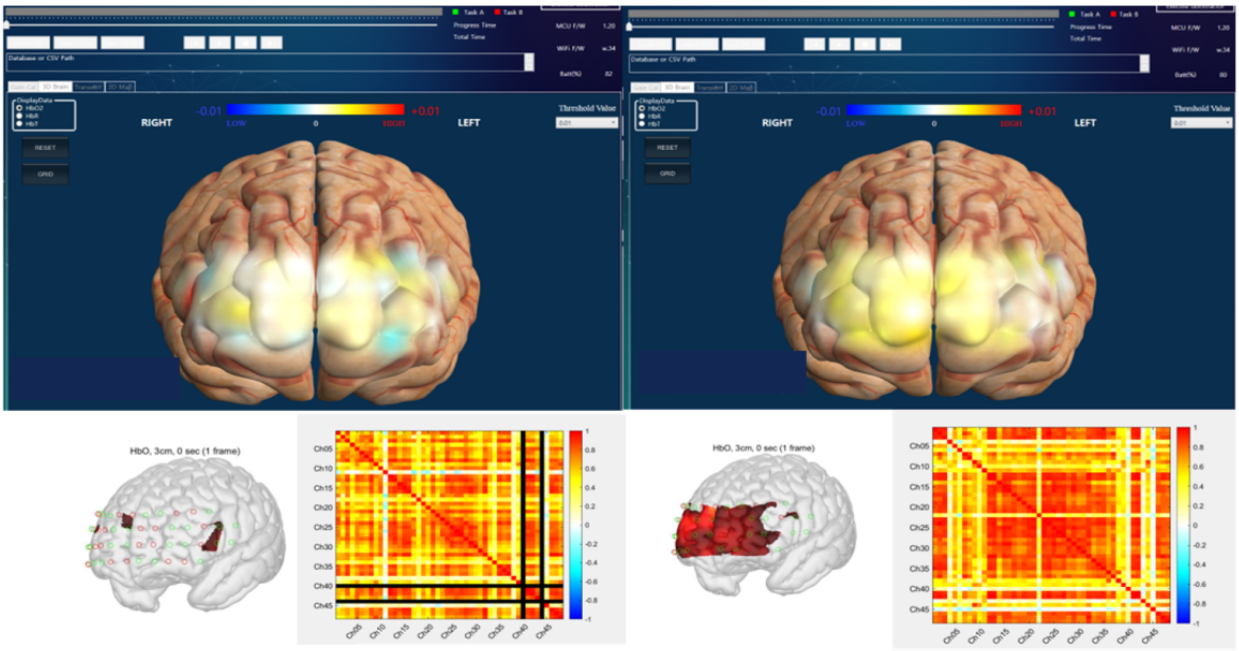
This study aims to explore the immediate neural mechanisms of the acute response to acupuncture stimulation associated with CR in normal aging and disease status and identify the neural substrates of CR.

The primary outcomes will be as follows: (1) differences in brain activation and resting-state brain connectivity according to disease status (the groups with vs without cognitive impairment); (2) differences in brain activation before and after acupuncture between study and control groups (verum acupuncture vs sham acupuncture); and (3) differences in brain activation according to CR (high CR group vs low CR group).

Secondary outcomes are brain connectivity or network metrics (graph theoretic metrics) associated with the CRIq index, differences in brain activity between working memory tasks and resting states, and network metrics associated with cognitive function scores (MMSE-K, K-MoCA).

The brain connectivity matrix will be obtained as Pearson correlation between 48 channels using time-series data during the scan period (Figure 3). Network metrics, including the index of efficiency, clustering coefficient, and centrality, can be calculated using the connectivity matrix by the Brain Connectivity toolbox in MATLAB 2023b (The Mathworks).

Figure 3. Resting-state brain connectivity matrix before acupuncture stimulation (A) and after acupuncture stimulation (B).



(A) Before acupuncture stimulation (B) After acupuncture stimulation

Data Collection, Monitoring, and Dropout Criteria

Data Collection and Adverse Events Monitoring

Demographic information (age, sex, height, and weight), medical history, and concomitant medication will be collected for each participant at the start of the study. Researchers will record blood pressure, body temperature, respiratory rate, and pulse rate in visits 0 and 1. All adverse events will be fully reported in case report forms, and the association between the adverse events and intervention will be evaluated as not related, possibly related, or related. Severity will be evaluated as mild, moderate, or severe. When severe adverse events, including death, life-threatening events, and the need for hospital admission, occur, the investigator will suspend all or part of the clinical trial and notify other investigators and the Institutional Review Board within 24 hours.

Dropout Criteria

The participants will be excluded in the following cases: severe adverse events occur; difficulty proceeding with the trial due to adverse events; the participant or a legal representative wants to stop the trial; the participant withdraws consent to join the trial; the participant fails to finish the interview or the fNIRS scan; and progression of the trial is considered inappropriate by the principal investigator.

Statistical Analysis

Only data from participants who completed the fNIRS scan, cognitive function test, and measurement of CR will be contained in the statistical analysis. All categorical data are presented as frequencies or percentiles and will be analyzed using the chi-square or Fisher's exact test. All numerical data will be presented as the mean and standard deviation and analyzed using an independent *t* test or Wilcoxon rank-sum test. Preprocessing and analyses of fNIRS data will be performed using MATLAB and the NIRSIT analysis tool.

A two-sample *t* test will be performed to compare the brain activations and connectivity between the groups with and without cognitive impairment. A paired *t* test will be conducted to compare the brain activations and connectivity before and after acupuncture stimulation. The CR values from CRIq will be applied for correlation analysis in the form of continuous variables or divided into binary groups (high and low CR) by mean values for subgroup analysis. Since the expression of CR may appear differently depending on the disease status, a subgroup analysis will be conducted by dividing the healthy control and the patient group. Mixed model analysis will be adjusted to determine the interaction effect of intervention and CR in both groups. Pearson correlation will determine the CR-related brain connectivity or clinical score–related metrics. If there is a significant age difference between 2 groups, the age factor will be added as a covariate in the analysis to adjust the effect of age as much as possible.

Statistical significance in fNIRS imaging would be explored using uncorrected and corrected levels (false discovery rate and family-wise error). At the uncorrected level, uncorrected $P<.001$ will be used, and at the corrected level, $P<.05$ will be applied.

Data Management

The investigators will collect and record the medical information in each participant's case report form. All study data, including all patient confirmations, all original signed informed consent forms, and detailed original records, will be retained by the study institution for 3 years after the end of the trial.

Quality Control

Important protocol modifications must be reported to the IRB. The approval period of the trial is 1 year, and after 1 year,

regular reports must be submitted to the IRB, and re-approval should be obtained. Before the beginning of the trial, all investigators involved in the intervention will be trained in the process of the trial. In total, 2 independent research assistants will check the data and case report forms to avoid mistyping or errors during the trial. There is no plan for early termination of the study before February 2025. If the target number of participants is complete, additional recruitment may proceed depending on the research funding status.

Ethical Considerations

The trial will be performed in accordance with the Declaration of Helsinki. This trial has been approved by the Institutional Review Board of Sangji University (1040782-230426-HR-04-112). The protocol has been registered with the Clinical Research Information Service of the Republic of Korea (number KCT0008719), one of the WHO ICTRP Primary Registries. Written informed consent will be obtained from each participant or their legal representative. All data will be anonymized, and the identification information of all documents will be recorded according to the identification code. The information will be kept confidential in a locked place. Participants in this study will be paid a small compensation fee, approximately 50,000 won (equivalent to approximately US $30), for participation in the study.

Results

The recruitment and enrollment of the study began in August 2023, and to date, there have been 50 participants, divided into 20 in the group with cognitive impairment and 30 in the unimpaired group. Within the group with cognitive impairment, 16 participants (80%) had dementia and 4 subjects had MCI. The percentages of female participants in the group with cognitive impairment and the group without cognitive impairment were 70% and 57%, respectively. Ongoing recruitment is in progress. The protocol version used in this study is V.1.0 (2023.06.12). This study will continue until February 2025, after which the communication of final results will be made in accordance with the CONSORT checklist.

Discussion

Overview

Dementia affects an estimated 57 million people worldwide, and AD is the most common dementia-inducing disease [41]. The neuropathologic hallmark of AD is extracellular amyloid beta deposition and neurofibrillary tangles consisting of phosphorylated tau protein [42]. Although various therapeutic drugs are being developed with the advancement of medical technology, there is no definitive treatment for AD. Therefore, early diagnosis and prevention are important for cognitive impairment disorder.

At first, CR originated from the observations of the mismatch between the pathological degree of brain damage and clinical symptoms. In a postmortem study, there were neuropathological alterations comparable to dementia; however, the participants had no symptoms of dementia in their lives [43]. In this context, CR is considered a factor mediating the relationship between the neuropathology of the disease and clinical manifestation and has clinical importance as a prognostic factor of the disease trajectory [44]. There are several CR surrogate markers, including years of education, occupation, leisure activities, composite scores, questionnaires, and residual methods using imaging markers. This study applies a CRIq, which consists of subscores of lifelong education, occupation, and leisure activity as the main CR proxy.

Acupuncture has been used to treat several neurological diseases in East Asian countries. Several studies have revealed the effects and mechanisms of acupuncture in MCI or AD using neuroimaging methods. Moreover, studies applying fNIRS have reported the neural mechanisms of acupuncture manipulation in patients with MCI and healthy participants [45,46]. However, there have been no studies on the neural mechanisms of acupuncture stimulation in relation to CR.

This randomized, placebo-controlled clinical trial aims to investigate the neural substrates of CR in both the normal group and the group with cognitive impairment and explore the neural mechanisms of acupuncture stimulation in relation to CR using fNIRS. The potential significance of this research lies in elucidating the connection between acupuncture and CR, thus providing insights into the therapeutic possibilities for cognitive impairments. We expect to contribute to identifying neural mechanisms of acupuncture stimulation in cognitive impairment in relation to CR. This study could provide a basis for further study about the long-term effects and mechanisms of acupuncture treatment in cognitive impairment.

Innovations and Limitations

This is the first study to identify the association between CR, an important factor related to the prognosis of dementia, and acupuncture stimulation. The application of the neuroimaging method (fNIRS) can provide new insights into the neural mechanisms of complementary medicine in the field of convergence research. This randomized, controlled trial can contribute to elucidating the genuine neural response to the acupuncture stimulation. However, as a cross-sectional study, it is not possible to identify the long-term effect of acupuncture treatment on cognitive impairments and explore the longitudinal neural mechanism of acupuncture treatment. Additionally, to ensure the reliability of the data, we still further expand the sample size.

Conclusions

This study will provide data on the neural substrates of acupuncture stimulation associated with CR as well as brain network alterations depending on disease status. More importantly, if the acute neural mechanisms of acupuncture stimulation are identified, the results could serve as a basis for the long-term effects of acupuncture treatment on cognitive impairments. This study could provide a scientific foundation for further clinical application of acupuncture as a complementary medicine for cognitive impairments, which induce a high socioeconomic burden.

Acknowledgments

This work was supported by the National Research Foundation of Korea (NRF) grant funded by the Korean Government (MSIT; number NRF-2022R1F1A1061004). This research was supported by the Korea Basic Science Institute (National Research Facilities and Equipment Center) granted by the Ministry of Science and ICT (number RS-2024-00403722). Funders only provided financial support and were not involved in this article, including the review, editing, or submission for publication.

Data Availability

All study data will be retained by the study institution for 3 years after the end of the trial. All investigators participating in this trial will have access to the final dataset after recruitment is completed. The datasets generated or analyzed during this study are available from the corresponding author on reasonable request.

Conflicts of Interest

None declared.

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Abbreviations

AD: Alzheimer disease
CR: cognitive reserve
CRIq: Cognitive Reserve Index Questionnaire
fMRI: functional magnetic resonance imaging
fNIRS: functional near-infrared spectroscopy
HbO2: oxyhemoglobin
HbR: deoxyhemoglobin
HbT: total hemoglobin
MCI: mild cognitive impairment
MMSE: Mini Mental Status Examination
MoCA: Montreal Cognitive Assessment
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials

Edited by A Schwartz; submitted 24.09.24; peer-reviewed by LM Jiang; comments to author 16.12.24; revised version received 14.01.25; accepted 22.01.25; published 19.02.25.

Please cite as:
Shin H, Seong W, Woo Y, Kim JH, Park KR, Lee DH
Neural Mechanism of Cognitive Reserve in Acupuncture Stimulation: Protocol for a Randomized, Placebo-Controlled Functional Near-Infrared Spectroscopy Trial
JMIR Res Protoc 2025;14:e66838
URL: https://www.researchprotocols.org/2025/1/e66838
doi:10.2196/66838
PMID:

Protocol

Auricular Acupressure Versus an Intermittent Low-Carbohydrate Diet in Children With Overweight or Obesity With Gastric-Heat and Dampness-Obstruction Syndrome: Protocol for a Randomized Controlled Trial

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Abstract

Background: Childhood obesity frequently persists into adulthood and is associated with an increased risk and earlier onset of cardiovascular disease in later life. Behavioral change strategies have been proposed as the first-line weight management approach for children and adolescents with obesity. Nonpharmacological interventions, such as traditional Chinese medicine (TCM) auricular acupressure treatment and intermittent low-carbohydrate diet (ILCD), are increasingly being investigated in the young obese population. However, there is limited high-quality evidence about effectiveness and safety in weight control and reducing cardiometabolic risk in the pediatric population.

Objective: This study aimed to compare the effect of cardiometabolic risk reduction between TCM auricular acupressure treatment (TAAT) and ILCD in children with overweight or obesity with gastric-heat and dampness-obstruction syndrome.

Methods: This is a randomized controlled trial. Eligible participants are children with overweight or obesity and enrolled at the obesity clinic of the department of TCM at a tertiary children's hospital. Eligible participants must meet the following criteria: (1) be aged between 6 and 18 years, (2) be overweight, and (3) have gastric-heat and dampness-obstruction syndrome. Recruited children will be randomized 3:1 to receive either TAAT or a self-administered ILCD for 1 month: 150 in the TAAT group and 50 in the ILCD group. The primary outcome is the change in body weight from the beginning of treatment to the end of 1 month. Secondary outcomes included body weight, waist circumference, waist-to-height ratio, BMI, blood pressure, body fat content, indexes of liver and renal function, indexes of glucose metabolism, gut microbiota, and TCM syndrome scores at the end of 1 month and 3 months, respectively. Primary statistical analyses were conducted using the intention-to-treat strategy. A generalized linear model was used to compare the difference in weight change between the groups, with the baseline body weight as the covariate, to obtain the estimate of the mean difference in body weight change and its 95% CI, using Gaussian for family function and identity for link function.

Results: The study protocol was approved by the institutional ethical committee and registered on ClinicalTrials.gov on May 5, 2023, before recruitment. Recruitment began in June 2023 and is expected to be completed by December 2025. As of November 2024, we have enrolled 112 participants.

Conclusions: This randomized controlled trial will provide evidence on the treatment effects and safety of TAAT versus ILCD among children with overweight or obesity with gastric-heat and dampness-obstruction syndrome, in reducing body weight and

improving cardiometabolic risks. Exploratory aims include potential underlying mechanisms of the 2 kinds of interventions, based on biosamples.

Trial Registration: ClinicalTrials.gov NCT05847478. https://clinicaltrials.gov/study/NCT05847478

International Registered Report Identifier (IRRID): DERR1-10.2196/59856

(JMIR Res Protoc 2025;14:e59856) doi:10.2196/59856

KEYWORDS

children with obesity; traditional Chinese medicine; TCM auricular acupressure treatment; intermittent low carbohydrate diet; study protocol

Introduction

The Report on Cardiovascular Health and Disease in China (2022) [1] shows that cardiovascular disease is the leading cause of death among urban and rural residents in China, which is mainly caused by hypertension, dyslipidemia, diabetes, overweight or obesity, physical inactivity, inappropriate diet, and metabolic syndrome. It is important to note that obesity, especially abdominal obesity, is a direct risk factor for cardiovascular disease. Unfortunately, obesity can persist from childhood and adolescence into adulthood [2,3]. Obesity in children and adolescents is a global health issue [4], with China, India, the United States, Indonesia, and Brazil being the top-ranked countries, each estimated to have more than one million children with obesity in 2030 [5].

First-line treatments for obesity should be supported by behavioral change strategies [4]. Family-based interventions that address diet, physical activity, sedentary behavior, and sleep quality are recommended. However, the weight loss effect is not ideal and is difficult to maintain. Although evidence for pharmacotherapy and bariatric surgery as supplemental therapies is emerging, they are not recommended for weight loss in children [6]. In fact, safer and more acceptable nonpharmacological interventions, such as traditional Chinese medicine (TCM) and TCM auricular acupressure treatment (TAAT), are increasingly used.

The earliest known mention of TAAT dates back to Huang Di Nei Jing (circa 100 BC) [7,8]. Currently, auricular therapy is widely used in clinical settings for pain relief, epilepsy treatment, improving sleep quality, and obesity [9-11]. This approach offers the advantage of individualized treatment based on the dialectical theory of governance. TAAT has been found effective on children, adolescents, and adult obesity [12-14]. The study found that auricular acupuncture stimulation clearly modulates the feeding-related hypothalamic neuronal activity of experimental (both hypothalamic and dietary) obese rats. The results suggest that auricular acupuncture stimulation may not reduce appetite but is more likely concerned with satiation formation and preservation [15]. However, high-quality clinical evidence is lacking. According to TCM, obesity is located on the spleen and stomach, followed by the liver and kidney. TCM identifies several syndrome types of obesity, including gastric-heat and dampness-obstruction syndrome, spleen-deficiency and dampness-stagnation syndrome, liver-qi stagnation syndrome, and spleen-kidney deficiency syndrome [16,17]. Among these, gastric-heat and dampness-obstruction syndrome is the most common type [18]. In order to ensure the sample size is attained, the gastric-heat and dampness-obstruction syndrome has been selected for inclusion in the study. In addition, the choice of a single syndrome in preference to multiple options ensures comparability in the evaluation of efficacy between groups.

Numerous studies have demonstrated the effectiveness of low carbohydrate diets (<50 g per day or <10% energy from carbohydrates) in combating obesity [19], deemed feasible and acceptable [20,21]. Our previous research has shown that the intermittent low carbohydrate diet (ILCD) was effective in improving weight-related outcomes in children and adolescents [22]. However, the efficacy needs to be further investigated, and long-term effects are uncertain. So far, there are currently no randomized controlled trials comparing the effectiveness between ILCD and TAAT. At the same time, our secondary aim is to explore the mechanistic differences between the 2 nondrug interventions. Therefore, this study aims to assess whether TAAT as the experimental arm is more effective than ILCD as the control arm in improving the cardiometabolic risk in children with overweight or obesity with gastric-heat and dampness-obstruction syndrome.

Methods

Objective and Trial Design

This is a randomized controlled superiority trial that aims to compare the effects of TAAT versus ILCD in reducing the cardiometabolic risk in children with overweight or obesity with gastric-heat and dampness-obstruction syndrome. Participants were allocated in a 3:1 ratio to either an auricular acupressure treatment group or a control group. The TCM clinicians were aware of the allocation but did not participate in the following research. Conversely, the outcome observers were blinded about the allocation.

Recruitment and Study Setting

Eligible participants were recruited by a pediatrician at the obesity clinic of the Department of TCM in Children's Hospital of Fudan University. All participants were required to provide written consent before intervention.

Participants Eligibility Criteria

Eligible participants must meet the following criteria: (1) be aged between 6 and 18 years, (2) be overweight [23], and (3) have gastric-heat and dampness-obstruction syndrome [16].

Overweight or obesity with gastric-heat and dampness-obstruction syndrome was defined as follows:

(1) The "Expert Consensus on Diagnosis, Assessment, and Management of Obesity in Chinese Children" states that BMIs between 85% and 95% were classified as overweight, while those above 95% were classified as obese for children of the same gender and age [23].

(2) The "Pediatrics of Traditional Chinese Medicine" framework [16] outlined the conditions that must be met for the gastric-heat and dampness-obstruction syndrome, which include (1) dizziness and heaviness in the head, (2) thirst, (3) rapid digestion of food and polyorexia, (4) heaviness of limbs, (5) fatigue body and lack of strength, (6) a red tongue, (7) greasy fur, and (8) a slippery pulse. It is important to note that conditions (7) and (8) must be satisfied, while conditions (1) to (6) must be satisfied at least 3 conditions.

Participants who met any of the following exclusion criteria were excluded: (1) having hereditary obesity or obesity caused by endocrine disorders, such as Cushing syndrome, primary hypothyroidism, and hypothalamic obesity; (2) currently being enrolled in other clinical trials or having participated in another clinical trial in the past 3 months; (3) self-administration of oral weight-loss medications or other forms of meal replacements; and (4) having serious organic diseases of the heart, liver, kidneys, or brain, or infectious diseases or psychiatric disorders.

Interventions

Experimental Group (TAAT Group)

Specialized TCM clinicians conducted TAAT following a standardized procedure. The location and operation of the ear acupoints followed the guidelines outlined in the "National Standard of the Peoples Republic of China for Nomenclature and Location of Auricular Points (GB/*t* 13734-2008)." In addition, all TCM clinicians had received specialized training to ensure a comprehensive understanding of the auricular acupressure intervention program and to standardize the procedures performed by different clinicians.

The study selected the following ear acupoints for acupressure treatment: Shenmen (TF4), Xiaoping (TG2), Endocrine (CO18), Stomach (CO4), Mouth (CO1), and Subcortex (AT4) (refer to Figures 1 and 2) [24]. The acupressure was administered using an opaque patch with Vaccaria seed. Participants were instructed to apply pressure for 1 minute before and after meals each day, for a total of 2 to 3 days per week. They were followed weekly and received a 3-course treatment, with 1 course per month.

Figure 1. Location of the subcortex (AT4).

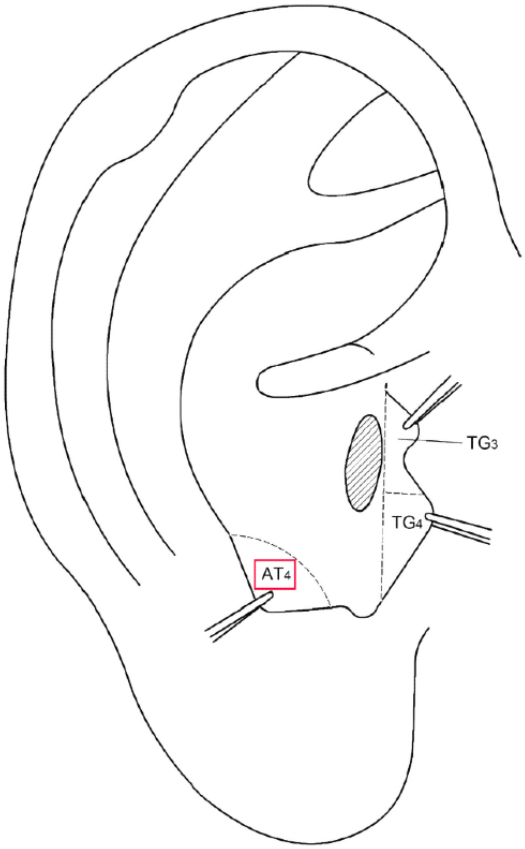
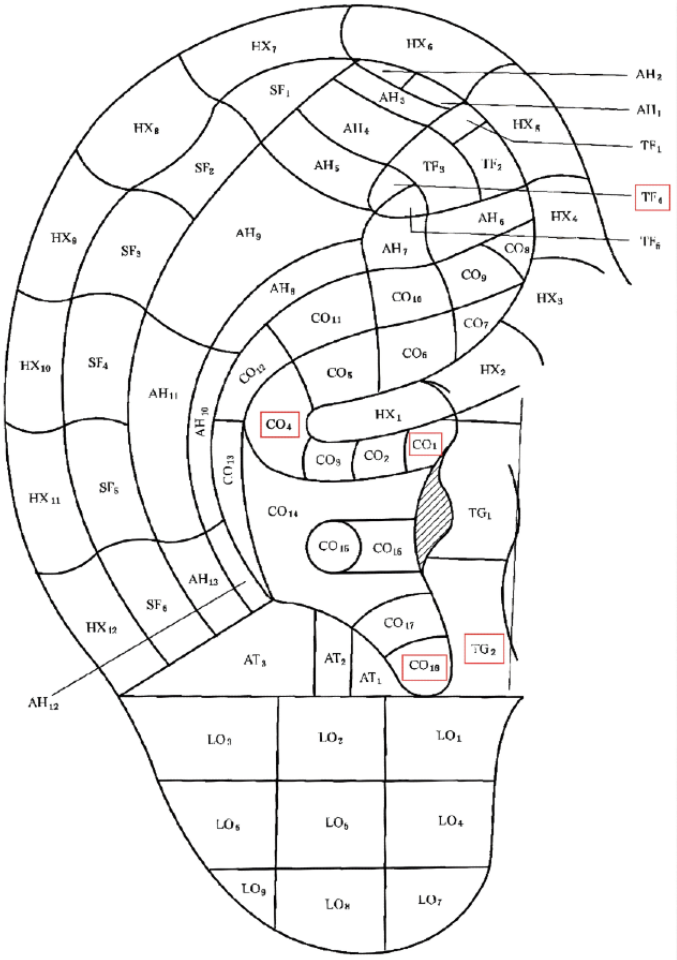


Figure 2. Location of the shenmen (TF4), Xiaoping (TG2), endocrine (CO18), stomach (CO4), mouth (CO1).



Control Group (ILCD Group)

Participants were required to limit their daily carbohydrate intake to 50 g or less, while their dietary calorie intake was not restricted for nonconsecutive 7 days of 2 weeks, corresponding to 14 days in a month. On the remaining days, participants should maintain their normal diet. The intervention period lasted for 1 month, followed by a 2-month follow-up period [20].

Follow-Up Period

First, a WeChat group was created for parents of participants to facilitate communication and monitoring about diet and exercise recording, as well as scheduling follow-up appointments. Second, adherence to the study interventions were uniformly assessed in both groups at each visit. Third, if participants missed any visits, investigators would contact them directly by telephone to encourage continued participation and evaluate barriers.

The research assistant attempted to establish contact with the missed participants. A dropout participant was defined as someone who had not been reached for 3 months. If participants decided to withdraw before completion, all collected data would be remained for analysis.

Outcomes

Primary Outcome

Change in body weight from the beginning of the treatment to 1 month.

Secondary Outcomes

Secondary outcomes included body weight, waist circumference, waist-to-height ratio, BMI, blood pressure (BP), body fat content, glucose metabolism, blood lipid levels, liver and kidney function, composition of gut microbiota, and TCM syndrome score, and were assessed at the end of 1 month and 3 months, respectively.

Measurement

Anthropometry

Including the measurements of weight, height, waist circumference (WC), and BP. These measurements should be taken by the same person, using the same instruments, at the same time of day. Each measurement should be taken 3 times in a row, and the average of the 3 values should be used.

(1) **Weight measurement:** The participant should be weighed in light clothing and preferably with an empty bladder. They should also remove shoes, heavy jewelry, and watches. The electronic weight scale should display 0.0 before the participant stands on it. The participants should stand with their feet

together in the center and their heels against the back edge of the scales. The participant's arms should be hanging loosely at their sides and their head should be facing forward. The weight measurements were recorded in kilograms and were accurate to 0.1.

(2) **Height measurement:** Height should be measured using a stadiometer with the participant standing barefoot and with feet together. The head should be positioned level with a horizontal Frankfurt plane, which is an imaginary line from the lower border of the eye orbit to the auditory meatus. Any hair knots or braids that may interfere with the measurement should be untangled. The press plate should be in contact with the head with moderate tightness. The height measurements were recorded in centimeters with an accuracy of 0.1.

BMI was a widely used tool for assessing the risk of overweight and obesity in individuals. It was calculated using the following equation:

(3) **Waist circumference measurement:** The measurement should be taken while the participant exhales. WC was measured by placing a tape measure around the waist, 1 cm below the navel, with the participant standing and arms naturally at their sides. Record the data in centimeters with an accuracy of 0.1.

Waist-to-height ratio had emerged as a surrogate for abdominal obesity that also takes into account body size and allows the same cut of across age and gender [25]. It was calculated using the following equation:

(4) **Blood pressure measurement:** BP was measured on the right arm using the CONTEC08A electronic sphygmomanometer (CONTEC Medical Systems Co). The participant should be seated in a quiet room for 3-5 minutes before measurement, with the back supported and feet uncrossed on the floor. The right arm should be at heart level, supported, and uncovered above the cuff. The correct cuff size should be used. The bladder length should be 80%-100% of the circumference of the arm, and the width should be at least 40%.

Body Fat Content

Body composition was measured by determining the body fat percentage using the LUNAR dual photon X-ray dual-energy X-ray absorptiometry equipment (General Electric Company). Dual-energy X-ray absorptiometry was a medical imaging technology that used low dose radiation for a whole-body scan to provide accurate measurements of fat percentage. The equipment was operated by qualified professionals.

Venous Blood Tests

The tests were conducted after a 10-hour overnight fast to avoid any influence of diet on the test results. The tests included glucose metabolism, blood lipid levels, and liver and kidney function. The remaining blood samples were stored in a –80°C refrigerator for further testing. The operators conducting the tests possessed professional qualifications.

TCM Syndrome Score

"Pediatrics of Traditional Chinese Medicine" listed a number of TCM symptoms in obesity with gastric-heat and dampness-obstruction syndrome: (1) dizziness and heaviness in the head, (2) thirst, (3) rapid digestion of food and polyorexia, (4) heaviness of limbs, (5) fatigue body and lack of strength, (6) a red tongue, (7) greasy fur, and (8) a slippery pulse. Each item was scored on a scale of 0-2, with 2 points for obvious symptoms, 0 points for nonsymptomatic, and 1 point for symptoms that are between obvious and nonsymptomatic. The total syndrome score was obtained by adding up the scores for each item. A qualified clinician performed the score evaluation.

Gut Microbiota Test

Stool samples were collected using Boyou nucleic acid storage tubes (Shanghai Biotechnology Corporation) and stored in a laboratory refrigerator at –80°C. To study intestinal flora diversity, the 16S rDNA target region would be amplified, and information on intestinal microbial diversity and community composition will be obtained by detecting sequence variation and abundance of the target region. The operators possessed professional qualifications.

Dietary and Exercise Data

Diet and exercise data were recorded by the children and their families, but they were educated by qualified clinicians before recording [26,27].

(1) **From the baseline to the first month:** The weight of the food was measured using an electronic scale before and after each meal, and photographs were taken as well. Participants were required to wear sports watches every day, including during sleep, but not while bathing, swimming, or in other special cases. Dietary data included the type and weight of the foods consumed, while exercise data included step count, calorie consumption, resting heart rate, sleep duration, and exercise type. All data was meticulously recorded daily in the "Diet and Exercise Handbook."

(2) **From the second month to the third month:** The method and content remained unchanged. Dietary and exercise data were recorded on Thursdays, Fridays, and Saturdays during 1 week, and distributed at the beginning, middle, and end of the month, rather than every day.

Participant Timeline

The participant timeline was shown in Table 1, following the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) diagram [28].

Table 1. Schedule of enrollment, interventions, and assessments for the trial. t1, preinclusion assessment; t0, baseline; t1, intervention for one 1 month; t2, intervention for 3 months.

Time point	Enrolment ($-t_1$)	Allocation (t0; Day 0)	Post allocation		Closed out
			t_1 *1 month*	t_2 *3 months*	
Enrolment					
Eligibility screen	✔	N/A[a]	N/A	N/A	N/A
Informed consent	✔	N/A	N/A	N/A	N/A
Allocation	N/A	✔	N/A	N/A	N/A
Interventions					
Auricular acupressure	N/A	N/A	✔	✔	N/A
Intermittent carbohydrate restriction diet	N/A	N/A	✔	N/A	N/A
Assessments					
General investigation	N/A	✔	✔	✔	N/A
Anthropometry (Height, Weight, WC[b], and BP[c])	N/A	✔	✔	✔	N/A
Body fat content	N/A	✔	✔	✔	N/A
Indexes of liver and renal functions	N/A	✔	✔	✔	N/A
Indexes of glucose metabolism	N/A	✔	✔	✔	N/A
Levels of serum lipid	N/A	✔	✔	✔	N/A
TCM[d] syndrome score	N/A	✔	✔	✔	N/A
Gut microbiota	N/A	✔	✔	N/A	N/A
Dietary data	N/A	✔	✔	✔	N/A
Exercise data	N/A	✔	✔	✔	N/A
Adverse events	N/A	N/A	✔	✔	N/A

[a]N/A: not applicable.

[b]WC: waist circumference.

[c]BP: blood pressure.

[d]TCM: Traditional Chinese Medicine.

Sample Size

The primary outcome was the change in body weight from baseline to 1 month. The sample size calculation was based on the difference in weight change between the 2 groups: the TAAT group and the ILCD group.

Our pilot data from 12 patients revealed a weight loss of 1.9 kg after 4 weeks of TAAT and a weight reduction of 1.4 kg after 4 weeks of ILCD, with an SD of 1.1 kg. We assumed a 0.5 kg difference in weight reduction between the 2 arms, power of 0.80, a 2-sided α of .05, and a sample size ratio of 3:1, a minimum sample size of 150 for the TAAT group and 50 for the ILCD group were required, respectively. Assuming a dropout rate of 15%, the trial enrolled at least 240 participants. The “test for 2 means module” of the PASS 16.0 software was used.

Recruitment

The estimated period for recruitment, intervention, and data collection would take probably 30 months to complete. Eligible clients attending the obesity clinic at the Children’s Hospital of Fudan University were invited to participate in the study through collaboration with TCM clinicians. The time required for participant recruitment and baseline assessment was approximately 30 to 45 minutes.

Randomization and Blinding

Participants were randomly assigned to either the experimental or control group through a simple randomization process generated by the R Language (version 4.2.2; R core team). This process was designed by the clinical trial unit of the Children’s Hospital of Fudan University and follows a 3:1 allocation ratio.

The study coordinator, who was not involved in data collection, performed the allocation. The randomization list was kept strictly confidential. Allocation was done by the study coordinator in a sequentially numbered fashion using identical, opaque, sealed envelopes. The recruiting clinicians were blinded to study group allocation and did not have access to the allocation sequence.

Eligible participants were enrolled by trained clinicians. The study coordinator independently assigned participants to either the intervention or control groups. Outcome observers were blinded. The analysis team received aggregated data obtained for the control and experimental groups. Study participants

could be blinded, but they were scheduled for separate follow-up dates.

Adverse Events and Assessment of Safety

After participants provided informed consent and enrolled in the study, any adverse events were collected and recorded until the end of the study period. Adverse events that occurred after consent was signed, but before receiving the study intervention was reported as not related to our intervention. Any serious adverse event that occurred would be reported to the principal investigator and documented.

Data Management and Monitoring

Trained clinicians were input data onto a paper-based clinical research form designed by the research team. Once data collection was complete for each participant, it would be entered into an electronic database with built-in checks to ensure completeness. Data monitoring has occurred periodically throughout the study. We used access to create a database, and 2 investigators independently performed dual data entry twice. Once verified, the database was saved appropriately. After confirming the accuracy of the database, it was locked and submitted to an independent statistical team for analysis.

Statistical Analysis

Primary statistical analyses were conducted using the intention-to-treat strategy. Sensitivity analyses were performed using per-protocol set analysis.

Analysis of Primary Outcome

The primary outcome in this study was the change in body weight from baseline to 1 month. A generalized linear model (GLM) was used to compare the difference in weight change between the groups, with the baseline body weight as the covariate, to obtain the estimate of the mean difference in body weight change and its 95% CI, using Gaussian for family function and identity for link function.

Analysis of Secondary Outcomes

GLM was used to obtain differences in effect sizes and their 95% CI for continuous variables between groups. Categorical variables were described in absolute numbers (percentages) and GLM was used to obtain differences in effect values and their 95% CI, using logistic for family function and logit for link function.

Statistical analyses were conducted using Stata 16.0 software (StataCrop). All statistical tests were 2-sided with a significance level of α=.05. Differences were considered statistically significant at P<.05.

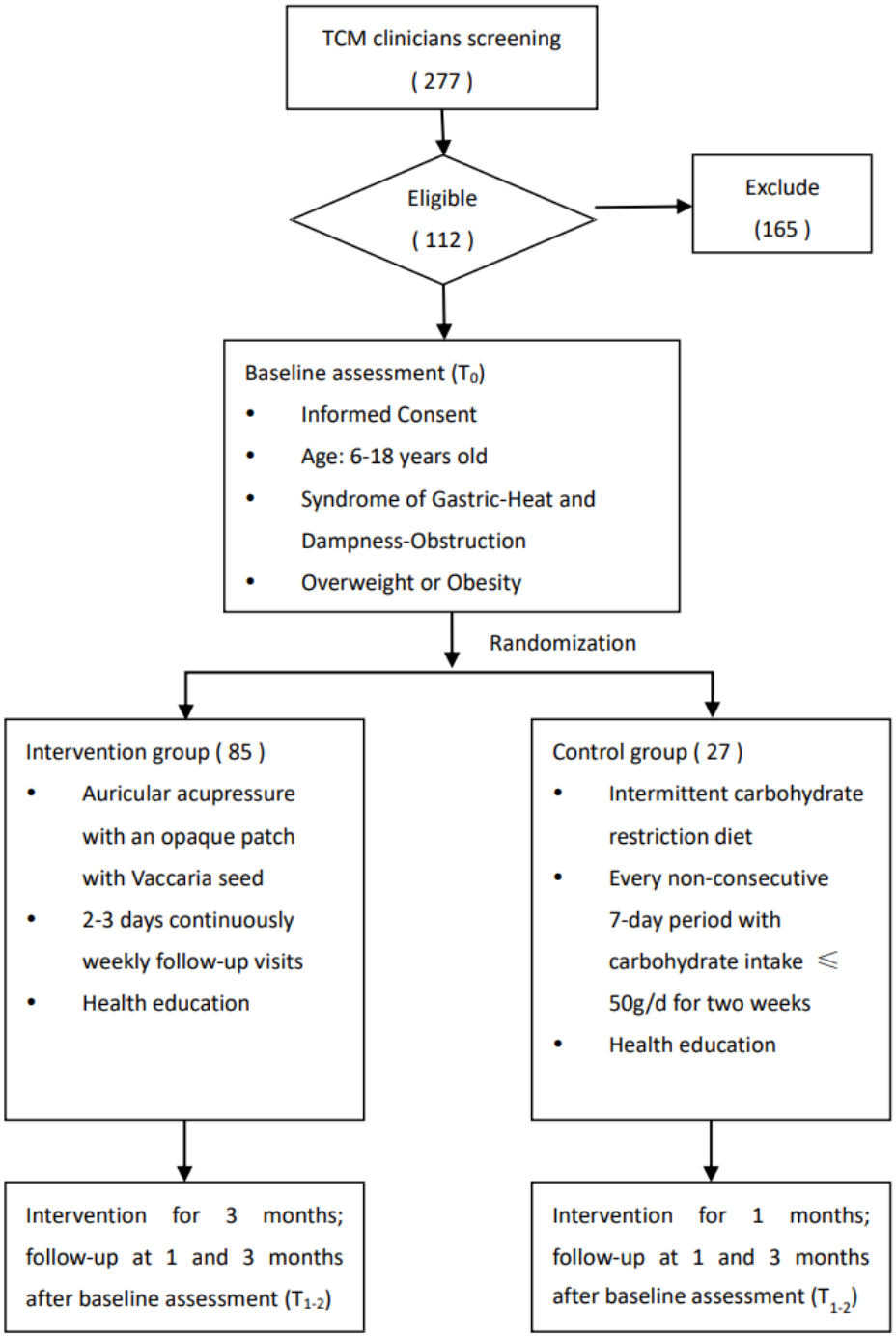
Ethical Considerations

This study has been approved by the Medical Ethics Committee of the Children's Hospital of Fudan University and will be conducted in accordance with the approved guidelines and regulations of the participating institution (approval number 2021 [.350]). This trial was conducted in accordance with the current version (AP_IDR_2.0) of the protocol, which has been registered at ClinicalTrials.gov. Informed written consent was obtained from all patients before inclusion in the study. As the involvement of the patients were voluntary, the study could be stopped at any time. All records that contain names or other personal identifiers were stored separately from study records identified by code number. The identification of participants in any images of the manuscript or supplementary material was impossible. For example, the researchers provided the necessary recording materials and sample collectors. The intervention method did not entail additional costs for the participants; thus, no compensation was required.

Results

The protocol was registered on ClinicalTrials.gov (NCT05847478) on May 5, 2023. The current protocol is version 2.0, dated February 28, 2023, which is the final version as approved by the institutional ethical committee. Recruitment started in June 2023 and is expected to be completed in December 2025. By November 2024, we had enrolled 112 participants (Figure 3).

Figure 3. Flowchart of the study. TCM: traditional Chinese medicine; T0: baseline; T1: intervention for 1 month; T2: intervention for 3 months.



Discussion

Anticipated Findings

It is hypothesized that TAAT will prove superior to ILCD in controlling body weight through this clinical trial. In addition, it is anticipated that the mechanistic differences between the 2 nondrug intervention methods will be elucidated. This study will be the first randomized controlled trial to investigate the effect and safety of TAAT compared with ILCD for overweight or obesity and other cardiometabolic risk factors. Previous studies on the effects of auricular treatment have mainly focused on adolescents and adults [12,14]. A study was conducted as a randomized controlled trial to examine the effects of auricular acupressure on obesity improvement in children. However, this trial had a small sample size and did not take into account the impact of diet, exercise, and lifestyle on body weight [15]. Consequently, there is a lack of high-quality clinical trials on the effects of TAAT in children with obesity, although we found some clinical evidence of this approach in children. Furthermore, the participants' gut microbiota will be studied in order to explore the underlying mechanisms of the 2 different interventions.

All participants in this study are patients from the Department of TCM and seeking TCM intervention. As one of the treatment methods in TCM, previous studies have shown that TAAT is effective in reducing body weight, WC, and body fat mass

[14,29]; therefore, we did not consider a blank control group, instead, using an ILCD, according to its effect indicated in recent randomized trials [30,31].

TAAT appears minimal side effects, including the pain caused by local noninvasive stimulation that can be tolerated by most children [32]. As participants are recruited from the obesity clinic of the Department of TCM, randomization is set in a 3:1 ratio, allowing that needs of more participants are satisfied.

Maintaining compliance remains challenging to the young population. To ensure better compliance, we use methods such as regular reminders and random checks. To avoid bias, the outcome observer is unaware of the grouping of the participants.

In conclusion, we will evaluate the efficacy and safety of the TAAT in losing weight and improving the cardiometabolic risk of overweight or obese children with gastric-heat and dampness-obstruction syndrome. The results of this study will lead to an update of the consensus on TCM intervention for obesity. However, given the limitations of the intervention time in the experimental design, it is hoped that in future clinical trials, the intervention and follow-up time will be extended in order to obtain a long-term evaluation of the intervention effect.

Conclusion

We conducted a pragmatic randomized controlled trial to investigate the effect and safety of TAAT compared with ILCD for overweight or obese children comorbid with at least one cardiometabolic risk factor. Furthermore, our study will investigate the participants' differential responses of gut microbiota and serum biomarkers to examine underlying mechanisms. The protocol of our study will provide methodologic information and obtain interesting evidence from children for the 2 kinds of nonpharmacological interventions.

Acknowledgments

We thank all the patients and doctors who participated in this study. The funding agency had no role in the study design, data collection, data analysis, data interpretation, writing of the report, or the decision to submit the report for publication.

This study was supported by grants from the Shanghai Municipal Comprehensive Hospital Integrated Traditional Chinese and Western Medicine Special Project Funding (project number ZHYY-ZXYJHZX-202111).

Data Availability

The datasets analyzed in this study are available from the corresponding author upon reasonable request.

Authors' Contributions

WS and JWH designed and wrote the manuscript. WLY and JY designed and revised the manuscript. WQW and CL prepared the figure. YLD prepared the table. YTL searched the literature.

Conflicts of Interest

None declared.

Multimedia Appendix 1
SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) checklist.
[DOC File , 114 KB - resprot_v14i1e59856_app1.doc]

Multimedia Appendix 2
CONSORT (Consolidated Standards of Reporting Trials) checklist.
[PDF File (Adobe PDF File), 83 KB - resprot_v14i1e59856_app2.pdf]

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Abbreviations

BP: blood pressure
GLM: generalized linear model
ILCD: intermittent low carbohydrate diet
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials
TAAT: TCM auricular acupressure treatment
TCM: traditional Chinese medicine
WC: waist circumference

Edited by A Schwartz, T Leung; submitted 01.05.24; peer-reviewed by TP Guo, X Zhang, Y Wang, F Ouyang, Y Yan; comments to author 22.10.24; revised version received 15.12.24; accepted 30.01.25; published 03.03.25.

Please cite as:
Sun W, He J, Wang W, Lu C, Lin Y, Dou Y, Yan W, Yu J
Auricular Acupressure Versus an Intermittent Low-Carbohydrate Diet in Children With Overweight or Obesity With Gastric-Heat and Dampness-Obstruction Syndrome: Protocol for a Randomized Controlled Trial
JMIR Res Protoc 2025;14:e59856
URL: https://www.researchprotocols.org/2025/1/e59856
doi:10.2196/59856
PMID:40053799

Protocol

Evaluation of the Efficacy of the Traditional Chinese Medicine Formulation Ru-Yi-Jin-Huang-Saan on Colles Fracture After Surgery: Protocol for a Randomized, Double-Blind, Placebo-Controlled Trial

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Abstract

Background: Colles fracture, a common wrist injury, often requires surgical intervention. After surgery, patients may experience persistent pain and reduced wrist function, potentially resulting in long-term disability. In clinical practice, traditional Chinese medicine practitioners frequently use Ru-Yi-Jin-Huang-Saan (RYJHS) to treat such patients in Taiwan. RYJHS is a traditional Chinese herbal formula with a history spanning centuries, primarily used topically for the treatment of bone fractures and the promotion of healing. However, there is currently a lack of substantial clinical evidence supporting its efficacy in the management of postsurgical Colles fractures. To the best of our knowledge, there are no studies evaluating the clinical effectiveness of RYJHS.

Objective: This study aims to investigate the therapeutic potential of RYJHS in postsurgical Colles fracture cases. An additional objective is to provide an alternative treatment option for postoperative patients unable to take anti-inflammatory and pain relief medications.

Methods: This is a protocol for a randomized, double-blind, placebo-controlled trial. A total of 100 postoperative patients with Colles fracture, aged 20-80 years, will be recruited for this study. They will be randomly assigned to either the experimental or control group in a 1:1 allocation ratio. Both groups will receive standard postoperative Colles fracture treatment. The primary outcome measure will assess wrist functional recovery using the Patient-Rated Wrist Evaluation score. Secondary outcomes will include C-reactive protein levels and ultrasound measurements of wrist swelling. All of these examinations will be assessed at baseline, 3 days after surgery, and 6 days after surgery. In addition, the Dyshidrotic Eczema Area and Severity Index will be used to monitor for adverse skin reactions.

Results: This protocol was registered at ClinicalTrials.gov on December 6, 2022. It was performed in accordance with the approved guidelines and regulations of the participating institutions. Recruitment began in May 2023, with data collection expected to conclude in May 2025. Study completion is expected in December 2025.

Conclusions: This is the first protocol discussing the assessment of the therapeutic efficacy and safety of topical traditional Chinese medicine in patients after fracture surgery. The protocol will establish an integrated care model combining both traditional Chinese medicine and Western medicine for postsurgical fracture cases.

Trial Registration: ClinicalTrials.gov NCT05638360; https://clinicaltrials.gov/ct2/show/NCT05638360

International Registered Report Identifier (IRRID): DERR1-10.2196/56849

(JMIR Res Protoc 2025;14:e56849) doi:10.2196/56849

KEYWORDS

traditional Chinese medicine; Ru-Yi-Jin-Huang-Saan; external application; Colles fracture; Patient-Rated Wrist Evaluation; PRWE; PRWE score; surgeries; fracture; randomized controlled trial; RCT; alternative treatment; postoperative; protocol; Western medicine; wrist evaluation; pain relief medication

Introduction

Distal radial fracture is the most common fracture clinically and is approximately one-sixth of cases in emergency departments in the United States [1]. Studies on the Taiwanese population have shown that the prevalence of Colles fracture was 10.2-14.5 per 10,000 people [2]. This situation causes huge losses to the social economy, as well as decreased school attendance, lost work hours, care needs, and permanent disability [3]. In the Western world, closed reduction and cast immobilization are the first choices of treatments in most cases of distal radius fracture [4]. However, surgery intervention is the first choice in Taiwan. Unfortunately, pain and swelling after surgery may hinder rehabilitation and the regaining of hand function, such as postponed recovery of range of motion, daily function, and muscle power [5]. To control pain and swelling, physicians often use ice packing [6], opioids, nonsteroidal anti-inflammatory drugs (NSAIDs), and steroids [7-9]. Some studies reported that these drugs can have the risk of addiction, lead to respiratory restriction, delay fracture wound healing, raise the risk of osteoporosis, and raise glucose levels [10-13]. Since internal medicine has side effects, external medicine should be used to reduce swelling and relieve pain after the operation.

Traditional Chinese medicine (TCM) has been used to treat fractures for thousands of years. In animal studies, TCM extracts have been shown to accelerate bone healing and prevent delayed fracture healing and nonunion [14]. Other studies have also shown that TCM inhibits the inflammatory response in osteoarthritis rat models [15,16]. Until now, there has been no published study on the application of TCM in the treatment of postoperative fractures. However, TCM for external application has been widely used to treat swelling and pain after fracture. Therefore, we have designed an experiment to verify the curative effect of the external application of TCM in fracture surgery.

Ru-Yi-Jin-Huang-Saan (RYJHS) is a TCM herbal patch composed of a fixed blend of TCM ingredients combined with water. It is traditionally applied to relieve swelling and pain in the early stages of musculoskeletal injuries, attributed in TCM theory to its heat-clearing and swelling-reducing properties. Modern pharmacological studies also confirm its antibacterial, anti-inflammatory, wound-healing, and hemostatic effects [17,18]. As recorded in the classic TCM text, *The Golden Mirror of Medicine*, RYJHS is prescribed for conditions such as furuncles, carbuncles, traumatic wounds, mumps, contact dermatitis, lower limb edema, mastitis, and cellulitis. An animal study also demonstrated that RYJHS significantly accelerated fracture healing, notably enhancing collagen formation and bone cell metabolism [19].

The primary components of RYJHS include *Trichosanthis radix*, *Rhei radix et Rhizoma*, *Phellodendri cortex*, *Curcumae longae rhizoma*, *Angelicae dahuricae radix*, *Magnoliae cortex*, *Glycyrrhizae radix et Rhizoma*, *Citri reticulatae pericarpium vetum*, *Atractylodis rhizoma*, and *Arisaematis rhizoma*. Pharmacological research highlights the various therapeutic properties of these components (given in Table 1). For example, *Trichosanthes kirilowii* extract has been shown to accelerate wound healing and possesses antibacterial and anti-inflammatory effects [20-22]. *Rhei radix et rhizoma* inhibits inflammation via NF-κB inactivation [23], and *Phellodendri cortex* has both anti-inflammatory and antibacterial properties [24,25]. Curcumin, the active component in *Curcumae longae rhizoma*, exhibits antioxidant, antimicrobial, and wound-healing effects through growth factor induction [26]. Studies on *Angelicae dahuricae radix* highlight its antinociceptive and anti-inflammatory activities [27]. *Magnoliae cortex*, rich in magnolol, is noted for its anti-inflammatory and antimicrobial activities [28-38]. *Glycyrrhizae radix et rhizoma* has shown anti-inflammatory effects through inhibition of PGE2, TXB2, and LTB4 [39], along with antimicrobial properties [40-42]. *Citri reticulatae pericarpium vetum* offers significant antioxidant and anti-inflammatory benefits [43-46]. *Atractylodis rhizoma* demonstrates antifungal, antibacterial, antioxidant, and anti-inflammatory activities [47-50], while *Arisaematis rhizoma* has been found to have anti-inflammatory and analgesic effects [51,52].

Table 1. The proportion of Ru-Yi-Jin-Huang-Saan (RYJHS) and the efficacy of its ingredients.

Latin crude drug name (English name)	Plant part	Proportion	Efficacy
Trichosanthis radix (Trichosanthes root)	Root	25%	Wound healing, antibacterial, and anti-inflammatory effects
Rhei radix et rhizoma (Rhubarb)	Root and rhizome	12.5%	Anti-inflammatory effect
Phellodendri cortex (Phellodendron bark)	Bark	12.5%	Antibacterial and anti-inflammatory effects
Curcumae longae rhizoma (Turmeric rhizome)	Rhizome	12.5%	Wound healing, antioxidant, radical scavenging, antimicrobial, and anti-inflammatory effects
Angelicae dahuricae radix (Dahurian Angelica root)	Root	12.5%	Antinociceptive and anti-inflammatory effects
Magnoliae cortex (Magnolia bark)	Bark	5%	Anti-inflammatory and antimicrobial effects
Glycyrrhizae radix et rhizoma (Liquorice root and rhizome)	Root and rhizome	5%	Anti-inflammatory and antimicrobial effects
Citri reticulatae pericarpium vetum (Aged tangerine peel)	Peel	5%	Antioxidant and anti-inflammatory effects
Atractylodis rhizoma (Atractylodes rhizome)	Rhizome	5%	Antifungal, antibacterial, antioxidant, and anti-inflammatory effects
Arisaematis rhizoma (Jackinthepulpit tuber)	Rhizome	5%	Anti-inflammatory and analgesic effects

Further research indicates that RYJHS can alleviate inflammatory pain without causing sensitization [53]. Clinically, it is used to manage conditions such as phlebitis [54], osteoarthritis of the knee [55], gout, diabetic foot ulcers [56], and herpes zoster.

However, despite the numerous studies mentioned above, there is still a lack of clinical research on RYJHS. This study aims to evaluate the efficacy and adverse effects of using RYJHS on Colles fracture after surgery.

Methods

Study Design

The study is a randomized, double-blind, placebo-controlled trial design based on SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) reporting guidelines (Multimedia Appendix 1) [57], and the results will follow the CONSORT (Consolidated Standards of Reporting Trials) guidelines [58]. Our research project is scheduled to recruit patients from May 1, 2023, to April 30, 2025. All postoperative patients with Colles fracture will be recruited through referrals from orthopedic physicians at Changhua Christian Hospital. Researchers will screen and select participants based on specific inclusion and exclusion criteria.

In this study, all participants are randomly assigned using a computerized block randomization schedule. We randomly generate a pool of 100 patients, who are assigned to sequentially numbered opaque envelopes. The treatment allocations are balanced within each group, with each group containing 50 patients. Researchers and patients are both blinded to the treatment allocation, with the exception of the statistician responsible for the randomization process. The two groups in the study consisted of the experimental group receiving RYJHS treatment and the control group receiving a placebo.

Study Settings and Participants

All participants undergo standard medical treatment after surgery and are involved in the efficacy assessment of RYJHS external application. Figure 1 shows the study's flowchart. Both groups apply a patch plaster on the back of the wrist without wounds (avoiding the suture of the fracture operation). Figure 2 shows the site of the medication application. The experiment group apply the RYJHS plaster, while the control group apply a placebo plaster. The patch is applied twice a day, for 6 hours each time, with a 6-hour break in between, repeated for 3 days, completing one course of treatment. Patients undergo two courses of treatment, with the first course completed during hospitalization, and the second course completed 3 days after discharge.

Figure 1. CONSORT (Consolidated Standards of Reporting Trials) flow diagram of enrollment, randomization, treatment, and evaluation. CRP: C-reactive protein; DASI: Dyshidrotic Eczema Area and Severity Index; ORIF: open reduction and internal fixation; PRWE: Patient-Rated Wrist Evaluation; RYJHS: Ru-Yi-Jin-Huang-Saan.

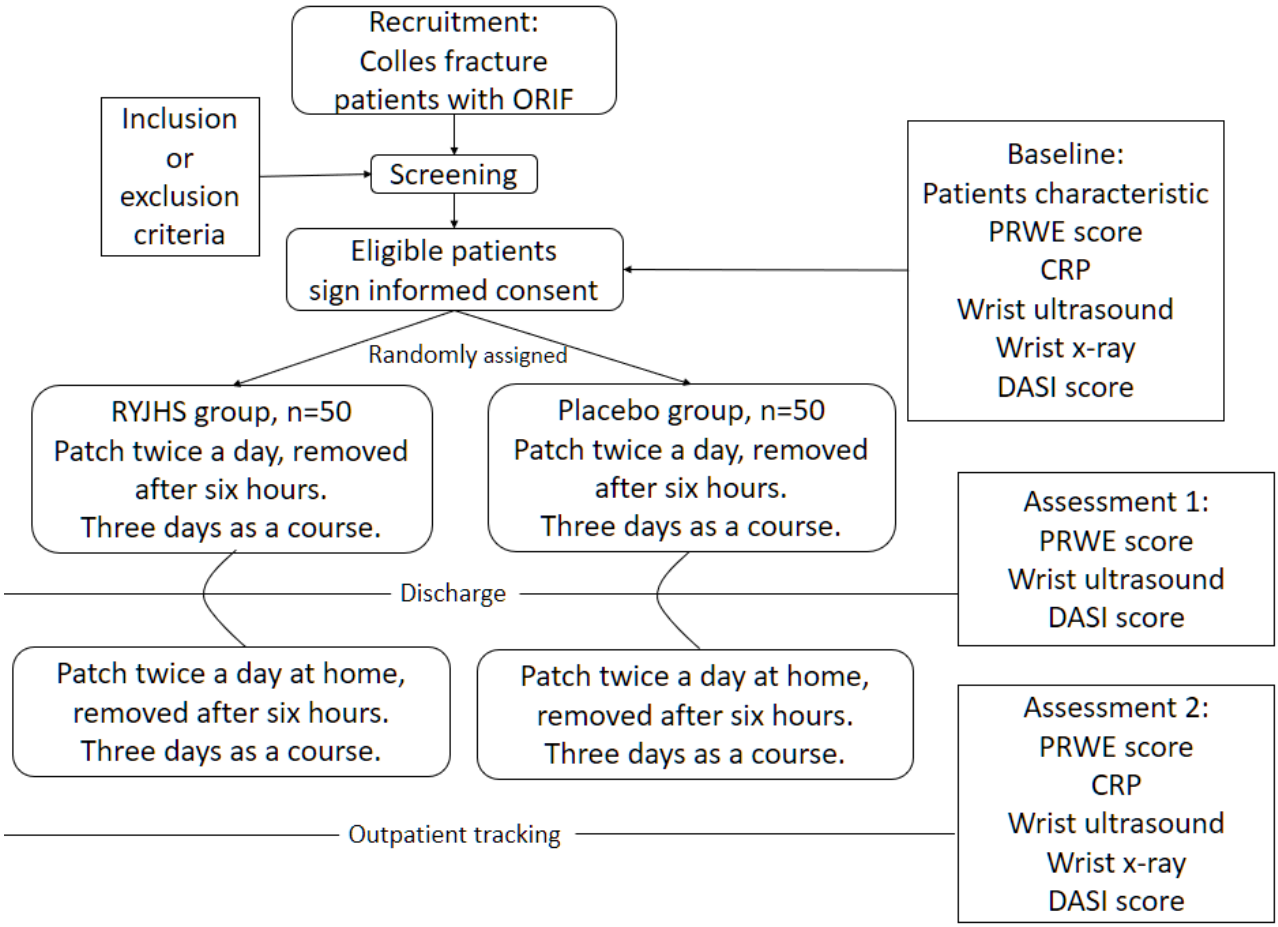
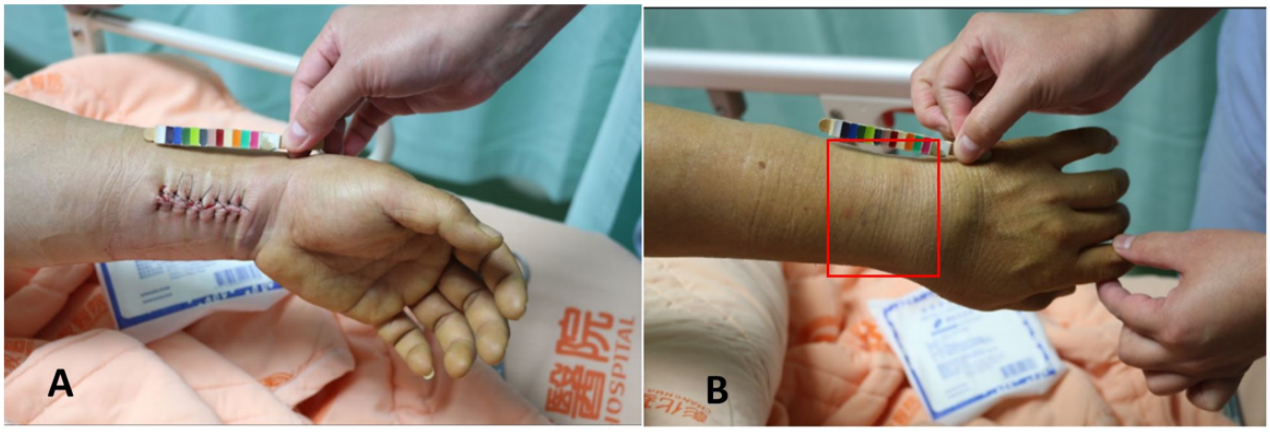


Figure 2. Applying Ru-Yi-Jin-Huang-Saan (RYJHS) plaster on Colles fracture after surgery. (A) The surgical incision site. (B) The site of the RYJHS plaster on a Colles fracture after surgery.



Inclusion Criteria

To be eligible for our study, patients must meet the following criteria: be 20-80 years of age, have a Colles fracture (Frykman classification type I-VI) [59] diagnosis that has been treated with open reduction and internal fixation (ORIF) surgery, and provide informed consent either personally or through their family members.

Exclusion Criteria

The following exclusion criteria will be applied: age older than 80 years or younger than 20 years; inability to comply with experimental procedures or complete questionnaires; presence of wounds on the back of the wrist; allergy to the herbal patch before; use of other Chinese herbal topical medicine after fracture; pregnancy; cancer; stroke; and systemic diseases such

as severe anemia, thyroid disease, and poorly controlled diabetes.

Sample Size Calculation

Our study closely resembles the design of phase-2 studies in clinical trials, which aim to assess the effectiveness of drugs in participants with specific conditions or diseases. We used G*Power (Heinrich-Heine-Universität Düsseldorf) to estimate the necessary sample size for our study, taking into account repeated-measures ANOVA within-between interactions with a medium effect size of f=0.25 and α level=.05. To achieve a statistical power of 0.95, we calculated a total sample size of 86 [60]. To account for potential dropouts and satisfy our inclusion criteria, we will enroll 100 individuals who have been admitted to our orthopedic care ward and diagnosed with Colles fracture after surgery.

Study Medication

RYJHS is a common TCM plaster that has been used for more than 500 years. RYJHS is composed of 10 herbs: *Trichosanthis radix*, *Rhei radix et rhizoma*, *Phellodendri cortex*, *Curcumae longae rhizoma*, *Angelicae dahuricae radix*, *Magnolite cortex*, *Glycyrrhizae radix et rhizoma*, *Citri reticulatae pericarpium vetum*, *Atractylodis rhizoma*, and *Arisaematis rhizoma* (given in Table 1). This herbal formula is a fixed prescription announced by the Department of Chinese Medicine and Pharmacy. The RYJHS used in our study is manufactured by Kaiser Pharmaceutical Co and meets the requirements of Good Manufacturing Practice. It has also been issued a drug certificate. The placebo powder, which uses computer color-matching technology in the color simulation of RYJHS [61], is also produced by Kaiser Pharmaceutical Co. Both RYJHS and the placebo are prepared by mixing 13 grams of powder with 23 mL of water, which is then evenly spread onto a cotton cloth and covered with gauze for later use. The aforementioned procedures are all carried out by the same experienced technician, as given in Figure 3.

Figure 3. Preparation of Ru-Yi-Jin-Huang-Saan (RYJHS) plaster. (A) Spread the paste onto a cotton cloth and (B) cover with gauze.

Outcome Measurements

In this study, we will gather data from each participant including their gender, age, affected hand and dominant hand, Patient-Rated Wrist Evaluation (PRWE) score, C-reactive protein (CRP) levels, wrist ultrasound results, wrist x-ray images, and Dyshidrotic Eczema Area and Severity Index (DASI) score. Patients who have undergone Colles fracture surgery are required to be evaluated, and data will be collected before the trial, as well as 3 days and 6 days after topical medication application. The participant timetable of enrollment, assessments, and treatments is given in Table 2. The primary outcome is the PRWE score, which is used to assess wrist function recovery. The PRWE score, collected via a questionnaire, was developed in Canada for patients with wrist problems to express their pain and level of function [62]. The secondary outcomes are CRP level and wrist imaging records, which are used to demonstrate the degree of inflammation and swelling reduction. In addition, the DASI score is used to monitor any allergic or adverse events that may occur at the application site [63].

Table 2. Timetable of enrollment and assessments.

Time	Screening	Baseline	Treatment 1 at hospital	Treatment 2 at home
	D_0[a]	D_1	D_3	D_6
Enrollment				
Inclusion or exclusion	✓	__[b]	—	—
Informed consent	✓	—	—	—
Demographic data	✓	—	—	—
Dominant and affected hand	—	✓	—	—
Medical history	✓	—	—	—
Randomization	—	✓	—	—
Assessment				
PRWE[c] score	—	✓	✓	✓
CRP[d]	—	✓	—	✓
Ultrasound	—	✓	✓	✓
X-ray	—	✓	—	✓
DASI[e] score	—	✓	✓	✓
Adverse events	—	Record at any time[f]	Record at any time	Record at any time

[a]D_x: number of days into the experiment.

[b]Not available.

[c]PRWE: Patient-Rated Wrist Evaluation.

[d]CRP: C-reactive protein.

[e]DASI: Dyshidrotic Eczema Area and Severity Index.

[f]If a patient has any side effects during the experiment, they must be recorded immediately.

Statistical Analysis

We will conduct statistical analyses using the SPSS software (version 22; IBM Corporation). Descriptive analyses will be performed on demographic data using frequencies and percentages to characterize the sample. Categorical variables will be compared using chi-square tests, while continuous variables will be compared using 2-tailed *t* tests. We will use repeated-measures ANOVA to determine if changes in wrist function (the dependent variable) are due to the interaction between the "type of treatment" (RYJHS) and "time" (measurement time). Multiple regression will be used to assess the impact of latent factors on primary outcomes (wrist function) and secondary outcomes (swelling and inflammation), adjusting for all possible covariates. Regression models will be performed in different outcome groups to compare the effects of different treatments (RYJHS intervention vs placebo).

Ethical Considerations

Approval for this trial (protocol ID 221006) was granted by the Institutional Review Board of Changhua Christian Hospital (CCH) on November 25, 2022, following the principles outlined in the Declaration of Helsinki. The study protocol has also been registered on ClinicalTrials.gov (NCT05638360). Individuals interested in participating will be required to provide written informed consent before the study's initiation. They will receive comprehensive information about the study, including procedures, potential benefits, and risks, excluding specific details regarding the RYJHS medication. Participants are free to withdraw at any time without any impact on their future medical care.

Data collected will be anonymized to protect participants' privacy, and all information will be kept confidential according to institutional data protection policies. No direct compensation will be provided to participants. The results of this research will be disseminated through publication in a peer-reviewed journal and presented at scientific conferences.

Results

The protocol was registered on ClinicalTrials.gov (NCT05638360) on December 6, 2022. Patient recruitment commenced in May 2023, with the first patient enrolled on June 15, 2023, and is projected to continue until April 30, 2025. As of December 2023, a total of 32 patients have been enrolled. Data analysis and report preparation are expected to be completed by the end of 2025.

Discussion

Expected Findings

The primary clinical treatments for Colles fractures, such as closed reduction, casting, percutaneous fixation, external fixation, and ORIF, generally yield positive functional outcomes.

However, both percutaneous and external fixation have reported a higher risk of infection, while percutaneous fixation has been shown to have a higher rate of soft tissue injuries [64,65]. Besides, the ORIF procedure including local dissection, reduction, and the insertion of plates or screws results in a higher incidence of tendonitis, tendon irritation, or tendon rupture [66,67]. In Taiwan, the routine conventional treatment for Colles fracture is ORIF surgery. However, operations often result in soft-tissue and lymphatic vessel damage. As a result, patients may experience heat, pain, redness, and swelling after the operation. The discomfort disrupts their willingness to undergo rehabilitation. Prolonged swelling can also affect the range of motion, hand function, muscle strength, and outward appearance of these patients [68]. Therefore, resolving pain and swelling is a significant problem for patients with Colles fracture after ORIF surgery.

The most common method of relieving swelling is ice packing. Ice packing can reduce swelling, capillary permeability, and delivery of inflammatory substances [69]. Besides, ice packing can decrease nerve conduction velocity, increase pain threshold, and provide analgesia [70]. However, many studies have reported that ice packing not only delays wound healing but also has a higher risk of cold injury [71,72]. Besides, pain management is also a concern for patients who undergo ORIF surgery. Physicians often prescribe opioids; NSAIDs; or a combination of opioids, NSAIDs, and steroids for pain management [73]. However, due to the potential side effects, these medications raise concerns for patients with diabetes, hypertension, gastrointestinal disorders, impaired liver function, or impaired kidney function.

There are several limitations in this study design. First, during the patients' hospitalization, patients were assisted by nurses who ensured regular medication application. However, it may be challenging to confirm whether the patients continued to apply the medication on schedule after discharge. Therefore, it might be necessary to use phone reminders to engage caregivers in assisting with regular medication application. Second, theoretically, the closer the topical medication is applied to the lesion, the more effective it is likely to be. However, due to concerns about postsurgical wound infections, the application of topical medication needs to be avoided on the site of surgical incision. Therefore, for the purpose of this experiment, only the uninjured area on the back of the wrist can be selected for topical medication application. Finally, the inclusion criteria for the trial of Colles fracture did not encompass comminuted fractures; thus, the efficacy of RYJHS may not be evaluated in patients with severe Colles fractures.

This study represents the first randomized, double-blind, placebo-controlled trial to investigate the efficacy of RYJHS for postoperative Colles fractures. RYJHS, with its natural ingredients known for anti-inflammatory and antibacterial properties, could serve as a noninvasive adjunctive therapy to reduce postoperative complications and enhance functional recovery. Its application aligns with patients' increasing interest in integrative medicine options that minimize reliance on pharmaceuticals. Future directions include exploring RYJHS's active ingredients, assessing formulation efficiency, and developing a more accessible application method, which may strengthen RYJHS's role as an adjunctive treatment for Colles fractures.

Conclusion

This randomized, double-blind, placebo-controlled trial aims to provide robust evidence of the efficacy and safety of RYJHS as a topical adjunctive treatment for postsurgical Colles fractures. With the potential to reduce inflammation and aid functional recovery, RYJHS could offer an alternative, nonpharmaceutical option for managing postoperative complications in patients with Colles fractures.

Acknowledgments

The authors sincerely thank all patients who participated in this study and health care workers not listed in the paper. This study was supported by China Medical University Hospital, Taiwan (DMR-110-007, DMR-111-197, DMR-HHC-111-1, and DMR-112-003). This work is financially supported by the Changhua Christian Hospital Special Research Project (112-CCH-IRP-070). No additional funding has been received.

Data Availability

Since this protocol does not contain any data, it will be provided after analysis and published in a journal upon trial completion. Data can be made available upon the author's request.

Authors' Contributions

Lien-Cheng Lin contributed to conceptualization, validation, visualization, writing-original draft and steering the primary author. WHW handled resources and writing–review and editing. WKC performed methodology and formal analysis. JLG assisted with data curation and project administration. RCY handled investigation and software. PCH and Lun-Chien Lo contributed to funding acquisition, supervision, and writing–review and editing.

Conflicts of Interest

None declared.

Multimedia Appendix 1
SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) checklist.
[PDF File (Adobe PDF File), 169 KB - resprot_v14i1e56849_app1.pdf]

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Abbreviations

CRP: C-reactive protein
CONSORT: Consolidated Standards of Reporting Trials
DASI: Dyshidrotic Eczema Area and Severity Index
NSAID: nonsteroidal anti-inflammatory drug
ORIF: open reduction and internal fixation
PRWE: Patient-Rated Wrist Evaluation
RYJHS: Ru-Yi-Jin-Huang-Saan
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials
TCM: traditional Chinese medicine

Edited by A Schwartz; submitted 28.01.24; peer-reviewed by A Hassan, YC Hung; comments to author 09.08.24; revised version received 24.08.24; accepted 24.01.25; published 05.03.25.

Please cite as:
Lin LC, Wang WH, Chang WK, Gao JL, Yang RC, Hsu PC, Lo LC
Evaluation of the Efficacy of the Traditional Chinese Medicine Formulation Ru-Yi-Jin-Huang-Saan on Colles Fracture After Surgery: Protocol for a Randomized, Double-Blind, Placebo-Controlled Trial
JMIR Res Protoc 2025;14:e56849
URL: https://www.researchprotocols.org/2025/1/e56849
doi:10.2196/56849
PMID:40053806

Protocol

Novel Versus Conventional Sequencing of β-Blockers, Sodium/Glucose Cotransportor 2 Inhibitors, Angiotensin Receptor-Neprilysin Inhibitors, and Mineralocorticoid Receptor Antagonists in Stable Patients With Heart Failure With Reduced Ejection Fraction (NovCon Sequencing Study): Protocol for a Randomized Controlled Trial

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Abstract

Background: Chronic heart failure has high morbidity and mortality, with approximately half of the patients dying within 5 years of diagnosis. Recent additions to the armamentarium of anti–heart failure therapies include angiotensin receptor-neprilysin inhibitors (ARNIs) and sodium/glucose cotransporter 2 inhibitors (SGLT2is). Both classes have demonstrated mortality and morbidity benefits. Although these new therapies have morbidity and mortality benefits, it is not known whether rapid initiation is beneficial when compared with the conventional, slower-stepped approach. Many clinicians have been taught that starting with low-dose therapies and gradually increasing the dose is a safe way of intensifying treatment regimens. Pharmacologically, it is rational to use a combination of drugs that target multiple pathological mechanisms, as there is potential synergism and better therapeutic outcomes. Theoretically, the quicker the right combinations are used, the more likely the beneficial effects will be experienced. However, rapid up-titration must be balanced with patient safety and tolerability.

Objective: This study aims to determine if early addition of ARNIs, SGLT2is, β-blockers, and mineralocorticoid receptor antagonists (within 4 weeks), when compared with the same therapies initiated slower (within 6 months), will reduce all-cause mortality and hospitalizations for heart failure in patients with stable heart failure with reduced ejection fraction.

Methods: This is a single-center, randomized controlled, double-arm, assessor-blinded, active control, and pragmatic clinical trial. Adults with stable heart failure with reduced ejection fraction and idiopathic dilated cardiomyopathy will be randomized to conventional sequencing (the control arm; over 6 months) of anti–heart failure therapies, and a second arm will receive rapid sequencing (over 4 weeks). Study participants will be followed for 5 years to assess the safety, efficacy, and tolerability of the 2 types of sequencing. Posttrial access and care will be provided to all study participants throughout their lifespan.

Results: We are currently in the process of obtaining ethical clearance and funding.

Conclusions: We envisage that this study will help support evidence-based medicine and inform clinical practice guidelines on the optimal rate of sequencing of anti–heart failure therapies. A third placebo arm was considered, but costs would be too much and not providing study participants with therapies with known morbidity and mortality benefits may be unethical, in our opinion. Given the post–COVID-19 economic downturn and posttrial access to interventions, a major challenge will be acquiring funding for this study.

International Registered Report Identifier (IRRID): PRR1-10.2196/44027

(JMIR Res Protoc 2025;14:e44027) doi:10.2196/44027

KEYWORDS

heart failure; SGLT2i; sodium/glucose cotransporter 2 inhibitors; ARNi; angiotensin receptor-neprilysin inhibitors; HFrEF; heart failure with reduced ejection fraction; idiopathic dilated cardiomyopathy; heart; chronic heart failure; patient; control; clinical; adult; cardiomyopathy; therapy

Introduction

Background

The current management of heart failure with reduced ejection fraction (HFrEF) has been revolutionized by the emergence of novel classes of drugs, namely, angiotensin receptor-neprilysin inhibitors (ARNIs) and sodium/glucose cotransporter 2 inhibitors (SGLT2is) [1,2]. With landmark clinical trials [3-6] demonstrating the efficacy of the latter drugs, there has been a paradigm shift in initiating and sequencing optimal anti–heart failure therapy and a concomitant reevaluation of the evidence base that guides conventional heart failure management. The American Heart Association heart failure guideline supports the rapid titration of guideline-based therapies every 1-2 weeks, with the goal of achieving target doses [7]. However, the European Society of Cardiology does not contain a timeline for the initiation of guideline-based heart failure therapy [8]. Pharmacologically, it is rational to use a combination of drugs that target multiple pathological mechanisms, as there is potential synergism and better therapeutic outcomes. Theoretically, the quicker the right combinations are used, the more likely the beneficial effects will be experienced. However, rapid up-titration must be balanced with patient safety and tolerability.

Sacubitril and valsartan, β-blockers, mineralocorticoid receptor antagonists (MRAs), and SGLT2is are disease-modifying agents that are used as combination therapy and are now regarded as a foundational therapy for HFrEF [1,2]. The conventional approach to initiating and optimizing HFrEF therapy reflects the sequence in which drugs were developed and trialed over the past 40 years [1]. Clinicians initiate therapy with an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker, followed by a β-blocker, then an MRA, then a neprilysin inhibitor, and, finally, an SGLT2i. Each drug required up-titration to the target dose, or the maximally tolerated dose, before initiating another class of drug, with a treatment period usually spanning >6 months [1].

This approach is limited by several clinical misconceptions and assumptions: first, the most efficacious anti–heart failure therapies were developed first. The counterargument is exemplified by the fact that digitalis has been used in clinical practice for 200 years, yet it is no longer considered a key therapeutic agent. Second, drug efficacy is only achieved at maximum target doses [1]. However, studies have demonstrated morbidity and mortality reduction with the use of low-dose anti–heart failure therapy in HFrEF, with maximum target doses adding only a smaller clinical benefit. Third, the efficacy and safety of individual anti–heart failure drug class were assessed in clinical trials that required patients to be receiving all background therapy at target doses. However, most trials were conducted with patients receiving subtarget doses of anti–heart failure therapy [2].

Initiating drugs over a 6-month period is undesirable for several reasons. Practically, target doses of anti–heart failure therapy are infrequently achieved due to patient factors (nonadherence, perceived adverse effects, and costs), drug factors (adverse effects and frequency of dosing), physician factors (clinical inertia and limited time), inadequate patient follow-up, and a lack of perceived benefit of higher drug doses. Furthermore, there is a strong evidence base suggesting that the use of each of the foundation drugs has demonstrated morbidity and mortality reduction within 30 days of therapy initiation [1,2,9].

The aim of this study is to determine if early addition of ARNIs, SGLT2is, β-blockers, and MRAs (within 4 weeks), when compared with the same therapies initiated slower (within 6 months), will reduce all-cause mortality and hospitalizations for heart failure in patients with stable HFrEF.

Rationale

The use of ARNIs and SGLT2is in low- to middle-income country settings is limited by high cost and accessibility. Despite the strong body of evidence supporting the safety and efficacy of ARNIs and SGLT2is, these agents are not yet included in the South African Essential Drug List. ARNIs and SGLT2is are available to private funders, yet access is limited as costs are only partially reimbursed by medical insurance schemes. Furthermore, SGLT2is have not yet been approved for heart failure by the South African Health Products Regulatory Authority, and use within clinical practice is predominantly off-label. Donations by the pharmaceutical industry have enabled limited access to ARNIs and SGLT2is in the public sector.

The challenge in this regard is maximizing access and rationalizing the use of ARNIs and SGLT2is while canvassing for widespread cost-effective rollout in the public sector.

The data on ARNIs and SGLT2is from high-income country settings suggest that morbidity and mortality reduction is achieved early in the clinical presentation of heart failure [1,2]. There, however, remains a paucity of data on the safety and efficacy of these drugs in sub-Saharan Africa.

Within sub-Saharan Africa, the main driver of heart failure remains hypertension, with ischemic heart disease emerging as a key etiology. There, however, is a growing cohort of young patients with idiopathic dilated cardiomyopathy with HFrEF who are often suboptimally medically treated with minimum prospects of receiving heart transplants. In our opinion, such a group of patients would ideally benefit from ARNIs and SGLT2is. Data from key clinical trials have demonstrated the use of ARNIs as de novo therapy in patients presenting with heart failure [3,10,11]. The latter trials have argued against the use of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers upfront with a transition phase to ARNI therapy, as there would be merely a delay in using the most effective therapy with a concomitant risk of sudden cardiac death.

The rapid initiation of anti–heart failure therapy described above seems rational in a high-income country setting where drug monitoring and assessment of adverse reactions are facilitated by the ease and rapidity of access to health care facilities [1,2]. However, in low- to middle-income country settings, the infrequent and irregular access to health care facilities limits instituting the rapid initiation algorithm for heart failure therapy. Furthermore, there is a lack of robust data and randomized controlled trials comparing rapid initiation versus a slower, phased initiation of heart failure therapy [1].

Study Objectives

Primary Objective

The primary efficacy end point is the composite end point of all-cause mortality and hospitalization for heart failure.

Secondary Objectives

Secondary end points include death from cardiovascular causes (eg, cardiogenic shock, myocardial infarction, tachycardia, or brady-arrythmia), improvement in the 6-minute walk test, improvement in the New York Heart Association functional class, improvement in symptoms as per the Kansas City Cardiomyopathy Questionnaire, trans-esophageal echo-determined ejection fraction (chamber dilatation, left ventricular systolic function, global longitudinal strain, and speckle tracking), and N-terminal prohormone of brain natriuretic peptide levels. Adverse drug reactions will also be collected and analyzed.

Definitions

Heart Failure

Heart failure is defined as a “clinical syndrome consisting of cardinal symptoms (eg, breathlessness, ankle swelling, and fatigue) that may be accompanied by signs (eg, elevated jugular venous pressure, pulmonary crackles, and peripheral edema). It is due to a structural and/or functional abnormality of the heart that results in elevated intracardiac pressures and/or inadequate cardiac output at rest and/or during exercise” [7].

Reduced Left Ventricular Ejection Fraction

Reduced left ventricular ejection fraction is defined as an ejection fraction ≤40%, that is, those with a significant reduction in left ventricular systolic function [8].

Methods

Proposed Novel and Rapid Sequencing

The proposed algorithm for initiation of anti–heart failure therapy comprises of 3 steps once clinical euvolemia has been achieved with diuresis [2].

Step 1 is the concurrent initiation of treatment with a β-blocker and an SGLT2i. β-Blockers are pertinent in the treatment of HFrEF, especially in the context of reducing sudden cardiac death. Evidence has demonstrated reduced hospitalization for heart failure with the use of SGLT2is. The early diuretic effect of SGLT2is may attenuate the early risk of worsening heart failure when β-blockers are initiated [2].

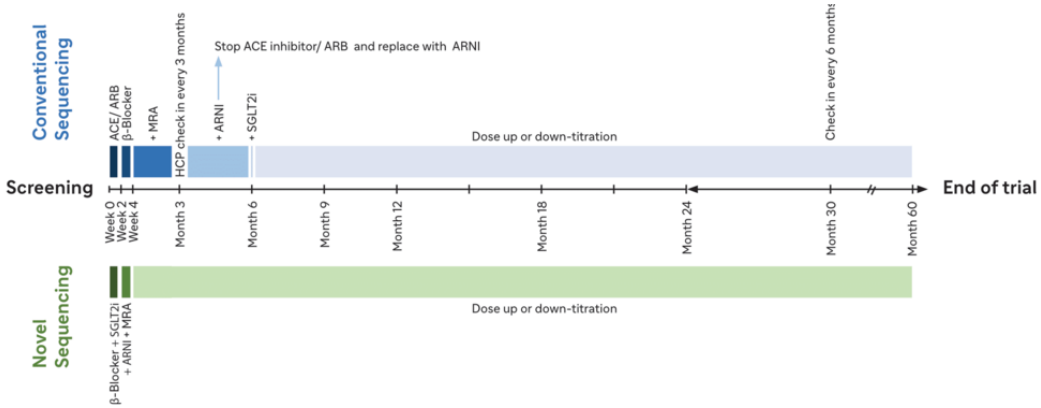
Step 2 comprises of the addition of an ARNI (sacubitril and valsartan) within 1-2 weeks of step 1. The presence of hypotension (systolic blood pressure <100 mm Hg) warrants evaluation of blood response with an angiotensin receptor blocker before switching to an ARNI [2].

Step 3 is the addition of an MRA, within 1-2 weeks of step 2, depending on the serum potassium and the presence and degree of renal impairment. ARNIs and SGLT2i may improve renal function and potassium homeostasis, thereby permitting the use of MRAs. In patients with hypotension, MRAs may be used as step 2 [2].

The above algorithm represents a generic approach and may be individualized to specific scenarios. Patients with decompensated heart failure are a subgroup that require greater caution when initiating anti–heart failure therapy. β-Blocker therapy should only be initiated in the hospital after discontinuation of intravenous therapy for several days and the patient is clinically euvolemic, defined as the absence of rales and ascites and the presence of minimal peripheral edema [2].

In the appropriate patient, treatment with all 4 foundational treatments may be achieved within 4 weeks, with subsequent dose up-titration. This strategy increases the probability that highly effective therapies will be implemented in a manner that reduces mortality and hospitalizations and enhances the tolerability of subsequently administered treatments [1]. Figure 1 shows the proposed study flow diagram, which contains the novel and conventional sequencing approaches. A key difference is the rate at which therapies are added, with the novel sequence arm having patients on all the efficacious therapies initiated within 4 weeks.

Figure 1. Study flow diagram. ACE: angiotensin-converting enzyme; ARB: angiotensin receptor blockers; ARNI: angiotensin receptor-neprilysin inhibitors; HCP: health care professional; MRA: mineralocorticoid receptor antagonists; SGLT2i: sodium/glucose cotransporter 2 inhibitors.



Study Design

This is a prospective, double-arm, randomized, assessor-blinded, and pragmatic clinical trial. The study will take place at a single site, that is, Tygerberg Hospital, Western Cape, South Africa.

Selection of Patients

Study participants will be adults with idiopathic dilated cardiomyopathy who consent to participate in the study. Patients will be free to withdraw at any time. The recruitment period will be 1 year.

Study participants will be randomized to the study arms by using a computer-generated randomization sequence.

Inclusion, exclusion, and withdrawal criteria are listed in Textbox 1.

Textbox 1. Selection criteria (inclusion, exclusion, and withdrawal criteria).

Inclusion criteria

- All patients aged <18 or >50 years who fulfill the clinical criteria for idiopathic dilated cardiomyopathy with reduced ejection fraction
- New York Heart Association Functional class II-IV

Exclusion criteria

- Aged >18 years or <50 years
- Unable or unwilling to provide informed consent to undergo any of the recommended investigations or to participate in the study
- Acute coronary syndrome, bypass graft surgery or other major cardiac surgery, stroke, or transient ischemic attack ≤90 days from visit 1
- Acute decompensated heart failure
- Systolic blood pressure ≥180 mm Hg or <100 mm Hg
- Estimated glomerular filtration rate <30 mL/min/1.73 m^2
- Serum potassium level >5.4 mmol/L
- History of angioedema

Withdrawal criteria

- Patient decision to leave the study
- Adverse drug reactions

Selection of Investigators

This study will be conducted at a tertiary-level public hospital's department of cardiology. Investigators will be the authors of this publication and other staff based at Tygerberg Hospital.

Statistical Considerations

Sample Size

We determined that a target number of 248 primary outcome events would provide a power of 80% to detect a 30% lower relative risk of the primary outcome in the novel sequencing arm than in the conventional sequencing arm at a 2-sided α level of .05. Assuming an incidence of the primary outcome of at least 50% over 5 years in the conventional sequencing arm and a dropout of 10% per arm, we established a planned enrolment of 584 patients (292 per study arm).

Analysis Population

The analysis population will include all study participants included in the study. This is an intention-to-treat analysis and even participants who have withdrawn, or dropped out, from the study after randomization will have their data analyzed.

Statistical Methods

Patient demographic and clinical profiles will be described using the statistical software SAS (version 9.4; SAS Institute). Continuous variables will be expressed as an absolute number, with associated percentage, mean, SD, median, and range where applicable. Clinical assessment of response to heart failure therapy will be performed using the Kansas City Cardiomyopathy Questionnaire, New York Heart Association functional classification, 6-minute walk distance, and hospital admission for heart failure. Objective measures of therapy response will be ascertained by serial N-terminal prohormone of brain natriuretic peptide levels and 2D echocardiography. Echocardiographic features of response to therapy will be characterized according to left ventricular ejection fraction as determined by the Simpson biplane method, global longitudinal strain, and speckle tracking.

Associations between outcomes and indicator variables will be explored through logistic regression. Where appropriate, indicator variables and specific outcomes will be investigated individually through a univariate analysis. Where significant, variables will be entered into and controlled for in a Cox-proportional hazards regression model. Adjustment for confounding will be performed by a competing risks analysis and propensity score matching (Table 1).

Table 1. Statistical methods.

Outcome measures	Hypothesis	Measure	Time points	Analysis methods
Primary end points	The intervention will reduce the outcome from baseline to 5 years.	—[a]	—	—
All-cause mortality	Rapid sequencing of anti–heart failure therapy will reduce all-cause mortality.	All-cause mortality (binary)	End of trial	Cox proportional hazards regression
Hospitalization	Rapid sequencing of anti–heart failure therapy will reduce all-cause mortality.	Hospitalized for heart failure (binary)	End of trial	Cox proportional hazards regression
Secondary end points				
Deaths (from cardiovascular causes)	Intervention will reduce cardiovascular-related deaths	Cardiovascular mortality (binary)	End of trial	Chi-square test
6-minute walk test	Improvement in distance walked in 6-minutes	Distance in meters (continuous)	Baseline and end of trial	✓
NYHA[b] functional class	Improvement in dyspnea	Functional class 1, 2, 3, and 4 (ordinal)	Baseline and end of trial	✓
KCCQ[c]	Improvement in symptoms of heart failure	Questionnaire (ordinal)	Baseline and end of trial	✓
Trans-esophageal echo	Improvement in ejection fraction	Ejection fraction measured in percentage (%; continuous)	Baseline and end of trial	✓
NT-pro[d] and BNP[e] levels	Reduction in levels	Concentration units (pg/mL; continuous)	Baseline and end of trial	✓

[a]Not applicable.

[b]NYHA: New York Heart Association.

[c]KCCQ: Kansas City Cardiomyopathy Questionnaire.

[d]NT-pro: N-terminal prohormone.

[e]BNP: brain natriuretic peptide.

Ethical Considerations

This study will be conducted in accordance with the principles laid down by the 18th World Medical Assembly [12]. Study participants' data will be deidentified of names and surnames and identifying information. An application for ethical approval will be submitted to the Stellenbosch University Research and Ethics Committee. The study will be performed in accordance with local regulations, including local data protection regulations and requisite hospital and Provincial Department of Health Approval. Posttrial access and care will be provided to all study participants, throughout their lifespan.

Results

We are currently in the process of generating funding. If funding is obtained, we will apply for ethical clearance and requisite permissions.

Discussion

Principal Findings

This study aims to determine if rapid sequencing of anti–heart failure drugs with proven morbidity and mortality benefits would be superior to slower titration of these therapies.

We chose a composite end point to reduce the sample size, as a larger sample size would result in greater costs and reduce the feasibility of the study. Given the high mortality and frequent hospitalizations for heart failure, we included both events in the combined primary efficacy endpoint.

Intuitively, it makes sense to ensure that the most efficacious heart failure therapies are initiated as soon as possible. Given that the therapies have varied modes of action, we hypothesize that if they are started together as soon as possible, they would have greater benefits than starting them later. Combination therapies are likely to target different pathophysiological aspects of heart failure and thus improve clinical outcomes. Issues with rapid initiation may potentially include hypotension and other adverse effects. We will guard against hypotensive events by starting with the lowest possible dose and stopping the drug if the patient becomes hemodynamically unstable. Furthermore, study participants are required to be euvolemic before rapid sequencing so that we do not worsen patients' heart failure and thus limit hemodynamic instability and decompensated heart failure. It is a standard clinical practice to ensure euvolemia before titration of anti–heart failure therapies. Euvolemia is usually achieved by loop diuretics [8].

We chose a relatively young group of patients so that underlying issues such as ischemic heart disease are less probable and would not serve as confounders. Furthermore, this group of patients may benefit from the increased life expectancy as compared with the older group.

The public health sector in South Africa has resource constraints. Often, there are not enough clinicians to adequately manage the patients. Thus, doing trials in this setting is challenging. However, given the proven safety and efficacy of ARNIs, SGLT2is, and MRAs, and their widespread use in high-income countries, we envisage limited problems. Furthermore, making these novel therapies available to a vulnerable population would serve as a motivation for clinicians who work in this setting. The setting is a teaching and training facility, and having exposure to these novel therapies will grow the expertise and skills of health care practitioners. Furthermore, we envisage reducing the complexity of the study by using a pragmatic study design so that we can integrate the trial into routine clinical practice in the department of cardiology. This will reduce the administration burden while also resulting in the collection of safety, efficacy, and tolerability data. We feel that the trial would not add to the administrative burden of the clinicians, as we will not ask them to do any work beyond what they usually do in the clinic. Furthermore, a separate designated individual will collect and analyze the data, so that clinicians will not be burdened with this task and not impinge on their demanding clinical work.

Posttrial access and posttrial care are contentious issues [13]. In this study, we plan to provide both posttrial access and posttrial care because it is, in our opinion, ethically justified. Given that the newer therapies are efficacious, safe, and tolerable, it would be unkind to stop the therapies after the trial is completed, as the study participants would not be able to procure the therapy privately because of their limited financial resources. The provision of posttrial care would also increase the cost of the study, but we will continue to provide posttrial care in our cardiology clinic at no cost to the study participants.

We hope to acquire funding from the manufacturers of ARNIs, SGLT2is, β-blockers, and MRAs, as the data generated from this study have the potential to inform clinical practice guidelines. Given the high costs of doing such trials, we hope companies will assist if they are only providing the drug and not covering the other clinical trial costs like investigator fees, protocol development, manuscript writing, and statistical analysis, and so on. The study has dual objectives of generating of evidence while also providing patients with access to highly efficacious and premium therapies for heart failure.

Given that both study groups will receive the same therapies, we do not pitch drugs head-to-head, as we feel that the combination of drugs with proven mortality and morbidity data would be most likely to have synergistic effects and further reduce morbidity and mortality. This approach is also more likely to generate funding as all companies can contribute to financing the study, not with the risk of their products being negatively affected by head-to-head trials that show one drug being superior to another drug.

We have tried to create a "win-win" situation by generating data to inform clinical practice guidelines and providing access to novel therapies in resource-limited settings. The research can help with master's and PhD degrees, given the rich dataset generated.

Limitations

The study is proposed to use one study site in the Western Cape of South Africa, which may not be reflective of the demographics of the South African population. Due to the nature of the study and means of intervention, implementation of a

placebo-controlled arm will not be possible but is nonetheless cited as a limitation.

Conclusions

Recent additions to the armamentarium of anti–heart failure therapies such as ARNIs and SGLT2is have demonstrated morbidity and mortality benefits. Earlier use of such therapy within patients with stable HFrEF may impact patient outcomes. This study will provide important data to support evidence-based medicine and will help inform clinical practice guidelines on the optimal rate of sequencing of anti–heart failure therapies.

Acknowledgments

We are grateful to Novartis for paying the article processing fee.

Data Availability

The dataset will be made available upon written request.

Conflicts of Interest

PN was sponsored by Novartis for online attendance at European Society of Cardiology (ESC) Congress 2022 and received drug sponsor for a phase IV clinical trial from Sandoz, a subsidiary of Novartis. PN was previously employed as a Medical Manager by Boehringer and was responsible for preregistration medical activities related to empagliflozin. KH was previously employed as Medical Director by Boehringer and was responsible for preregistration medical activities related to empagliflozin.

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Abbreviations

ARNI: angiotensin receptor-neprilysin inhibitor
HFrEF: heart failure with reduced ejection fraction
MRA: mineralocorticoid receptor antagonist
SGLT2i: sodium/glucose cotransporter 2 inhibitor

Edited by A Mavragani; submitted 03.11.22; peer-reviewed by S Setia, M Nomali; comments to author 28.02.23; revised version received 30.03.23; accepted 24.04.23; published 10.03.25.

Please cite as:
Karamchand S, Chipamaunga T, Naidoo P, Naidoo K, Rambiritch V, Ho K, Chilton R, McMahon K, Leisegang R, Weich H, Hassan K
Novel Versus Conventional Sequencing of β-Blockers, Sodium/Glucose Cotransportor 2 Inhibitors, Angiotensin Receptor-Neprilysin Inhibitors, and Mineralocorticoid Receptor Antagonists in Stable Patients With Heart Failure With Reduced Ejection Fraction (NovCon Sequencing Study): Protocol for a Randomized Controlled Trial
JMIR Res Protoc 2025;14:e44027
URL: https://www.researchprotocols.org/2025/1/e44027
doi:10.2196/44027
PMID:

Protocol

Comparative Evaluation of Effectiveness of Standard of Care Alone and in Combination With Homoeopathic Treatment in COVID-19–Related Rhino-Orbito-Cerebral Mucormycosis (ROCM): Protocol for a Single Blind, Randomized Controlled Trial

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Abstract

Background: Rhino-orbital-cerebral mucormycosis (ROCM) is the most common (45%-74%) mucormycosis in India. With contemporary medical care, ROCM has a mortality rate of 40%-50% and 70% of survivors are left with residual defects. Recently, several cases of mucormycosis in people with COVID-19 have been increasingly reported worldwide, from India, due to immune dysregulation caused by SARS-CoV-2. To reduce the high mortality rate and residual defect in most survivors under the guidelines of the Ministry of AYUSH, the Government of India recommended homoeopathy as an add-on therapy to maximize the effectiveness of standard treatment in conventional therapy.

Objective: This study aimed to evaluate the role of existing homoeopathic treatment as an adjuvant therapy in patients with COVID-19–related ROCM and enhancing the survival of the patients hospitalized due to COVID-19 infection and to access the initial treatment response and duration required for significant or complete recovery in patients receiving adjuvant treatment.

Methods: This superiority, randomized controlled clinical trial would include two parallel comparator groups A and B. Group A would be the experimental group and would receive homoeopathic treatment along with the standard line of treatment as per investigational medicinal product (IMP) and group B would be the control arm and would receive standard line of treatment as per IMP along with identical placebo. Allocation would be 1:1 through randomization. Based on the inclusion and exclusion criteria, 36 participants per arm would be screened. Participants would be assessed clinically twice a day and magnetic resonance imagery or endoscopy cum-biopsy would be assessed on days 1, 14, and 28. Laboratory investigations may vary as per demand of disease conditions.

Results: In India, the COVID-19 pandemic, particularly during the second wave, resulted in a surge of mucormycosis cases among patients with COVID-19. At the time this protocol was being developed, there was a significant spike in mucormycosis cases in India, particularly in Mumbai (June 2021). However, by the time the Central Council for Research in Homoeopathy obtained the necessary approvals and ethical clearance for the study, the incidence of mucormycosis had drastically declined (September 2021). As a result, the study was not initiated and registered. The authors feel it is their ethical responsibility to share the reviewed protocol with the medical community as a reference for future work.

Conclusions: This study aims to evaluate the role of existing homoeopathic medicines as an adjuvant therapy in managing COVID-19–related ROCM, potentially contributing to the use of homoeopathy as an evidence-based medical approach. The protocol can also serve as a valuable resource for clinicians and researchers addressing mucormycosis cases unrelated to COVID-19,

particularly in immunocompromised patients. It would help ensure preparedness, whether or not sufficient evidence is available, in the event of a future health emergency.

International Registered Report Identifier (IRRID): PRR1-10.2196/57905

(JMIR Res Protoc 2025;14:e57905) doi:10.2196/57905

KEYWORDS

Rhino-orbital-cerebral mucormycosis, randomized controlled trial, homoeopathy, fungus, CE-MRI PNS mucormycosis; India; medical care; mortality rate; conventional therapy; ethical; mortality; survival; recovery; homoeopathic medicines; management

Introduction

Immune dysregulation induced by SARS-CoV-2, along with the extensive use of glucocorticoids and immunomodulatory drugs like tocilizumab, has heightened the risk of secondary bacterial and fungal infections in patients with COVID-19 [1-3]. Recently in past, India experienced a significant surge in mucormycosis cases, caused by a group of molds known as mucoromycetes, commonly found in the environment. These molds release spores that are easily aerosolized and dispersed [4]. The most frequent genera causing infections in humans include *Rhizopus* and *Mucor* species, along with others like *Apophysomyces*, *Rhizomucor*, *Cunninghamella*, *Lichtheimia*, *Cokeromyces*, and *Saksenaea* [5]. *Rhizopus oryzae* is the most prevalent species, responsible for nearly 60% of human mucormycosis cases and about 90% of the rhino-orbital-cerebral mucormycosis (ROCM) form [6]. The primary mode of infection is through the inhalation of fungal spores.

Both *Aspergillus* and *Candida* have been identified as the primary fungal pathogens involved in co-infections among patients with COVID-19 [7]. Prolonged hospitalization, with or without mechanical ventilation, is also a contributing factor to these types of fungal infections [8]. Studies suggested that COVID-19 infection is associated with the destruction of β-cell of the pancreas [9,10]. A history of corticosteroid use for treating COVID-19 was found in 76.3% of mucormycosis cases, with remdesivir use in 20.6%, and tocilizumab in 4.1%. The most commonly affected organs were the nose and sinuses (88.9%), followed by rhino-orbital involvement (56.7%), and the ROCM type (22.2%) [8]. Uncontrolled hyperglycemia and the onset of diabetic ketoacidosis are often linked to corticosteroid use. COVID-19 infection can lead to endotheliitis, endothelial damage, thrombosis, lymphopenia, and reduced CD4+ and CD8+ lymphocyte counts, which increase susceptibility to secondary or opportunistic fungal infections [8]. Mucormycetes can invade blood vessels and spread to the brain and other organs through the bloodstream, leading to disseminated infections [11]. Diagnosis of ROCM should include early radiological imaging with a magnetic resonance imaging (MRI) of the paranasal sinuses (PNSs) and the brain with contrast, and confirmation can be made through fungal staining or culture from properly collected specimens [12].

ROCM is the most common form of mucormycosis in India, accounting for 45%-74% of cases. Complications of ROCM include blindness [13] cerebral infarction, cerebral abscess, cavernous sinus thrombosis, and intracranial hemorrhages [14]. The disease progresses rapidly and has a poor prognosis if not diagnosed early. Early detection, aggressive management of the underlying condition, surgical debridement, systemic and local antifungal treatments, and hyperbaric oxygen therapy significantly improve prognosis and survival rate [15]. The standard treatment for mucormycosis involves correcting diabetic ketoacidosis or other metabolic disturbances, daily irrigation and packing of the affected orbital and paranasal areas with amphotericin B, along with intravenous amphotericin B therapy [16].

Staging of ROCM

Stage 1 of ROCM has involvement of the nasal mucosa and subdivision 1a is limited to the middle turbinate, 1b involves inferior turbinate and ostium of the nasolacrimal duct, 1c involves nasal septum, and 1d involves bilateral nasal mucosal involvement.

Stage 2 of ROCM has involvement of paranasal sinuses and subdivision 2a involves only 1 sinus, 2b involves 2 ipsilateral sinuses, 2c involves more than 2 ipsilateral sinuses and palate or oral cavity and 2d has involvement of bilateral paranasal sinuses, the zygoma and mandible [17].

Despite all efforts in the conventional line of treatment, ROCM has a mortality rate of 40%-50% and 70% of survivors are left with residual defects [18]. To reduce the high mortality rate and residual defect in most of the survivors, Ministry of AYUSH, Government of India [19] has recommended homoeopathy as an add-on therapy to maximize the effectiveness of the standard line of treatment in conventional therapy. It is a well-established fact that homoeopathy is helpful as an adjuvant therapy along with the standard line of treatment for treating various disease conditions where conventional medicine has its own limitations [20].

In various research studies undertaken on various fungi, in vitro models showed that homoeopathy medicine could prevent the growth of the fungus. Prajapati et al [21] showed that showed that homoeopathic drugs, namely *Zingiber officinale*, *Holarrhena antidysenterica*, *Terminalia chebula*, *Allium cepa*, *Caesalpinia bonducella*, *Eucalyptus globulus*, *Ruta graveolens*, and *Thuja occidentalis* have significant antifungal activity against human pathogenic fungi *Aspergillus niger* whereas Gupta and Garg [22] revealed that homoeopathic medicines Mezereum 1000 potency showed maximum inhibition of growth of Candida albicans.

Hence, this study is intended to evaluate the role of homoeopathy as an adjuvant therapy in COVID-19–related mucormycosis and to enhance the survival of the hospitalized patients with ROCM. Due to the decline in COVID-19 cases in September 2021, the period when approvals could be sought,

the study was deemed unfeasible and had to be canceled. The authors consider it their ethical responsibility to share this reviewed protocol with the professional community as a resource for further research applicable to mucormycosis cases not specifically linked to COVID-19 infection. This initiative aims to ensure preparedness with evidence, regardless of its availability if similar emergencies arise in the future. Thus, we present this protocol to the community in hopes it would be used for immunocompromised or diabetes-related mucormycosis in individuals.

Objectives

Primary Objective

The primary objective is to evaluate the role of adjuvant homoeopathy in addition to the standard treatment of patients with COVID-19–related ROCM through standard parameters in respective conditions.

Secondary Objective

This study also aims to enhance the survival of the patients hospitalized due to COVID-19–related mucormycosis.

Methods

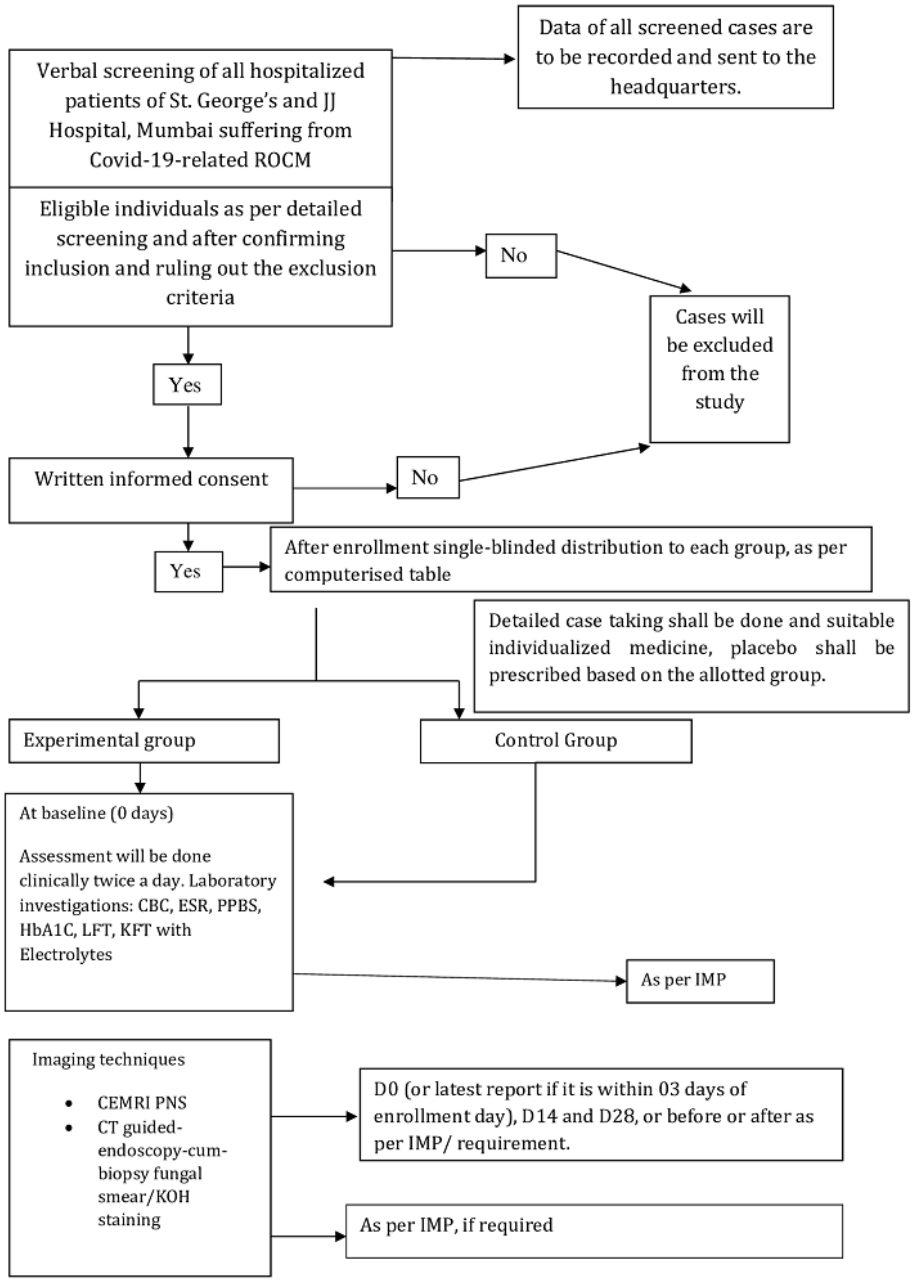
Study Design

The study is a superiority, single-blind, randomized controlled trial (RCT) with 2 groups: group A (experimental) and group B (control). Group A would receive homeopathic treatment in addition to the standard treatment for COVID-19–associated mucormycosis, as recommended by the Investigational Medicinal Product or Fungal Infections Study Forum (IMP or FISF; Multimedia Appendix 1) [23]. Group B would receive conventional treatment per the same guidelines, along with an identical placebo. Participants would be randomly assigned to either group in a 1:1 ratio using a computerized random number generator.

The trial would be planned to be conducted in a hospital setting, with informed consent obtained from patients admitted for the treatment of COVID-19–related mucormycosis. The study duration is 3 months, with an extension if needed to complete the required sample size. Patients with stage 1 or 2 COVID-19–related ROCM would be enrolled and randomized based on the trial's inclusion criteria. Both groups would receive the same auxiliary care, with dose repetition following the same pattern in both groups.

Participants would be assessed clinically twice a day, and MRI or endoscopy with biopsy would be performed on days 1, 14, and 28, with variations depending on the disease progression. The study protocol adheres to the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) 2013 guidelines, as illustrated in Figure 1.

Figure 1. Flow diagram of study design. CEMRI PNS: Contrast-Enhanced Magnetic Resonance Imaging of Para Nasal sinus; CBC: complete blood count; CT: computed tomography; ESR: erythrocyte sedimentation rate; HbA1c: hemoglobin A1c; IMP: investigational medicinal product; KFT: kidney function test; KOH: potassium hydroxide; LFT: liver function test; PPBS: postprandial blood sugar; ROCM: rhino-orbital-cerebral mucormycosis.



Study Setting and Duration

This RCT was planned for the St. George's and JJ Hospital, Mumbai, which was the hospitals of Sir JJ Group of hospitals, and had a common Institutional Ethics Committee. An informed consent of the patients admitted in the inpatient department for treatment of COVID-19–related mucormycosis planned to be taken before inclusion. Duration of the study would be 3 months and maybe extended if the desired sample size is not achieved.

Eligibility Criteria

The eligibility criteria are shown in Textbox 1.

Textbox 1. Eligibility criteria.

Inclusion criteria

- Both male and female participants aged 18 years or older and confirmed cases of COVID-19–related rhino-orbital-cerebral mucormycosis (ROCM) diagnosed as stage 1 and stage 2 (Multimedia Appendix 2) by potassium hydroxide staining (KOH staining) or magnetic resonance imaging (MRI) or biopsy would be included in the study. MRI would show Mucosal thickening with T2 hypointense components at T2W images, nonenhancement of involved mucosa or soft tissue at postcontrast T1W images, Marrow edema and enhancement of adjacent bones and skull base at fat-saturated T2W and postcontrast T1W image [24]. A hyperintense lesion extending from paranasal sinus along orbital apex into intracranial structures and narrowing or slow flow in the ipsilateral internal carotid artery in the vicinity of mucor invasion seen in T2W [25]. KOH staining or microscopy and biopsy of affected area would show nonseptate or pauci-septate, ribbon-like hyphae (at least 6-16 µm wide), and vessel occlusion [26].

Exclusion criteria

- ROCM at stage 3 and 4 (Multimedia Appendix 2) presenting with bony erosion, cerebral vascular invasion, invasion into the cranium, orbital apex or cribriform plate of the ethmoid bone, cavernous sinus (II-VI cranial nerve palsies) and diagnosed cases of pulmonary, cutaneous, gastrointestinal, advanced disseminated mucormycosis, pregnant and lactating women, cases where progression to death is inevitable and imminent within the next 24 hours according to the clinical team irrespective of the provision of treatments would be excluded from the study.

Intervention

Preparation of Study Intervention and Placebo Materials

Homoeopathic medicines to be used in the trial are known pharmacopeial preparations. As no new remedy is proposed to be investigated, there is no potential risk due to intervention. Intervention medicines would be administered orally. The medicine would be repeated depending on the potency and complaints of the patient in accordance with the principles of homoeopathy. Once the improvement sets in, placebo would be continued till the main medicine continues to act. The placebo (30 CH) would be identically prepared using only purified water, and pharmaceutical-grade ethanol, without glycerin or any medicinal active component.

Details of Intervention

The intervention would be a homoeopathic medicine which would be given as pills medicated with an ultradiluted homeopathic remedy. As a basic rule, increased dilution is proportionate to increased therapeutic power and no side effects. Owing to the nanoparticle nature of the drugs particles in serial dilutions above the Avogadro constant [27], homoeopathic intervention does not have any safety issue since inception. As the medicines used for this trial are already in use for decades and therefore, practical safety of medicines is well-established, this trial would be phase 3 trial and further validate the efficacy of these medicines, specifically in ROCM.

Through patient information sheet, patient would be duly informed about equal chances of receiving placebo or homoeopathic medicine, depending on the group she or he's allotted, and then consent would be taken. Furthermore, patients would be getting standard care of conventional medicine in both groups, and, therefore, would not be at risk. A detailed history and examination would be gathered from the already available information of the patient in the admission records at hospital. The patients randomized into experimental group would be interrogated by the homoeopathic physician only for the additional information required from homoeopathy perspective. Daily recording of the administered dose would be recorded and also captured in the case record form developed by the homoeopathy team, which would be having content other than, and in addition to the standard form, which would be filled at the hospital. If there is any change in dosage or prescription of medications during the study period, that would be mentioned with reason in the prescription chart. If these medicines are stopped, that too would be recorded with reason.

The patients assigned to the placebo group would be given placebo in the form of similar looking homoeopathic pills of size 30, dispensed with the 30% V/V dispensing alcohol. The prescribed medicine would be changed if no change in the next scheduled laboratory investigations or patient reports to be clinically unwell, even after at least 3 doses of the prescribed medicine.

In either arm, no patient would be devoid of conventional management as per IMP at any given point of time. Till the end point of the study in hospitalized patients, if required to enquire about well-being of the patient, phone call may be done in both groups and it would be considered as a phone follow-up.

FISF recommendations on Treatment of COVID-19–associated mucormycosis [23] (Multimedia Appendix 1) would be followed for regime of medication under standard care of intervention, which includes 3-6 weeks of amphotericin B therapy, followed by consolidation therapy for 3-6 months, strict control of hyperglycemia, steroids for lifesaving purposes in patients with COVID-19; abuse or misuse or untimely use to be avoided, judicious immunomodulating drugs, surgical debridement of the infected tissues, and regular monitoring through clinical, radio-imaging, and microbiological assessment.

For Homeopathic Intervention

As the condition is immunocompromised, very acute and progressive in nature, the homoeopathic medicines would be recommended in low potency and in frequent repetition. Medicine will be repeated in the following instances (Textbox 2).

Textbox 2. Condition where medicine would be repeated.

Repetition of medicine:

- If improvement stops, repeat the same medicine in the same potency.
- If no further amelioration occurs even after repeating the medicine in the same potency or improvement lasts for a very short period, give higher potency of the same medicine.
- If there is too short relief of symptoms (lasting for a few hours and diminishing further on subsequent repetition of the doses), reassess the case and observe.
- If the medicine remains appropriate after reassessment, it should be administered in a next higher potency.
- If no further amelioration occurs, reassess the case and prescribe the indicated remedy.
- If aggravation is quick, short, and strong with rapid improvement of the patient, discontinue the medicine and prescribe placebo.
- If the appearance of new symptoms is observed, and if the symptoms are not of a serious nature, wait till the new symptoms pass off. Then select another indicated remedy after reassessing the case.
- In case of serious symptoms, change the medicine and check for safety end point.

Withdrawal of a trial participant:

- If the patient worsens, and mucormycosis expands beyond the range of inclusion criteria.
- If the patient is in need of ventilator support.
- If the participant is unwilling to continue or turns noncompliant.

Outcome Measures

Primary Outcome

The following changes would be observed in MRI contrast:

1. Mucosal thickening with reduction in Transverse Relaxation time T2 hypointense components at T2-weighted (T2W) images.
2. Infiltration of mucosa/soft tissue at postcontrast T1-weighted (T1W) images.
3. Marrow edema and enhancement of adjacent bones and skull base at fat-saturated T2W and postcontrast T1W image.
4. Hyperintense lesion extending from paranasal sinus along orbital apex into intracranial structures and narrowing or slow flow in the ipsilateral internal carotid artery in the vicinity of mucor invasion seen in T2W.
5. Staging of Code Mucor as per Guidelines for the Diagnosis, Staging and Management of ROCM in the setting of COVID-19 pandemic [17]. The absence of stage 1 would be considered as cured and progression from stage 1 to stage 2 or stage 2 to stage 3 or 4 would be considered as worse outcome.

Secondary Outcomes

The median survival rate of the patients would be assessed in both the groups during hospitalization.

Participant Timeline

Each patient would be followed up for 28 days. Participant would be followed up every 4 hours, or sooner, as per the case and would be asked a few questions as per case recording form, before commencing the treatment. Participants would be requested to be available on phone for follow up by the doctor on day 14 and day 28, in case they are discharged from the hospital before day 14 of the illness.

The following variables would be clinically assessed in every follow up:

1. Nasal stuffiness
2. Nasal discharge
3. Foul smell
4. Epistaxis
5. Facial pain
6. Facial edema
7. Dental pain
8. Malaise
9. Fever

Sample Size

Based on the computation of sample size, literature, and expert opinions and assuming a type 1 error of 5% and type 2 error of 20% with a power of 80%, it was estimated that there would be 36 participants each in the intervention and control group, with a total of 72 participants. This could be escalated based on attrition due to loss in follow-up. If this loss to follow-up is considered at 25%, a total of 45 participants have to be enrolled in each group, with a total sample of 90 for the study.

Randomization and Blinding

The study participants were planned to be recruited from St. George's and JJ Hospital, Mumbai. The recruitment would be based on the inclusion criteria. The participants would be allocated to either intervention or placebo groups as per the randomization sequence generated by using GraphPad (GraphPad Software) by Dotmatics (Insightful Science) software. Coded or prenumbered identical containers would be used for allocation concealment. The principal investigator (PI) at Central Council for Research in Homoeopathy (CCRH) headquarters would be involved in the sequence generation process and allocation concealment procedure. The PI would label the interventions as per the randomization codes, which would be handed over to the site PIs. The site PIs would enroll

participants and randomly assign participants to interventions. The only trial participants interventions would be blinded. To ensure the quality of blinding the packaging for both the interventions and placebo would be identical in odor, color, size, and taste. The unblinding would be done by the PI at CCRH headquarters at the end of the study. If severe adverse events would be reported by the participants during the trial, unblinding may be performed per Data and Safety Monitoring Board (DSMB) or ethical committee recommendations. The reason for urgent unblinding should be well-documented.

Screening and Enrollment

All the participants would be voluntarily invited to the study and then required to sign an informed consent form containing information on the regulatory authorities and the related procedures, including laboratory investigations and subsequent randomization after enrollment. Enrollment of the participants would be based on inclusion criteria. The hospital must maintain a log register that records all the details of the screened participants and the reasons for exclusion. After enrollment the participants would be randomized and allocated to the intervention or the placebo arm as per the generated randomization sequence using GraphPad by Dotmatics software.

Data Collection Methods

Considering the critical importance of COVID-19–related ROCM, data from the trial participants would be collected extensively. The following documents below would be developed and retained.

1. Case record form of COVID-19–related ROCM.
2. A database that stores the above information for each patient with the subsequent observations by the physician at every visit.
3. Reports of all laboratory investigations to help physicians understand efficacy of diagnostic tools or interventions.
4. All data pertaining to homoeopathy, like case taking, repertorization chart, and prescription decisions would be maintained.

Assessment and Data Analysis

Potassium hydroxide staining and Contrast-Enhanced Magnetic Resonance Imaging (CEMRI PNS) would be used for diagnosis and staging of ROCM. However, for assessment of the progress of the condition, following parameters would be evaluated on days 14 and 28:

1. CEMRI PNS impression
2. Code Mucor staging
3. Clinical assessment
4. Laboratory parameters

The participants would be assessed clinically twice a day and the laboratory parameters complete blood count, erythrocyte sedimentation rate, fasting blood sugar, postprandial blood sugar, hemoglobin A_{1c} levels, liver function test, and kidney function test with electrolytes would be assessed on days 0, 14, and 28. These tests would be repeated as many times as required as per Institutional Management Protocol, which is essentially based on FISF guidelines. However, the assessments would be done only on the fixed days, as mentioned above.

CEMRI PNS would also be done on day 1 (or latest report if it is within 03 days of enrolment day), day 14, and day 28, or before or after as per IMP or FISF requirement Multimedia Appendix 3.

Follow-Ups

Each patient would be followed up for 28 days. Participants would be followed up daily as long as they are hospitalized; in case of discharge before this follow up period, they would be followed up telephonically on day 14 and day 28.

The following variables would be clinically assessed in every follow-up:

1. Nasal stuffiness
2. Nasal discharge
3. Foul smell
4. Epistaxis
5. Facial pain
6. Facial edema
7. Dental pain
8. Malaise
9. Fever

The case would be said to be completed when there is either recovery of the participant as per the outcome parameters, followed by discharge from the hospital, or has advanced in the form of advanced disseminated mucormycosis or death of the patient.

Data Analysis

The study center would send a weekly report as per weekly report proforma on case recruitment to headquarters either by fax or email every week. The DSMB would assess the research data regularly. The conclusion report on completion of the study (after 3 months) is to be submitted to Headquarters as per concluding report proforma.

Withdrawal Criteria

The participant would be withdrawn from the study if the condition of the participants worsens and the mucormycosis expands beyond the inclusion criteria (safety end point), participants require ventilator support, it suggests a severe respiratory condition, possibly due to complications from mucormycosis or other underlying health issues, or participants become unwilling to continue or become noncompliant in the RCT and request the site PI to withdraw them for the RCT would be withdrawn from the study. Every participant can withdraw from the trial anytime for any reason and without prejudice.

End Point

A case would be considered complete when the participant either recovers based on the defined outcome parameters and is discharged from the hospital within or before 28 days. Safety end points include advanced disseminated mucormycosis and patient death.

Statistical Analysis

Data collected would be compiled on to a Microsoft Excel worksheet and would be subjected to statistical analysis using

an appropriate package like SPSS (IBM Corp) software. Descriptive statistics like frequency and percentage of categorical data, mean (SD) of numerical data in each group or subgroup would be depicted. Frequency and percentage of various categories in each group or subgroup would be compared using chi-square test. Normality of numerical data would be checked using Shapiro-Wilk test or Kolmogorov-Smirnov test. Depending on the normality of data, statistical tests would be determined. For a numerical continuous data following a normal distribution, inter group comparison (2 groups) would be done using *t* test, else a nonparametric substitute like the Mann-Whitney *U* test would be used. Intra group comparisons for a numerical continuous data following a normal distribution would be carried out using paired *t* test (for 2 observations) or repeated measures ANOVA for >2 observations, else a nonparametric substitute like Wilcoxon signed-rank test (for 2 observations) or the Friedman test for >2 observations would be used. Frequency and percentage of various responses in each time interval would be compared using the chi-square test or McNemar test. Having set the α error at 5%, β error at 20%, and power at 80%, $P<.05$ would be considered statistically significant (Multimedia Appendices 4, 5, and 6).

Data Monitoring and Management

Project Monitoring and Reviews

Record of each enrolled case is also to be electronically maintained and this electronically maintained record is to be sent to headquarters through email to the study coordinator at CCRH headquarters as soon the case is enrolled for verification of the case record with annexures. Concerned authority shall do on-site monitoring at 1-month interval till completion of the study.

Quality Control

A centralized workshop would be organized for the investigators (to be involved in specific study) to ensure standardization and quality control. A periodical review would be conducted at all the sites for quality assurance. A random subset of records from each site would be evaluated for quality control. Investigators would be asked to bring all medical records for selected subjects to the data analysis workshop. Information in the medical records would be compared with the data on the case report form to assess completeness and accuracy of reported data.

Harms

Homoeopathic medicines which shall be used in the trial are known pharmacopeial preparations. As no new remedy is proposed to be investigated, there is no potential risk due to intervention.

Auditing and Inspecting

The study center would send a weekly report as per weekly report proforma on case recruitment to headquarters either by fax or email every week of the month. The DSMB would assess the research data regularly. The conclusion report on completion of the study (after 3 months) is to be submitted to hqrs. as per concluding report proforma.

Ethical Considerations

Protocol Development

This is carried out in consultation with experts of St. George's and JJ Hospital, Mumbai and then subsequently reviewed by Dr V Shankar Kumar, Consultant ENT Surgeon Apollo Spectra Hospitals, Chennai and Dr Sushil Kabra, Department of Pediatrics, AIIMS New Delhi before it was submitted to ethics committee.

Human Subject Ethics Review Approvals or Exemptions

The study protocol shall be in accordance with the latest revision of the Helsinki Declaration on human experimentation and Good Clinical Practices India. Although medicines proposed to be used during the study are known homoeopathic pharmacopeial preparations, necessary clearance of the Ethical Committee shall be obtained before undertaking the study. The Scientific Advisory Board and the Central Ethics Committee of the CCRH have approved the study protocol and the amendments (1-29/2021-22/CCRH/Tech/Post-covid Mucormycosis/887; July 15, 2021). The investigator must meet the study requirements as specified in the protocol. Protocol amendments are possible only in exceptional cases (eg, where the health or well-being of the participant is affected) and only after authorization by the Scientific Advisory Committee (SAC) of the Council. If there is any modification in the protocol, an addendum of the same shall be circulated to all the investigators after due approval of SAC and EC. The investigator shall update the protocol by attaching the addendum of the amendment to the already circulated protocol. In case of any administrative or technical amendments, which do not affect the health of the participant, agreement of all the concerned shall be made. These changes shall also be justified in writing and all those concerned are to be informed.

Informed Consent

Individuals aged 18 years or older would be considered eligible for consent. The site PI would obtain voluntary consent from the participants before the screening test after explaining the study. The participants would be provided with the participant information sheet describing the study details and would voluntarily sign the consent form if they agree to take the intervention.

Privacy and Confidentiality

The investigator would inform the participants that all trials results recorded would be treated in strict confidence. During documentation and analysis, the participants would only be identified by their subject code and unique identifier number. The confidentiality of the participants' personal data would be maintained as per data protection regulations.

Compensation Details

CCRH would provide insurance cover in the trial for the said study duration, according to the terms finalized under clinical trial cover with the identified insurance firm.

Protocol Violation

If the patient stops taking the intervention medication on their own, this would be considered as protocol violation. So, these participants would not be considered for per protocol analysis.

Declaration of Interest

No conflict of competing interest of the PI or site PI, or any other member of the investigation team.

Access to Data

The access to data would be restricted for analysis and interpretation only by CCRH and other collaborating organization, as and when involved. For all purposes, the data would remain strictly confidential, and anonymity would be assured through the best possible means.

Ancillary and Posttrial Care

The participant would be provided with all ancillary care during the study and other ancillary techniques. Besides, she/he would be provided with regular outpatient department care, even after the study is over.

Dissemination Policy

The investigators would communicate trial results to participants, health care professionals, the public, and other relevant groups (through publication, reporting in results databases, or other data sharing arrangements) after completion of the study. However, no information based on unjustified claims, or the findings of interim analysis would be communicated in any form.

Results

India faced a significant impact from the COVID-19 pandemic, with 44,587,307 confirmed cases and 528,629 deaths reported as of January 17, 2023, according to the World Health Organization [28]. The second wave placed tremendous strain on the nation's health care system, resulting in severe shortages of drugs, vaccines, ventilators, and oxygen. During this period, there was a notable increase in mucormycosis cases among patients with COVID-19, leading the government to classify it as a notifiable disease under the Epidemic Diseases Act of 1897 on May 20, 2021 [29]. To address the high mortality rate and long-term complications experienced by many survivors, the Ministry of AYUSH, Government of India, recommended homoeopathy as an adjunct therapy to enhance the effectiveness of standard conventional treatments. The CCRH developed a protocol to incorporate homoeopathy as an additional therapy for treating COVID-19–associated mucormycosis. However, when this protocol was created, there was a significant number of mucormycosis cases in India, particularly in Mumbai (June 2021). By the time CCRH obtained all necessary approvals and ethical clearance for the study, the incidence had decreased dramatically (September 2021), resulting in the study not being initiated or registered. The authors believe it is their ethical duty to share this reviewed protocol with the medical community as a reference for future research.

Discussion

Principal Findings

This study was conceived during the exponential increase in Mucormycosis cases in India since March 2021. This opportunistic infection was being observed in patients with severe COVID-19. Globally, the prevalence of mucormycosis varied from 0.005 to 1.7 per million population in 2019-2020. Its prevalence in India was 0.14 per 1000 population. In May 2021, the cases peaked to 11,717 cases of mucormycosis across 18 states of India [24]. ROCM is extremely fatal with mortality rates ranging from 85%-93%, despite the best treatment in immunocompromised patients [30]. Patients with poorly controlled diabetes mellitus are the primary group at risk for developing ROCM. Other recognized risk factors worldwide include diabetes-associated ketoacidosis, hematological malignancies, solid organ or bone marrow transplants, surgeries, trauma, neutropenia, protein-calorie malnutrition, autoimmune diseases, chronic kidney disease or renal failure, HIV infection, deferoxamine therapy, and corticosteroid therapy [31]. ROCM typically starts in the paranasal sinuses and then spreads to adjacent structures, such as the orbit and neurocranium. Most reported cases are from Iran (26%), India (22%), China (17%), and the United States (15%), regions where diabetes prevalence is significantly increasing [32]. Chavda et al [33] state that mucormycosis affects the nose, eyes, and brain and is a potentially fatal intrusive fungal infection that frequently affects immunodeficient individuals.

In conventional treatment, surgical and pharmaceutical interventions are key to treat mucormycosis, thus necessitating a multidisciplinary approach team of otolaryngology, ophthalmology, neurosurgery, and infectious disease specialists in a facility setting. Intravenous antifungal pharmacotherapy is the first line of treatment, amphotericin B deoxycholate and posaconazole or isavuconazole being the 2 antifungal agents recommended for the primary therapy of mucormycosis [34]. However, the scope of treatment in limited in this condition, and resulting side effects are known. Chakraborty et al [34] have reported side effects from liposomal amphotericin B, which include fever, chills, nausea, vomiting, loss of appetite, headache, and some serious side effects which include swelling or pain at injection site, muscle or joint pain, unusual tiredness, weakness, muscle cramping and signs of kidney problems (such as a change in the amount of urine or painful urination) and so on after infusion of the drug, which, in turn, causes hindrance to continue the required conventional treatment [17]. Sachdeva et al [35] states that hepatotoxicity and nephrotoxicity are well-known serious side effects of intravenous Amphotericin B and posaconazole treatment. Pal et al [36] reports palatal, facial soft tissue necrosis, loss of vision, and invasion of soft tissues of the infratemporal fossa, orbit or palate through neurovascular structures as complications of ROCM.

Due to limited scope of conventional medicine, side effects that are serious or interfere in the treatment, advance complications and poor prognosis with high mortality rate, the authors felt a need of exploring the usefulness of alternative system of medicine to complement the standard line of treatment for

COVID-19–related ROCM. The authors have had a successful experience of providing adjunct homoeopathic treatment in severe cases of COVID-19 before planning this RCT, which, is now reported [37]. Planning this RCT, thus, seemed to be a step in the right direction.

The evidence for similar studies in the past in homoeopathy sector is limited. The literature was, therefore, looked up for role of homoeopathy in fungal studies, instead. A study on dermatophytosis and its management by homoeopathic medicines reports successful reduction in the NRS and DLQI scores, thus suggesting it as a feasible integrative treatment option for tinea infections [38]. An in vitro study on antifungal activity of homoeopathic medicines against plant fungus *Aspergillus niger* observed that homoeopathic medicines with various potencies (6C to CM) had a significant antifungal activity, compared with the controls, which is bavistin (Carbendazim) and ethanol (Dispensing alcohol 90%) [39]. A case series by Roy et al [40] reports positive effect of homoeopathic medicines against dermatophytosis. Furthermore, a pilot study by Sherr et al [41] reported that homoeopathic medicine Bacillinum had a potential to improve long term tinea status and reduces the chances to relapse as compared with the standard treatment for tinea and homoeopathy can be used as an alternative to standard treatment care. Other in-vitro studies have also reported homoeopathy medicines to have worked effectively against the growth of different forms of fungus [21,22].

There was, however, no study reported so far to assess the role of homoeopathic medicines in mucormycosis. Hence, to the authors' knowledge, this protocol was a first with the aim to evaluate the efficacy of homoeopathic medicines as an adjuvant in the treatment of COVID-19–related ROCM. However, with the decline in COVID-19 cases in September 2021, which was the time when the approvals could be sought, the study had to be called off due to nonfeasibility reasons. The authors feel this as their ethical duty to share this reviewed protocol with the profession as a reckoner or source of further work for the clinicians or scientists alike, in a more generalized manner, which is to say, in the cases of mucormycosis not particularly resulting from COVID-19 infection. This would help in being prepared with the evidence, or the lack of it, should such an emergency situation arise in future. We, thus, share this protocol with the community with the hope that it may be adopted for mucormycosis cases that are generally seen in immunocompromised individuals.

Conclusion

This study aimed to evaluate the role of existing homoeopathic medicines as an adjuvant therapy in managing COVID-19–related ROCM, potentially contributing to the use of homoeopathy as an evidence-based medical approach. The protocol can also serve as a valuable resource for clinicians and researchers addressing mucormycosis cases unrelated to COVID-19 infection, particularly in immunocompromised patients. It would help ensure preparedness, whether or not sufficient evidence is available, in the event of a future health emergency. The authors have tried to adopt universally acceptable, standardized parameters for determining the improvement, with secondary parameters intended for evaluating the survival rate of the hospitalized patients besides other parameters that have been selected for assessing initial treatment response through laboratory and imaging techniques. A planned outcome of the study includes comparing the time required for significant or complete recovery between patients receiving adjuvant treatment and those in the control group. The authors welcome future studies based on this protocol and would be pleased to see their work advanced by fellow professionals.

Acknowledgments

Dr VK Gupta, Chairman of the Scientific Advisory Board of the Central Council for Research in Homoeopathy (CCRH), and Dr LK Nanda, Chairman of the Special Committee on Clinical Research at CCRH, along with their respective committees, are acknowledged for granting technical approvals. Additionally, reviewers Dr V Shankar Kumar, Consultant ENT Surgeon at Apollo Spectra Hospitals, Chennai, and Dr Sushil Kabra, Department of Pediatrics at the All India Institute of Medical Sciences, New Delhi, are thanked for their valuable comments that enhanced the protocol during its development. The funding authority was the Central Council for Research in Homoeopathy under the Ministry of AYUSH.

Data Availability

No data are associated with the protocol as the study could not be initiated because mucormycosis cases started declining.

Authors' Contributions

RB and HK conceptualized the study. JS planned its conduct and methodology under the guidance of HK. JS and TG developed the protocol and contributed in final manuscript writing. All authors agreed with the final version of the manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Treatment for COVID-19-associated mucormycosis recommended by the FISF.
[PNG File , 314 KB - resprot_v14i1e57905_app1.png]

Multimedia Appendix 2
Staging of rhino-orbital-cerebral mucormycosis.
[DOCX File , 15 KB - resprot_v14i1e57905_app2.docx]

Multimedia Appendix 3
SPIRIT flow diagram.
[DOC File , 52 KB - resprot_v14i1e57905_app3.doc]

Multimedia Appendix 4
Dummy table for Baseline.
[DOCX File , 15 KB - resprot_v14i1e57905_app4.docx]

Multimedia Appendix 5
Dummy table for follow ups.
[DOCX File , 14 KB - resprot_v14i1e57905_app5.docx]

Multimedia Appendix 6
Dummy table for Survival time.
[DOCX File , 13 KB - resprot_v14i1e57905_app6.docx]

Multimedia Appendix 7
Original Protocol.
[DOCX File , 71 KB - resprot_v14i1e57905_app7.docx]

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Abbreviations

CCRH: Central Council for Research in Homoeopathy
CEMRI PNS: Contrast-Enhanced Magnetic Resonance Imaging of Para Nasal sinus
DSMB: Data and Safety Monitoring Board
FISF: Fungal Infection Study Forum
IMP: investigational medicinal product
MRI: magnetic resonance imaging
PI: principal investigator
PNS: paranasal sinus
RCT: randomized controlled trial
ROCM: rhino-orbital-cerebral mucormycosis
SAC: Scientific Advisory Committee
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials
T1W: T1-weighted
T2W: T2-weighted

Edited by A Schwartz; submitted 29.02.24; peer-reviewed by A Krishnan, K Ghosh; comments to author 19.06.24; revised version received 05.08.24; accepted 20.11.24; published 19.03.25.

Please cite as:
Kaur H, Sachdeva J, Bawaskar R, Goyal T
Comparative Evaluation of Effectiveness of Standard of Care Alone and in Combination With Homoeopathic Treatment in COVID-19–Related Rhino-Orbito-Cerebral Mucormycosis (ROCM): Protocol for a Single Blind, Randomized Controlled Trial
JMIR Res Protoc 2025;14:e57905
URL: https://www.researchprotocols.org/2025/1/e57905
doi:10.2196/57905
PMID:

Protocol

Evaluation of the Clinical Nursing Effects of a Traditional Chinese Medicine Nursing Program Based on Care Pathways for Patients With Type 2 Diabetes: Protocol for a Randomized Controlled Clinical Trial

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Abstract

Background: To improve the performance of health care institutions, reduce overmedication, and minimize the waste of medical resources, China is committed to implementing a clinical pathway management model. This study aims to standardize nursing practices, foster clinical thinking in nurses, and promote patient recovery.

Objective: The purpose of this study is to evaluate the clinical effects of a traditional Chinese medicine (TCM) nursing program based on nursing pathways for patients with type 2 diabetes mellitus (T2DM).

Methods: This study uses a prospective, randomized, single-blind, parallel-controlled design. Based on sample size calculations, the study will include 594 patients with diabetes, with 2 groups of 297 patients: an observation group will receive a TCM nursing program based on clinical pathways, while a control group will receive routine care. Both groups will be evaluated before and after the intervention using assessment indicators. The primary outcome is the quality of life score, measured by a diabetes-specific quality of life questionnaire. Secondary outcomes include hospital stay duration, medical expenses, health knowledge, blood glucose control, symptom scores, and patient satisfaction.

Results: This study was funded in August 2021 and has received approval from the Ethics Committee of Guang'anmen Hospital, China Academy of Chinese Medical Sciences (2022-022-KY-01). The trial is ongoing, with the first patient enrolled in September 2022. The study is expected to conclude in April 2025. To date, 380 patients have been recruited, with 202 randomized into the study, though no statistical analysis of the data has yet been conducted. A single-blind method is used; nurses are aware of group assignments and intervention plans, while patients remain blinded. Final results are planned for release in the first quarter of 2025.

Conclusions: This study seeks to integrate existing national standardized nursing protocols with clinical pathways to implement more efficient and higher-quality nursing practices. The goal is to standardize nursing procedures, enhance patients' quality of life, and improve self-care and medication adherence after discharge.

Trial Registration: International Traditional Medicine Clinical Trial Registry ITMCTR2022000048; https://tinyurl.com/y4jd68h4

International Registered Report Identifier (IRRID): DERR1-10.2196/58951

(JMIR Res Protoc 2025;14:e58951) doi:10.2196/58951

KEYWORDS

type 2 diabetes; traditional Chinese medicine; TCM nursing program; clinical pathway; application research; diabetes; diabetes mellitus; research protocol; nursing; nursing program; nursing care; chronic disease; disease monitoring; prevalence; China; adult; patient recovery; psychological care; health education; quality of life; blood glucose; self-care; medication; control group; patient satisfaction

Introduction

According to the Guideline for the Prevention and Treatment of Type 2 Diabetes Mellitus in China (2020 Edition) [1], the prevalence of diabetes in China has surged from 0.67% in 1980 to 11.2% in 2015-2017 [2,3]. Diabetes management in China faces significant challenges, particularly in rural areas where awareness, treatment, and control rates remain low. Large-scale epidemiological surveys conducted in 2010 and 2013 reported diabetes awareness rates of 30.1% and 36.5%, treatment rates of 25.8% and 32.2%, and control rates of 39.7% and 49.2%, respectively [3-5].

Most existing studies have focused on evaluating clinical nursing pathways or nursing programs. For instance, a study by Li [6] analyzed the effectiveness of clinical nursing pathways in type 2 diabetes mellitus (T2DM) care, demonstrating that a research group using clinical nursing pathways achieved better control of fasting blood glucose and postprandial 2-hour glucose levels compared to a control group (P<.05). The research group also had significantly fewer instances of improper hypoglycemia treatment, insulin injection errors, dietary mistakes, inadequate exercise, and nonadherence to medical advice (P<.05). Additionally, compared to the control group, the research group had shorter hospital stays, lower hospitalization costs, and higher overall nursing satisfaction (P<.05), indicating that the application of clinical nursing pathways can effectively control blood glucose levels, improve nursing quality, and enhance patient satisfaction.

Similarly, a study by Ren et al [7] showed that implementing traditional Chinese medicine (TCM) nursing programs in general hospitals resulted in higher quality-of-life scores for patients in an observation group 1 month after discharge compared to a control group. At discharge, the observation group had a significantly higher nursing satisfaction rate (93%) than the control group (77%; P<.05). This suggests that the TCM nursing program model can improve both quality of life and nursing satisfaction. These studies demonstrate that clinical nursing pathways or TCM nursing programs can effectively control blood glucose levels and reduce medical costs while enhancing patients' quality of life. However, no studies to date have explored the combined clinical application of these two nursing methods, which is the focus of our study.

The evolution of national standards and their integration with nursing practices have increasingly shifted the focus toward nursing pathways aligned with these standards. This development combines nationally standardized nursing protocols with nursing pathways to create a coherent, interconnected, and progressive nursing model. Pathway-based TCM nursing interventions built on TCM clinical pathways standardize the care of single diseases, promote systematic intervention processes, highlight the efficacy and unique features of TCM, and make nursing operations more standardized. This enables nurses to provide planned and anticipatory care based on structured procedures. A preliminary retrospective analysis of clinical data from 4196 patients with diabetes revealed that integrating traditional Chinese nursing techniques with clinical treatments effectively alleviated patients' discomfort. Nurses found this approach more practical and valuable in standardizing care, reducing variability, lowering costs, and improving care quality for patients with T2DM [8,9]. Nevertheless, no research has yet examined the simultaneous clinical application of these two nursing methods, which is the aim of our study.

Thus, we conducted a prospective, randomized, single-blind, parallel-controlled trial to further investigate the impact on patient outcomes of integrating nationally standardized nursing protocols with TCM nursing programs based on clinical pathways. These outcomes include hospitalization indicators (eg, length of stay and medical costs), self-management (health knowledge), clinical efficacy (blood glucose control, clinical symptoms, and quality of life), and patient satisfaction. We expect that the findings of this study will provide robust evidence for delivering personalized care, standardizing procedures, improving patients' quality of life, and enhancing self-care and medication adherence after discharge.

Methods

Study Design

The intervention protocol for this study is titled "TCM Nursing Protocol for Type 2 Diabetes Based on Care Pathway." The study uses a prospective, randomized, single-blind, parallel-controlled clinical design and aims to assess and demonstrate differences, supported by high-quality evidence, in outcomes between an intervention group and a control group that received standard care. The research team comprises nurses from the Department of Endocrinology at Guang'anmen Hospital, China Academy of Chinese Medical Sciences. The study participants are patients with T2DM admitted to our department between September 2022 and December 2024. The study is registered with the International Traditional Medicine Clinical Trial Registry (ITMCTR2022000048). Inclusion, exclusion, and elimination criteria are shown in Textbox 1.

Textbox 1. Inclusion, exclusion, and elimination criteria.

Inclusion criteria

- The primary diagnosis must align with *International Classification of Diseases, Tenth Revision* codes for type 2 diabetes mellitus, specifically in the range of E11.2 to E11.9.
- Admission criteria must be met for inpatient treatment, as determined by the clinical physician.
- In cases where patients have concurrent diagnoses of other diseases, if these conditions do not require special treatment during the hospital stay and do not hinder the implementation of the clinical nursing pathway for the primary diagnosis, the patient can be included in that nursing pathway.
- Informed consent must be obtained from the patient and documented, indicating their understanding and agreement with the proposed care plan.

Exclusion criteria

- Patients who meet the diagnostic criteria for type 2 diabetes mellitus but are unable to comply with the treatment regimen.
- Patients with cognitive impairments or cognitive dysfunction.
- Patients with concurrent diagnoses of other diseases that require treatment during the hospitalization period.

Elimination criteria

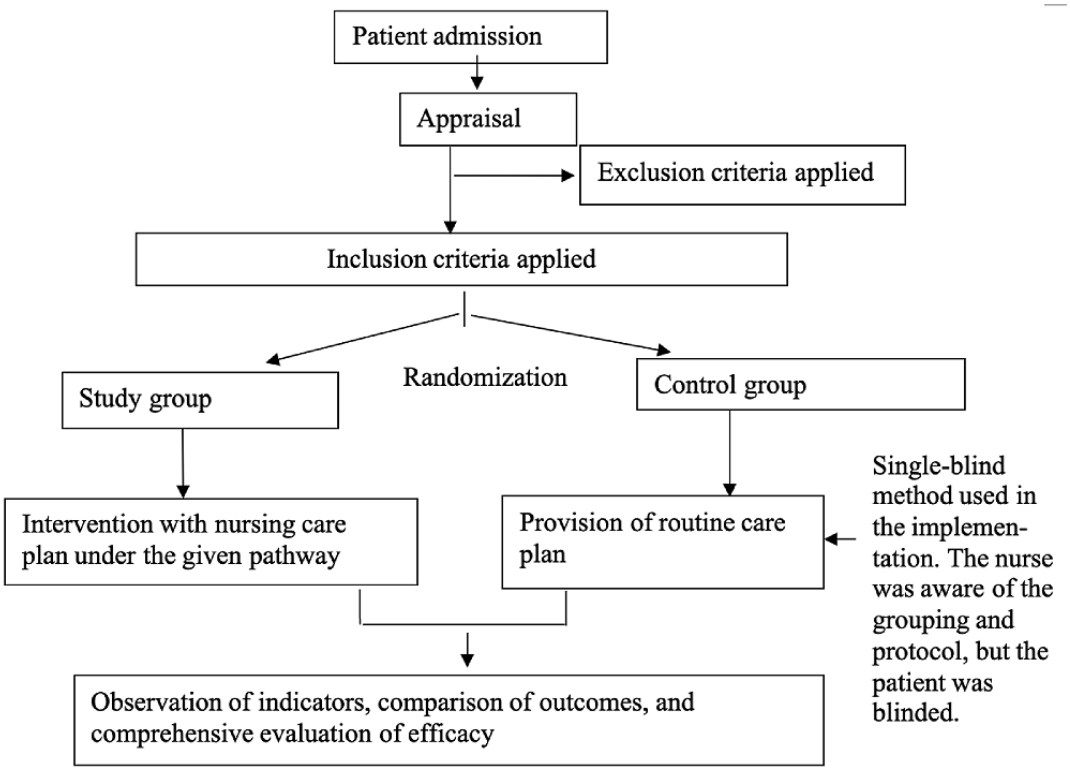
- Patients whose condition worsens, resulting in a hospitalization duration exceeding 14 days and increased hospitalization costs.
- Patients with concomitant systemic diseases that require special treatment, leading to a hospitalization duration exceeding 14 days and increased costs.
- Patients with serious complications that arise during the course of treatment and necessitate discontinuation of the nursing pathway.
- Patient and family preferences and wishes that affect the implementation of this nursing pathway.

Interventions

Intervention Plan

Upon admission, nurses provide admission education and assign eligible patients to the study group or the control group based on the time of admission (Figure 1). The intervention plans for both groups are outlined in a pathway form and include 3 components: executing medical orders, nursing tasks, and health education, along with TCM-specific treatments (Multimedia Appendix 1). For the control group, nurses subjectively implement the nursing plan according to the pathway form. The study group strictly follows the TCM nursing pathway for T2DM.

Figure 1. Study design and flow.



Implementation of the TCM Nursing Pathway for T2DM

Upon admission, nurses provide admission education and assess the patient's condition using an evaluation form for the TCM nursing pathway for T2DM. This assessment determines whether the patient qualifies for inclusion in the study. Eligible patients receive the TCM nursing pathway for T2DM. For patients included in the study, nurses ensure that physicians perform a thorough examination upon admission. The TCM nursing pathway form for T2DM is distributed, and patients are informed about their treatment and the nursing plan during hospitalization. This ensures patients understand the medical and nursing measures to be implemented.

During hospitalization, the responsible nurse uses the evaluation form of the TCM nursing pathway for T2DM to develop an appropriate care plan. This plan may include TCM techniques, syndrome differentiation–based dietary therapy, exercise and health practices, herbal prescriptions, and emotional regulation. The study group strictly adheres to the schedule outlined in the TCM nursing pathway for T2DM. Nurses coordinate with relevant departments promptly to complete necessary examinations. The control group receives routine care.

If there are any changes in the patient's condition, the responsible nurse promptly analyzes and addresses the changes, adjusting the sequence of items in the TCM nursing pathway as necessary. The head nurse checks the implementation of the TCM nursing pathway for T2DM and the routine care plan daily. The head nurse ensures compliance with the nursing pathway protocol and evaluates the quality of care promptly. Relevant data are collected and evaluated at the time of the patient's discharge.

Sample Size Calculation

A literature-based approach was used to compare the preset effect, with α=.05 and β=.10, against the known efficacy of general nursing from previous studies. Based on methods found in the literature [10] and conclusions from earlier research, the historical effective rate (very satisfied + satisfied) was determined to be approximately 74.5% [9]. The effective rate for this pathway nursing program is projected to be 85%. Using *Z* values from standard tables ($Z1 - \alpha / 2 = 1.96$; $Z1 - \beta = 1.28$), the sample size for each group was estimated as follows:

$N1 = N2 = (Z1 - \alpha / 2 + Z1 - \beta)\ 2\ [P1(1 - P1) + P2(1 - P2)] / \delta 2 = (1.96 + 1.28)\ 2\ [0.745 \times (1 - 0.745) + 0.85 \times (1 - 0.85)] / (0.85 - 0.745)\ 2 = 296$. Thus, 242,272 indicated 297 cases, and the sample size of this study was 297 × 2 = 594 cases.

Randomization Method

The randomization method used in this study involves selecting an appropriate block size and assigning participants into 2 groups (the study group and the control group) in a 1:1 ratio. Using the *PROC PLAN* procedure statement in SAS (version 9.2; SAS Institute) and specifying a seed number, a randomized allocation was generated for 594 participants. This process produced a complete randomization table, listing the treatment assignments corresponding to sequential serial numbers from 001 to 594.

Blinding Method

This is a single-blind study, and patients with diabetes are unaware of their group assignment.

Outcomes

Researchers use standardized questionnaires to collect baseline data. The primary efficacy indicator is a quality of life scale (the Diabetes-Specific Quality of Life Scale) [11]. Secondary efficacy indicators include the length of hospital stay, medical costs, blood glucose control, patient symptom scores, patient satisfaction, and the level of health knowledge acquired at admission. Data are collected 1 day before discharge and at 4 weeks, 12 weeks, and 24 weeks after discharge.

Harm

Apart from the risk of data violations, there is no anticipated harm to the study participants. The investigator will be identified by experimenter number to reduce the risk. Although greater adherence to treatment is expected in the intervention group, no systematic differences in diabetes management are expected.

Ethical Considerations

The ethical principles guiding this study include the Measures for Ethical Review of Biomedical Research Involving Humans, Good Clinical Practice for Drug Trials, Regulations on Clinical Trials of Medical Devices, Ethical Review Guidance for Drug Clinical Trials, Clinical Ethical Review Management Guidelines for Traditional Chinese Medicine Hospitals, the Declaration of Helsinki, and the International Ethical Guidelines for Biomedical Research Involving Human Subjects.

The trial has been approved by the Ethics Committee of Guang'anmen Hospital, China Academy of Chinese Medical Sciences (2022-022-KY-01). Prior to the implementation of the study, informed consent must be obtained from patients. Participation in this study is entirely voluntary. Patients may choose not to participate or withdraw from the study at any time without providing a reason, and participation requires signing an informed consent form.

All patient data collected during the trial will remain confidential. Medical records will be identified using research ID numbers instead of names. Identifiable information will not be disclosed to anyone outside the research team unless the patient provides explicit permission.

In accordance with relevant national regulations, in the event of research-related injuries, the study institution, Guang'anmen Hospital of the China Academy of Chinese Medical Sciences, will bear the corresponding medical costs and provide appropriate financial compensation.

For any questions regarding participant rights in this study, individuals can contact the Ethics Committee of Guang'anmen Hospital, China Academy of Chinese Medical Sciences.

The study form will be kept by the data collector in a folder in the study office. Study data will be processed without participants being recognizable. Only the researcher responsible for the analysis can access the final data set; after the trial study is published, we will provide research references and the scientific basis for relevant clinical practice, formulate the

implementation specifications of the nursing program under the chosen pathway, and promote the research results in the industry.

Statistical Analysis

We will use SPSS (version 26.0; IBM Corp) to perform the statistical analysis. Descriptive statistics for quantitative variables will include at least the mean and SD or the median and IQR. Descriptive statistics for qualitative variables will include at least the frequency and percentage for each category. Comparisons between the 2 groups will be conducted using an independent-sample *t* test (for normally distributed data with equal variances) or the nonparametric rank-sum test. For unordered categorical data, comparisons between the 2 groups will be made using the χ^2 test or Fisher exact test, while ordinal categorical data will be analyzed using nonparametric tests. All statistical tests will be 2-sided, with a $P<.05$ considered statistically significant.

Results

This trial received funding in August 2021 and is currently ongoing. The first patient was enrolled in September 2022, and the study is expected to conclude in December 2024. The trial uses a single-blind design where nurses are aware of group assignments and intervention details, but the patients remain blinded. Final results are planned for publication in the first quarter of 2025.

To date, 380 patients have been recruited, with 172 excluded, resulting in 202 randomized participants (101 in the study group and 101 in the control group). Details on the screening process are provided as a Consolidated Standards of Reporting Trials (CONSORT) flowchart in Multimedia Appendix 2.

This study primarily aims to compare health knowledge, comprehension, and scores between the 2 groups, with the goal of optimizing an innovative model for the TCM nursing pathway for T2DM. The findings are expected to enhance the standardization and precision of clinical nursing practices. The pathway will be validated clinically, combining theory with practice through prospective research to provide high-level clinical evidence. This will contribute to the development of a high-quality TCM nursing pathway, expand the global influence of TCM, and support national economic growth and public health.

Discussion

Overview

Data show a significant increase in China in the incidence of diabetes over 30 years, leading to a high prevalence of acute and chronic complications. Simultaneously, deficiencies in patient awareness, understanding, treatment rates, and control rates have become evident in diabetes care. This underscores the urgent need to explore and improve diabetes care methods.

In recent years, China's economic growth has created opportunities for more targeted and standardized care, providing promising prospects for development. Under the framework of National Standards + Nursing Pathways, TCM-based nursing models have become prominent in diabetes clinical care. However, despite positive outcomes with existing standards, a comprehensive clinical pathway management model has yet to be established, resulting in inconsistencies and nonstandardized practices.

Thus, it is crucial to conduct in-depth research to integrate these methods and improve the effectiveness of nursing practices. Exploring and developing nursing plans that combine clinical pathways with TCM principles is essential. High-quality prospective clinical research is needed to meet patients' increasing demand for improved health care quality and to refine standardized nursing protocols.

Since the Ministry of Health launched the clinical pathway pilot project in 2009, the effectiveness of clinical pathway management in improving health care quality and controlling medical costs has become increasingly evident. Against the backdrop of advocating "high quality, high efficiency, and low cost," studying the application of clinical nursing pathways in China's health care quality management is of significant importance. This emphasizes the need for further development and research into the implementation of a TCM nursing model for T2DM based on National Standards + Nursing Pathways.

Principal Findings

This study focuses on comparing health knowledge and scores in the 2 groups, aiming to optimize an innovative model for the TCM nursing pathway for T2DM. This approach should help enhance the standardization and precision of clinical nursing practices. Its application in the clinic will combine theory with practice, providing high-level clinical evidence through prospective research. The goal is to establish a high-quality TCM nursing pathway that will expand the international influence of TCM and support economic and public health development.

Strengths and Limitations

Building on prospective findings from previous studies, this study will use a prospective design to enhance the level and reliability of evidence. The study's significance also lies in providing a foundation for high-quality clinical evaluation that will enable selecting targeted and distinctive TCM clinical nursing pathways. The aim is to improve the clinical application and quality of standard nursing procedures within nursing projects based on a T2DM nursing pathway.

However, this study uses a single-center design and does not include additional hospitals, which is a limitation. Nevertheless, the focus is on optimizing the TCM nursing pathway at this center and obtaining high-quality evidence of its effectiveness to facilitate broader future applications and clinical use.

Future Directions

The TCM nursing pathway explored in this study has a solid foundation, demonstrating its potential for effective care. We anticipate that as the study progresses, high-quality evidence will confirm its efficacy. Subsequently, this TCM nursing pathway will be promoted in more hospitals, benefiting a larger population of patients with diabetes.

Conclusions

This study aims to integrate existing national standardized nursing protocols with clinical nursing pathways to implement more efficient and higher-quality clinical nursing practices. It seeks to standardize nursing procedures, improve patients' quality of life, and promote self-care and medication adherence after discharge.

Acknowledgments

The study was funded by the Science and Technology Innovation Program of the Chinese Academy of Chinese Medical Sciences (CI2021A03212).

Authors' Contributions

NS contributed to conceptualization, critical revision of the study design, data collection and analysis, manuscript writing, and final approval of the manuscript. YZ and SL contributed to data collection and analysis, critical revision, and final approval of the manuscript. TH contributed to data collection and manuscript writing. JZ, XH, and YC made contributions to the implementation of the planned intervention.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Clinical pathway form.
[DOC File , 96 KB - resprot_v14i1e58951_app1.doc]

Multimedia Appendix 2
Consolidated Standards of Reporting Trials (CONSORT) flowchart of participant recruitment and allocation to date.
[PDF File (Adobe PDF File), 38 KB - resprot_v14i1e58951_app2.pdf]

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Abbreviations

CONSORT: Consolidated Standards of Reporting Trials

TCM: traditional Chinese medicine
T2DM: type 2 diabetes mellitus

Edited by A Schwartz; submitted 28.03.24; peer-reviewed by AN Ali, C Chiaranai; comments to author 11.07.24; revised version received 21.08.24; accepted 27.02.25; published 31.03.25.

Please cite as:
Zhao Y, Huang T, Chen Y, Li S, Zhao J, Han X, Ni Q, Su N
Evaluation of the Clinical Nursing Effects of a Traditional Chinese Medicine Nursing Program Based on Care Pathways for Patients With Type 2 Diabetes: Protocol for a Randomized Controlled Clinical Trial
JMIR Res Protoc 2025;14:e58951
URL: https://www.researchprotocols.org/2025/1/e58951
doi:10.2196/58951
PMID:

Protocol

Effects and Safety of Press-Needle Therapy for Improving Visual Function and Eye Blood Circulation in Patients With Glaucoma With Controlled Intraocular Pressure: Study Protocol for a Multicenter Randomized Controlled Trial

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Abstract

Background: Glaucoma is the leading cause of irreversible blindness worldwide, causing continuous and progressively worsening damage to visual function, which leads to vision loss. Optic nerve protection is an important treatment for glaucoma with controlled intraocular pressure (GPCI), but to date, there is no universally accepted effective optic nerve protection agent. Acupuncture can protect the optic nerve by increasing blood flow to the eye. However, fear of pain or the limitations of treatment place and time lead to poor patient compliance. Press-needle therapy is a characteristic of traditional Chinese medicine (TCM) external treatment methods; its safety is high, the effect is fast and lasting, it is easy to conduct, and it has high patient compliance.

Objective: The objective of the trial is to evaluate the safety and clinical efficacy of press-needle therapy and investigate whether it can improve visual function by regulating eye blood circulation in patients with GPCI.

Methods: In total, 192 participants aged 18-75 years with GPCI from the Mianyang Central Hospital, the Mianyang Hospital of Traditional Chinese Medicine, and the Mianyang Wanjiang Eye Hospital will participate in this study. Participants will be allocated to 2 treatment groups (experimental and control groups) in a ratio of 1:1 and will undergo press-needle therapy and sham press-needle therapy, respectively, for the same 4-week period. Primary outcomes will include the best-corrected visual acuity (BCVA), optical coherence tomography angiography (OCTA), color Doppler flow imaging (CDFI), and visual field assessment results. Secondary outcomes will include the intraocular pressure (IOP) and traditional Chinese medicine (TCM) clinical symptom scales. The primary outcomes and safety assessments will be measured at baseline and 4 weeks thereafter, while the secondary outcomes will be measured at baseline and 1, 2, 3, and 4 weeks thereafter.

Results: Recruitment and data collection began in February 2023. The final outcomes are expected in September 2025. As of October 2024, the project had recruited 220 eligible participants, of whom 192 (87.3%) will complete the study, exceeding initial projections for the study time frame. The remainder of the participants will provide the ability to explore cross-level interactions

that could not be statistically powered at the outset. The strengths of the project include rigorous data collection, good retention rates, and high compliance rates.

Conclusions: This study will provide data on the effects of press-needle therapy on visual function and ocular circulation in patients with GPCI, and these results will help demonstrate whether acupuncture can improve patients' visual function by regulating ocular circulation, thus providing a clinical and theoretical basis for the wider application of acupuncture therapy in GPCI.

Trial Registration: Chinese Clinical Trial Registry ChiCTR2300067862; https://tinyurl.com/mrxd58x9

International Registered Report Identifier (IRRID): DERR1-10.2196/67737

(JMIR Res Protoc 2025;14:e67737) doi:10.2196/67737

KEYWORDS

press needle; press-needle therapy; needling technique; glaucoma; acupuncture; visual function; eye blood circulation; randomized controlled trial; traditional Chinese medecine

Introduction

Glaucoma is a leading cause of irreversible blindness worldwide [1]. Progressive degeneration of retinal ganglion cells (RGCs) and the optic nerve is the basic pathological characteristic of glaucoma [2]. Optic nerve protection is the focus of glaucoma treatment based on intraocular pressure (IOP) control. Neuroprotective targets include glutamate-induced neurotoxicity, nitric oxidase synthetase, neurotropins, calcium channel receptors, free radicals, vascular insufficiency, and the rho-kinase pathway [3]. Nevertheless, at present, there is no satisfactory neuroprotective agent for glaucoma.

Ocular blood flow disorder is a potential cause of visual field deterioration in patients with glaucoma [4]. Therefore, therapeutic options to protect the optic nerve in glaucoma by improving ocular blood flow have attracted increasing attention [3]. Acupuncture therapy has been used to treat glaucoma for thousands of years and has demonstrated favorable safety and convenience [5]. Acupuncture can modify glaucoma blood flow parameters to protect the optic nerve, such as increasing the flow of blood in the eye [6] and reducing anomalies of blood flow in the central artery of the retina [7]. Acupuncture treatments relay electrical signals via the dorsal root ganglion (DRG) and spinal cord, finally regulating ocular blood flow [8].

However, the fear of acupuncture pain or the limitations of the treatment place and time lead to poor patient compliance. Press-needle acupuncture is one kind of acupuncture that has a longer treatment duration and simpler operation with less pain [9]. The theoretical basis of press-needle therapy is the combination of acupuncture theory and skin meridian and acupoint theory. *Suwen: Treatise on the Dermis* states that "all twelve meridians are also part of the skin" and that "the skin is closely related to the veins. The skin is also part of the pulse." The dermis is connected with the 12 meridians by qi and blood. Through the 12 meridians, the 12 dermises are in close contact with the 5 viscera, 6 internal organs, and the eye orifices, forming a coordinated and unified organic whole. Press-needle therapy has been widely used to treat glaucoma with controlled intraocular pressure (GPCI), but useful empirical research is insufficient for its popularization and application. The disadvantages of less rigorous designs, small sample sizes, and low quality have led to many traditional Chinese medicine (TCM) studies being insufficient to convince people of its value. Hence, a randomized, sham-controlled trial will be conducted to assess the potential of press-needle therapy in improving visual function and eye blood circulation in patients with GPCI.

Methods

Research Objectives

The main objectives of this study are twofold: (1) to observe the clinical efficacy of press-needle therapy in patients with GPCI and provide feasible and affordable press-needle treatment for them and (2) to investigate whether press-needle therapy improves the visual function of patients with GPCI by regulating eye blood circulation.

Trial Design and Setting

This multicenter, sham-controlled, blinded, randomized trial of press-needle therapy (Seilini Ltd) for GPCI will be executed in the Mianyang Central Hospital (Sichuan, China), the Mianyang Hospital of Traditional Chinese Medicine (Sichuan, China), and the Mianyang Wanjiang Eye Hospital (Sichuan, China). The study time schedule is presented in Table S1 in Multimedia Appendix 1.

Ethical Considerations

The trial protocol was approved by the Science and Technology Department of Sichuan Province (approval no: 2021YJ0443), the National Natural Science Foundation of China for the Youth (approval no: 82305324), Mianyang Central Hospital Incubation Subjects (approval no: 2020FH07), and the Medical Ethics Committee of the Mianyang Central Hospital (approval no: S2021046 (02)). It has been registered with an identifier (ChiCTR2300067862) with ClinicalTrials. The study will be strictly conducted according to the principles of the Declaration of Helsinki, as well as Good Clinical Practice (GCP) guidelines. The trial will be performed in accordance with the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) checklist [10]. Signed informed consent will be obtained from all patients or their legal guardians by specific researchers prior to beginning the trial. If there are changes to the eligibility criteria, outcomes, or analyses, a new version of the protocol will be submitted to the Medical Ethics Committee of the Mianyang Central Hospital for approval.

Participants and Recruitment Strategy

In total, 192 patients with GPCI recruited from the Mianyang Central Hospital, (Sichuan, China), the Mianyang Hospital of Traditional Chinese Medicine (Sichuan, China), and the Mianyang Wanjiang Eye Hospital (Sichuan, China) will participate in this study. All patients will be screened by specialists and acupuncturists according to the diagnostic criteria in the *European Glaucoma Society Terminology and Guidelines for Glaucoma* [11]. The TCM syndrome of kidney deficiency and blood stasis will be diagnosed based on guidelines delineated in the *Clinical Research Guideline of New Investigational Drugs in Traditional Chinese Medicine* [12].

Inclusion and Exclusion Criteria

Participants who meet the following inclusion criteria will be eligible for the study:

- Diagnosed with primary open-angle glaucoma (POAG) [13]: open anterior chamber angle, pathologically high intraocular pressure (HIOP), with a peak IOP exceeding 21 mmHg (1 mmHg=0.133 kPa) within a 24-hour period, indicative of glaucomatous neuropathy (retinal nerve fiber layer defect [RNFLD] or optic disc changes) or visual field loss or both. Other causes resulting in HIOP were excluded for this diagnosis. Note that only 1 eye from each patient will be selected for examination.
- Having a visual field defect that can be assessed through standard automated perimetry with a reliability factor of less than 15%, as well as an IOP below 18 mmHg, at least 3 months after undergoing antiglaucoma surgery.
- Exhibiting a Chinese syndrome pattern associated with kidney deficiency and blood stasis.
- Refraining from the use of any other optic nerve protective agents, except for methylcobalamin, for a minimum of 2 months.
- Having a spherical refractive error ranging between +3.00 and –6.00 diopters, a fundus clearly visible without the need for pupil dilation, and a BCVA equal to or greater than 0.3.
- Within the age bracket of 18-75 years.
- In a conscious state and capable of cooperating with the examination and treatment process.
- Displaying a willingness to actively participate in the study and provide informed consent.

Participants who have any of the following conditions will not be eligible to participate:

- Poorly controlled IOP (≤7 mmHg or >18 mmHg), accompanied by a thin filtering cystic bleb or bleb leakage.
- Glaucoma that is not open-angle glaucoma.
- A Chinese syndrome pattern that does not meet the criteria of kidney deficiency and blood stasis.
- Other conditions, such as macular degeneration, cataract, proliferative diabetic retinopathy, retinal vascular occlusion, or any other diseases that may cause visual field loss.
- Pregnancy or lactation.
- Abnormal primary liver or kidney function or serious systemic conditions, such as heart disease, primary hypertension, diabetes mellitus, or peptic ulcer disease.
- A history of allergic reactions to the ingredients of press-needle therapy or mecobalamin tablets.

TCM Syndrome Differentiation

The TCM syndrome of kidney deficiency and blood stasis will be based on guidelines delineated in the *Clinical Research Guideline of New Investigational Drugs in Traditional Chinese Medicine* [12]: primary signs and symptoms include blurry visual acuity, narrow visual field, and eye distension, while secondary signs and symptoms include dry eye, limp aching lumbus, and knees.

The conditions for a diagnosis of kidney deficiency and blood stasis are the presence of at least 2 or more primary signs/symptoms and at least 2 or more secondary signs/symptoms. The necessary condition is a dark-purple tongue and a thready deep, stringy, or unsmooth pulse. The investigators must receive training in standard operating procedures (SOPs) for examining TCM symptoms. They will then conduct a symptom assessment survey using the TCM Symptom Score Scale (Figure 1) for each participant.

Figure 1. TCM Symptom Score Scale. TCM: traditional Chinese medicine.

Blurry visual acuity	□ 0: None □ 2: Mild blurred visual acuity □ 4: Unable to read □ 6: Difficult to see anything
Narrow visual field	□ 0: None □ 2: As if something obscures visual acuity □ 4: Inconvenient to walk □ 6: Difficult to walk
Eye distension	□ 0: None □ 2: Mild eye distension □ 4: Endurable eye distension □ 6: Intolerable eye distension
Dry eye	□ 0: None □ 2: Mild dry eye □ 4: Obvious dry eye, as if there is a foreign body in it □ 6: Intolerable dry eye, frequent blinking
Limp aching lumbus and knees	□ 0: None □ 2: Early morning aching lumbus, which can be alleviated by beating; mild limp knees □ 4: Continuous aching lumbus, which is aggravated when working knees are too limp to carry a heavy weight □ 6: Severe aching lumbus, which is not relieved by rest; knees are too limp to desire to walk
Dark-purple tongue	□ 0: None □ 2: Exist
Thready deep, stringy, or unsmooth pulse	□ 0: None □ 2: Exist

Recruitment Procedure

Potential participants with GPCI were recruited from the Mianyang Central Hospital (Sichuan, China), the Mianyang Hospital of Traditional Chinese Medicine (Sichuan, China), and the Mianyang Wanjiang Eye Hospital (Sichuan, China). We used the internet, hospital announcements, and posters to provide a hotline calling for potential volunteers. If patients were interested in our study, researchers informed them in detail of the purpose and content of the research and the benefits and risks of participating.

After screening, participants meeting the inclusion criteria will be enrolled. Frequent follow-up phone calls are an important aspect of adherence monitoring. Every participant will have the right to withdraw from the trial at any time. Furthermore, it will be obligatory for all subjects to sign an informed consent document prior to commencement of the trial.

Randomization and Allocation

Baseline evaluation will be conducted for eligible subjects. All eligible patients will be stratified according to early, moderate, and advanced stages of glaucoma [14]. Patients with early glaucoma exhibit early glaucomatous visual field impairment, as characterized by a mean deviation (MD) of >–6 dB. Conversely, patients with moderate glaucoma present a moderate glaucomatous visual field loss, defined as MD≤–6 to ≥–12 dB. Patients with advanced glaucoma experience advanced glaucomatous visual field loss, defined as MD<–12 dB. SAS software will be used to automatically generate a set of random numbers ranging from 001 to 192. These numbers will be further classified into 3 ranges based on the disease stage. The early stage will incorporate random numbers from 001 to 064, the moderate stage will encompass numbers from 065 to 128, and the advanced stage will comprise numbers from 129 to 192. Following stratification, the participants will be assigned randomly to either an experimental group or a control group in a 1:1 ratio. Random numbers will be inserted into identical envelopes of equal dimensions, which will then be sealed to ensure concealment of group allocation and minimize the risk of selection bias. The random sequence allocation will be preserved and withheld from the investigators, statisticians, and outcome assessors to avoid detection bias.

Blinding

The researcher assistants, outcome assessors, statisticians, and subjects will be blinded to the group assignment. All participants will undergo press-needle therapy while lying on a bed in a tranquil clinic setting. For the control group, a nonpenetrating sham apparatus, similar in appearance to acupuncture needles, will be used to achieve blinding. Moreover, every participant will be asked about their experience subsequent to the acupuncture session to evaluate the efficacy of blinding. Unblinding of researchers is permitted only in exceptional circumstances, such as when there is a strong need to know about the actual treatment in order to manage the subject appropriately.

Interventions

Experimental Group

Acupoints will be selected based on acupuncture combined with clinical experience [15]: main acupuncture points (BL2 Cuanzhu, TE23 Sizhukong, EX-HN5 Taiyang, and ST2 Sibai) and matching points (PC6 Neiguan, SP10 Xuehai, BL17 Geshu, BL18 Ganshu, BL23 Shenshu, SP6 Sanyinjiao, and K13 Taixi) (Figure 1). These points can exert a concerted effect to nourish the liver and kidneys, promote blood circulation, and dredge collaterals. Press-needle treatment will be performed by acupuncturists with more than 3 years of clinical experience. The acupuncturist will disinfect the skin around the acupoints (on the same side of the affected eye) with povidone iodine when the subject lies down on the treatment bed in a supine position. Disposable sterile press needles (0.2 mm in diameter and 0.6 mm in length; Seirin Corporation) will then be inserted into the right acupoints (Figure 1). The needles will be pressed so that they can adhere and be tied, the peelable paper will be removed, and the adhesive tape will be pressed down to ensure a secure fit. The needles will be left in place for 2 days, and participants will be asked to press the needles themselves 3-4 times/day, every 4 hours, for 1 minute each time to achieve deqi sensations, including soreness, numbness, heaviness, fullness, and aching.

Control Group

Sham press needles are the same as press needles but lack the needle element [9]. The procedures and manipulations carried out in the control group will be indistinguishable from those implemented in the experimental group. Subjects will be treated individually in a secluded room to prevent any disruptions from family members or other individuals.

Criteria for Discontinuing or Modifying Allocated Interventions

Participants will have the freedom to withdraw from the clinical study and opt for alternative treatments (eg, citicoline sodium tablets) if they believe their condition will not improve. Reasons for discontinuing treatment may include, but are not limited to, the following: (1) the pregnancy, (2) severe side effects or complications, (3) taking other medications during the study, (4) failure to comply with the study protocol, and (5) request for withdrawal for other reasons.

Outcome Measures

Primary Outcome Measures

The primary outcomes will enable us to evaluate improvements in visual function, retinal blood circulation, and retrobulbar blood vessel circulation due to press-needle therapy. The outcomes will be as follows:

- The mean change in the BCVA will be measured at baseline and 4 weeks thereafter.
- The mean change in the values of the pattern standard deviation (PSD), mean defect, and square root of loss variance (sLV) will be determined using an Octopus 900 perimeter at baseline and 4 weeks thereafter.
- The whole-image vessel density (wiVD), radial peripapillary capillary vessel density (RPCVD), superficial macula vascular density (smVD), parafoveal vessel density (paraVD), perifoveal vessel density (periVD), macular ganglion cell complex (mGCC), and peripapillary retinal nerve fiber layer (pRNFL) will be determined using optical coherence tomography angiography (OCTA) at baseline and 4 weeks thereafter.
- The ophthalmic artery (OA), central retinal artery (CRA), short posterior ciliary artery (SPCA), peak systolic velocity (PSV), end diastolic velocity (EDV), and resistance index (RI) will be determined using CDFI at baseline and 4 weeks thereafter.

Secondary Outcome Measures

The following secondary outcomes will help us determine whether press-needle therapy improves TCM clinical symptoms and changes in the IOP:

- The mean change in the IOP in the study eye will be determined uisng a TX-20P full autotonometer at baseline and at 1, 2, 3, and 4 weeks thereafter.
- Changes in TCM symptoms will be assessed by the investigators trained in SOPs according to the TCM Symptom Score Scale (Table S1 in Multimedia Appendix 1) at baseline and at 1, 2, 3, and 4 weeks thereafter.

Safety Evaluation and Adverse Events

Safety assessments using 3 routine tests (blood, urine, and stool), electrocardiography, liver function tests (alanine aminotransferase [ALT], aspartate aminotransferase [AST], alkaline phosphatase [ALP], gamma-glutamyl transferase [GGT], and serum total bilirubin [TBIL]) and kidney function tests (blood urea nitrogen [BUN], serum creatinine [SCr], uric acid [UA], and β 2-microglobulin) will be measured at baseline and 4 weeks thereafter.

A research assistant will monitor and record data regarding adverse events (AEs) associated with interventions, which may include infection, hematoma, severe pain, needle breakage, bleeding, heart palpitations, fainting, and headaches, in case report forms (CRFs). Severe AEs will be managed by emergency medicine physicians or acupuncturists. Additionally, any significant AEs will be reported to the Ethics Committee of the Mianyang Central Hospital.

Data Collection and Quality Control

Thorough recording of all data will be performed on CRFs subsequent to in-person visits or telephonic communications with participants. The same examiner will assume responsibility for conducting the examination of every patient during each assessment. Baseline measurements, demographics, medical history, and prior medications will only be gathered during the initial visit. Primary outcomes, secondary outcomes, and safety indicators will be gathered at baseline and 4 weeks thereafter. Following adequate training and successful completion of a test, 2 data entry clerks will thoroughly review the CRFs and subsequently enter the collected data independently. Participants' personal information will be kept confidential the same way as their medical histories in the hospitals before,

during, and after the trial. The absence of a data monitoring committee in this study is justified by the anticipated low incidence of AEs and the limited participant numbers at each center. The Epidata 3.1 statistical application will be used for data entry. Subsequently, the collected data will be transferred to IBM SPSS 22.0 statistical software for the purpose of analysis.

Sample Size Calculation

The sample size calculation was based on previous studies. The basis of optic nerve protection effectiveness is 70% [16,17]. We hypothesized an 80% effective rate of the basis of optic nerve protection + press needles for GPCI in a larger sample size. According to the sample size of the estimation formula [18], α=.05 and β=0.10 in a 2-sided test, P_1=.67 and P_2=.87, 2-sided $u_{\alpha/2}=u_{0.05/2}=1.96$, and 1-tailed $u_{\beta}=u_{0.1}=1.282$. We substituted these values into the following formula:

This resulted in $n^1=n^2=79.02$, that is, approximately 80 cases each in the experimental and the control group, or 160 cases in both groups. To account for a 20% dropout rate, the calculation 160 + (160 × 20%) = 192 suggested that 192 patients be recruited.

Quality Control

To guarantee the quality of the proposed experiment, a unified and standardized training program will be conducted for the researchers in each role prior to commencement of the study. Subsequently, the researchers will be subjected to a proficiency assessment, and only those deemed competent will be permitted to participate in the study. Furthermore, to enhance participant compliance, regular health education activities will be conducted, humane care will be enhanced, and a long-term follow-up plan will be developed. Finally, in accordance with the requirements set forth in the Specifications for Quality Control and Quality Assurance of Clinical Research in Chinese Medicine [19], a 4-level quality monitoring system will be established to monitor the clinically collected data on a regular monthly basis, thereby ensuring the authenticity and reliability of the study results.

Statistical Analysis

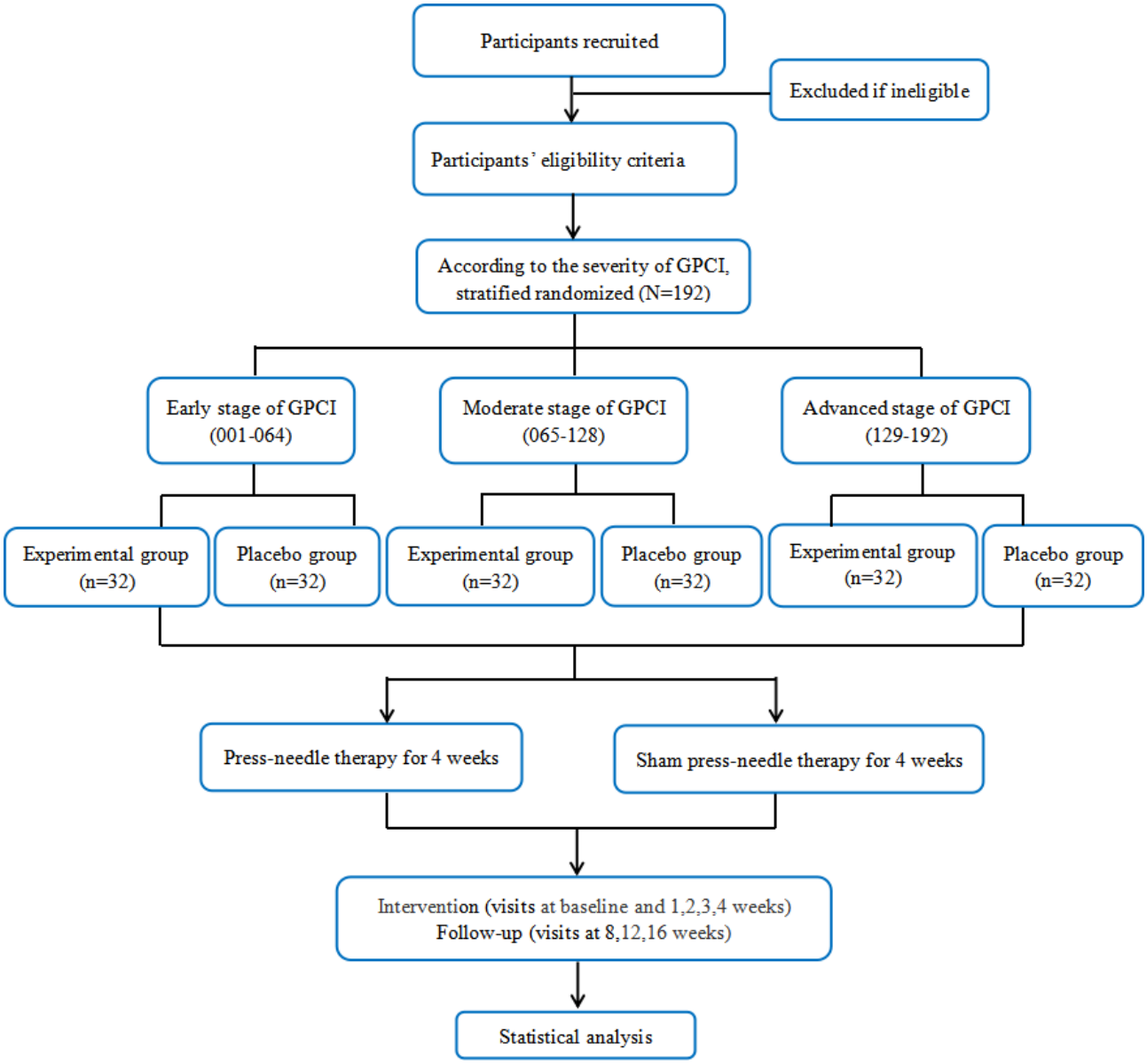
Statistical analysis will be conducted independently by statisticians. The data will be presented as means (SDs). IBM SPSS 22.0 statistical software will be used. All statistical tests will be 2-sided tests, and the limit for statistical significance will be set at P<.05. The chi-square test will be performed for categorical variables, the independent Student *t* test will be used for measurement data, and the rank-sum test will be used for grade data. To evaluate the covariate balance, baseline characteristics will be summarized and compared between the experimental group and the control group using simple descriptive statistics.

Due to the expected low number of missing data, we will deal with missing data by transferring the last data item to the final dataset. This participant's data will be invalidated in the full analysis set (FAS), and this case will not be included in the per protocol set (PPS). Finally, the statistical significance of the FAS and PPS will be analyzed. A consistent statistical significance will indicate a significant difference.

Results

The study flowchart is shown in Figure 2. The figure also presents an outline of the case distribution across each center, as well as comprehensive outline of precise measurements and designated data collection time points. Recruitment was conducted from February 2023 to March 2024. The first participant was enrolled in February 2023. As of October 2024, the project had recruited 220 eligible participants. At the time of submission, there were 192 (87.3%) participants, who will complete the study. The recruitment process is expected to continue until September 2025. The data will be further processed and analyzed in October 2025.

Figure 2. Flowchart of the clinical trial on patients with GPCI. GPCI: glaucoma with controlled intraocular pressure.



Discussion

Overview

Acupuncture is a major treatment in TCM, and studies have shown that acupuncture can protect the optic nerve in patients with glaucoma [20]. The press needle is a new kind of acupuncture device that can create a more lasting stimulus and simpler operation, while resulting in less pain, with the therapeutic effect of cumulative treatment characteristics. At present, press-needle therapy is widely used in various clinical diseases and has achieved satisfactory therapeutic effects [9,21]. Acupuncture is effective in protecting visual function in glaucoma [22]. Press-needle embedding can improve the deteriorating vision and shrinking visual field of patients with optic nerve atrophy and increase clinical efficacy [23]. Abnormal blood flow is an important factor in optic nerve damage in glaucoma [24], and acupuncture can modify the blood flow parameters in glaucoma [7]. Clinically, we have widely used press-needle therapy for glaucoma visual function protection and achieved good clinical efficacy, and we have further found that press-needle therapy can improve ocular circulation in patients with glaucoma. However, the quality of evidence supporting the use of press-needle therapy for GPCI is limited due to methodological limitations. Therefore, it is necessary to explore the effect of press-needle therapy on visual function and eye blood circulation in patients with GPCI. The double-blind method reduces the differential assessment of outcome events and improves subject adherence. Previous studies have shown that press needles and sham press needles (lacking the needle element) enable effective double-blind settings for acupuncture clinical studies [25]. Therefore, sham press needles were chosen as the control intervention for this study.

Due to the unique nature of glaucoma, patients experience progressive optic nerve damage as the disease progresses. To avoid violating medical ethics and reduce the rate of patient detachment, methylcobalamin has been chosen as the basic optic neuroprotective drug for the experimental and control groups in this study. In addition, to observe the effect of

press-needle therapy on GPCI of different disease severities, participants will be classified as early, moderate, and advanced based on their visual field defects.

This study is designed as a double-blind, placebo-controlled trial. To guarantee the quality of the study, its design and execution will be strictly performed with proper quality control. A training session for each center will be held to explain the detailed study protocol, the diagnosis of the TCM syndrome pattern, and the SOPs. The same investigator will be responsible for the examination of each patient at different times. All indicators will be assessed by independent assessors. The principal investigators, statisticians, and outcome assessors will be blinded to the treatment assignments until the database is locked.

Innovations and Limitations

This is the inaugural clinical trial protocol devised by our team to investigate the potential mechanisms of acupuncture for patients diagnosed with GPCI. We have selected eye blood circulation as the entry point for this study. The trial will be conducted in accordance with rigorous methodology. For example, patients with GPCI will be randomly assigned to 2 groups. For the control group, a nonpenetrating sham apparatus, similar in appearance to acupuncture needles, will be used to achieve blinding. Furthermore, each participant will be requested to provide feedback on their experience following the acupuncture session, with a view to evaluating the efficacy of the blinding process. The data will be subjected to statistical analysis in a blinded trial, with the intervener, efficacy assessor, and statistician all acting independently. However, it is not possible to eliminate gender bias in the randomization process. Consequently, to guarantee the reliability of the data, it is necessary to expand the sample size further.

Conclusion

In conclusion, the purpose of this research is to verify that press-needle therapy can effectively improve visual function and eye blood circulation in patients with GPCI. The outcome of this study will provide evidence-based data for the use of press-needle therapy to treat GPCI accompanied by liver-kidney deficiency, blood stasis, and fluid retention syndrome, thereby providing a new avenue for the treatment of GPCI.

Acknowledgments

We are grateful to all the researchers who participated in this trial. Upon completion of the study, the findings will be disseminated to relevant stakeholders, including health care professionals, the general public, and pertinent organizations, through the publication of academic papers and presentations at academic conferences.

This trial is supported by the Science and Technology Department of Sichuan Province (approval no: 2021YJ0443), the National Natural Science Foundation of China for the Youth (approval no. 82305324), and Mianyang Central Hospital Incubation Subjects (approval no: 2020FH07). The results of the research will be presented in the form of publication or conference reports. All the study funders have no role to play in the study design, data collection and management, or manuscript writing and publication.

Authors' Contributions

HJL designed the trial and drafted the manuscript. HJL, CW, and ST are the principal investigators at each hospital. XY (Xuemeng Yu) is responsible for assisting with patient recruitment. XY (Xing Yan) will perform press-needle treatment for patients with glaucoma with controlled intraocular pressure (GPCI). YD and MY will conduct the quality control of this trial. MX, FL, and RZ will be responsible for data collection. MS is responsible for the revision of this manuscript. All the authors have read and approved the final version of this manuscript. Patients and the public were not involved in the design, conduct, reporting, or dissemination plans of our research.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Measurement items and points of data capture.
[DOCX File , 23 KB - resprot_v14i1e67737_app1.docx]

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Abbreviations

AE: adverse event
BCVA: best-corrected visual acuity

CDFI: color Doppler flow imaging
CRF: case report form
FAS: full analysis set
GPCI: glaucoma with controlled intraocular pressure
HIOP: high intraocular pressure
IOP: intraocular pressure
MD: mean deviation
OCTA: optical coherence tomography angiography
PPS: per protocol set
RGC: retinal ganglion cell
SOP: standard operating procedure
TCM: traditional Chinese medicine

Edited by A Schwartz; submitted 20.10.24; peer-reviewed by H Tanabe, M Abdollahi; comments to author 05.02.25; revised version received 18.02.25; accepted 07.03.25; published 01.04.25.

Please cite as:
Liu H, Dai Y, Yu M, Zeng J, Wang C, Tan S, Xiong M, Zhang R, Yu X, Shi M, Yan X, Lai F
Effects and Safety of Press-Needle Therapy for Improving Visual Function and Eye Blood Circulation in Patients With Glaucoma With Controlled Intraocular Pressure: Study Protocol for a Multicenter Randomized Controlled Trial
JMIR Res Protoc 2025;14:e67737
URL: https://www.researchprotocols.org/2025/1/e67737
doi:10.2196/67737
PMID:

Protocol

Effectiveness of Stromal Vascular Fraction (SVF) and Platelet-Rich Plasma (PRP) in Patients With Knee Osteoarthritis: Protocol for a Phase 3, Prospective, Randomized, Controlled, Multicenter Study (SPOST Study)

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Abstract

Background: Available evidence on the conservative treatment of knee osteoarthritis still leaves questions about the efficacy of platelet-rich plasma (PRP) and whether stromal vascular fraction (SVF) offers a superior therapeutic tool.

Objective: This study aims to assess the clinical efficacy of SVF as adjuvant therapy to PRP on functionality and tissue regeneration for knee osteoarthritis.

Methods: In a multicenter, randomized, triple-blind, controlled trial, 108 individuals with knee osteoarthritis will be block-randomized in a 1:1 ratio. Patients will receive an initial single PRP or PRP + SVF injection followed by PRP doses at 1 month and 2 months. The primary endpoint is functional improvement measured with the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) at the 6-month follow-up. Secondary endpoints, collected at the 1-month, 2-month, 3-month, 6-month, and 12-month follow-ups, will include the pain visual analogue scale during maximal physical activity, WOMAC score, length of time to return to work and sports in days, magnetic resonance imaging (MRI)–based Whole-Organ Magnetic Resonance Imaging Score (WORMS), Magnetic Resonance Observation of Cartilage Repair Tissue (MOCART) score, MRI Area Measurement and Depth and Underlying Structures (AMADEUS) score at 6 months and at 12 months, adverse events, and serious adverse events.

Results: Participant recruitment and data collection are expected to begin in July 2025 and finish in July 2027. Final end points will be gathered in August 2027, and the results are expected to be published in late 2027.

Conclusions: The study results will provide insight into the clinical efficacy of SVF as adjuvant therapy to PRP on functionality and tissue regeneration in patients with knee osteoarthritis.

Trial Registration: ClinicalTrials.gov (NCT05660824); https://clinicaltrials.gov/study/NCT05660824

International Registered Report Identifier (IRRID): PRR1-10.2196/62659

(JMIR Res Protoc 2025;14:e62659) doi:10.2196/62659

KEYWORDS

stromal vascular fraction; platelet-rich plasma; osteoarthritis; adjuvant therapy; tissue regeneration; clinical efficacy

Introduction

Osteoarthritis, the most common joint disease [1], has a high social and individual impact, and the development of therapeutic options is a public health priority. Its multifactorial etiology is still a source of active research [2,3]. The most common conservative treatments for osteoarthritis include painkillers, active physical therapies, orthotics, corticosteroid infiltrations, hyaluronic acid, and platelet-rich plasma (PRP) [1,4].

PRP may be beneficial in osteoarthritis by interfering with catabolic and inflammatory events and by subsequently promoting anabolic responses. Activation of PRP releases biologically active components, including platelet-derived growth factor, transforming growth factor-β, type I insulin-like growth factor, and vascular endothelial growth factor. These proteins are responsible for a range of critical tissue healing roles, such as chondrocyte and mesenchymal stem cell (MSC) proliferation, bone and vessel remodeling, inflammatory modulation, and collagen synthesis [5].

Several clinical trials have found improvement in clinical outcomes for osteoarthritis [6,7], presumably associated with the chondroprotective effect of PRP. Nevertheless, despite the numerous studies on the subject, the evidence is inconsistent, there is a lack of uniform improvement in functional outcomes, and an in vivo effect on human cartilage regeneration has not yet been demonstrated [8,9].

Stem cell therapy has arisen as a new therapeutic option for knee osteoarthritis. Preclinical models have elucidated how injected adipose-derived mesenchymal stem cells (AD-MSCs) coordinate the cartilage regeneration process [10-12] through paracrine mechanisms [13], producing cytokines and trophic bioactive factors that stimulate cellular proliferation and reduce inflammation, fibrosis, oxidative stress, and chondrocyte senescence [1].

AD-MSCs seem to have a better hypoxic tolerance, fewer immunologic and inflammatory responses [14], better chondrogenic induction and gene expression [15], and less variable and more reliable clinical result [14] than bone marrow–derived mesenchymal stem cells (B-MSC).

Stromal vascular fraction (SVF), a product from processed adipose tissue, contains MSCs, endothelial precursor cells, T regulatory cells, macrophages, smooth muscle cells, pericytes, and preadipocytes. SVF extraction and injection techniques have recently been used as an alternative to harvest AD-MSCs due to their logistical simplicity and feasibility in clinical practice. The superiority or inferiority of SVF compared with AD-MSC has not yet been established.

Randomized trials indicate that intra-articular SVF injections can provide clinical benefits in knee osteoarthritis [16], with some studies noting cartilage quality improvements [16-19]. Despite their potential, SVF treatments are invasive, costly, and supported by a limited number of studies, many of which lack the homogeneity needed for clinical guideline endorsement, even though research in this area is steadily increasing and yielding promising results. Although PRP is often recommended in sports medicine for knee osteoarthritis, it is unclear whether combining it with SVF offers greater benefits for patients unresponsive to conservative treatment. This randomized controlled trial (RCT) will be the first to provide comparative data on the efficacy of SVF as an adjunct to PRP, addressing a critical gap in osteoarthritis treatment research.

The objectives of this study are to assess the clinical efficacy of SVF as adjuvant therapy to PRP on (1) functionality for knee osteoarthritis and (2) tissue regeneration for knee osteoarthritis.

Methods

Study Design

This multicenter, parallel-group, triple-blind study will enroll 108 patients who will be randomly assigned in a 1:1 ratio to either the intervention (SVF+PRP injection at baseline) or control group (PRP-only injection at baseline) using stratified randomization. The study will use a superiority framework.

The follow-up will last 12 months, with endpoints at 1 month, 2 months, 3 months, 6 months, and 12 months.

Study Setting

In this multicenter study, we aim to recruit all patients between July 2025 and August 2027 in the Sports Medicine Division of La Providence Hospital and in the Rehabilitation division, Hôpital Fribourgeois, both in Switzerland. The lead center is the Sports Medicine Division of La Providence Hospital where author AS is the sponsor-investigator. All the interventions will be performed in the lead center.

Eligibility Criteria

Patients will be recruited if they have knee osteoarthritis with persistent symptoms despite appropriate first-line treatment (ie, active physical therapies, sport and daily activity adaptations, orthotics use, medication) and for whom a surgical procedure is not indicated nor recommended.

The following main inclusion criteria will be used: (1) age older than 16 years; (2) symptomatic knee osteoarthritis confirmed by magnetic resonance imaging (MRI); (3) absence of free or displaced meniscal or cartilage fragments on the MRI of the affected knee; and (4) failure of first-line conservative management, including medical or infiltrative treatment, orthotics use, active rehabilitation plan, and adaptation of sports and work habits, in the last 3 months.

The following main exclusion criteria will be used: (1) patients familiar with the lipoaspiration process; (2) significant disease of the contralateral member with a disability, as evaluated with a Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) score >80%; (3) co-existence of microcrystalline disease (ie, gout, pseudogout); (4) active inflammatory rheumatic disorders; (5) a need for regular anti-inflammatory treatment (either nonsteroidal

anti-inflammatory drugs [NSAIDs] or corticosteroids) or anticoagulants; (6) patients with decompensated renal failure, hepatic dysfunction, or severe pulmonary or cardiovascular disease; (7) patients with an immunocompromised status; and (8) women who are pregnant or intend to become pregnant during the study.

If bilateral disease is present and both sides require either the experimental or control intervention, only the most symptomatic side will be studied.

Informed consent will be obtained by the local site investigator. Other physicians in associated structures (ie, orthopedists, general practitioners, physiotherapists) are informed of the study and will be asked to refer patients to the referent sports medicine departments.

Interventions

In both study groups, the intervention will be performed in the operating room under aseptic conditions and following the Arthrex protocols to prepare the autologous conditioned plasma [20], which is our PRP, and autologous conditioned adipose [21], which is our SVF, as described in the following paragraphs.

The patient is placed with a surgical drape hiding the interventional zone from the patient's sight. The blinded investigator performs a 1.5 mm incision under local anesthesia on each abdomen side in order to introduce the microcannula used to extract the SVF. Tumescent solution is prepared by mixing 500 mL NACL with 30 cc 2% lidocaine + adrenaline 1:200000 and 3 cc 8.4% sodium bicarbonate, then 60 mL of this preparation are injected into each side and left in place. An interval of 20 minutes is allowed, which is necessary to let the tumescent solution act on the abdominal adipose tissue. At this point, the blinded investigator leaves the room. In the experimental arm, the unblinded investigator uses a double syringe system to extract 30 mL adipose tissue from the abdominal incisions. This is then centrifugated at 2500 rpm for 4 minutes. The oil and water are discarded. The lipoaspirate is then filtered using two 20 mL syringes and a 1.4-mm diameter transfer hub. One last centrifugation is performed at 2500 rpm for 4 minutes obtaining 2 mL to 6 mL SVF and the remaining oil. This last mixture is then discarded. In the control arm, the unblinded investigator performs a sham adipose tissue extraction by introducing the extraction cannula and moving it for 2 minutes on each side. In both study arms, the venipuncture is then performed, and 15 mL blood are extracted for the PRP preparation using the Arthrex double syringe system [20]. The blood is then centrifuged at 1500 rpm for 5 minutes, resulting in 4 mL to 7 mL of PRP. No anticoagulant, calcium chloride, nor other PRP activator is added. Following the aseptic technique, the unblinded investigator prepares the SVF-PRP mixture or PRP alone in an opaque 10-mL syringe. In parallel, the patient is prepared for the ultrasound-guided injection procedure. With an 18-gauge needle, the SVF-PRP mixture or PRP alone is then injected by the blinded investigator.

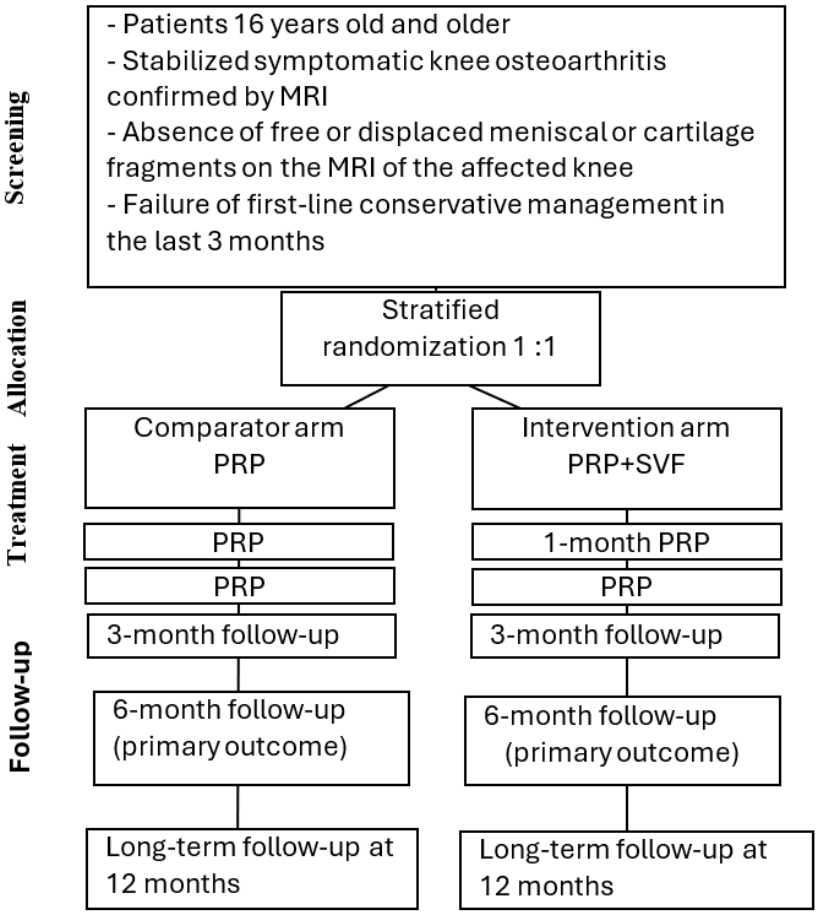
Postintervention care includes (1) partial weight-bearing for 1 month; (2) active strengthening of the muscles without overloading the knee using, if possible, the blood-flow restriction technique and gentle nonweight-bearing muscle activation, including core stability exercises; (3) mobility; and (4) modification of daily activities, work, and sports habits.

A total of 5 follow-up visits are planned for the study, during which principal and secondary outcomes will be gathered by a blinded investigator. At the 1-month and 2-month follow-up visits, patients in both study arms will receive 2 additional ultrasound-guided PRP injections performed by the blinded investigator and following the same Arthrex autologous conditioned plasma technique. The same postintervention care will be provided after these 2 PRP injections. Figure 1 shows the study flow chart.

Anticoagulants (eg, aspirin) and anti-inflammatory drugs (eg, ibuprofen, naproxen, meloxicam) should not be used 2 weeks before and 2 weeks after each injection as it can potentially interrupt the therapeutic acute inflammatory response and cytokine production.

Active physical therapies regimens, orthotics use, sports, and daily activities are adapted to the patient, on a day-by-day basis, during the postintervention care.

Figure 1. Study flow chart. MRI: magnetic resonance imaging. PRP: platelet-rich plasma.



Outcome Measurements and Assessments

The primary outcome is functional improvement measured with the 0%-100% normalized WOMAC at the 6-month follow-up, where 0% indicates complete absence of symptoms and 100% indicates maximal possible symptom severity. A clinically relevant functional improvement is a difference of 9.1 points out of 100 points.

The secondary outcomes will be clinical and radiological parameters gathered at the 1-month, 2-month, 3-month, 6-month, and 12-month follow-ups. These include a 10-point pain visual analogue scale (VAS) during maximal physical activity performed by the patient according to manageable pain and clinical recommendations, the 0%-100% normalized WOMAC [2], length of time to return to work and sports in days, adverse events (AEs), and serious adverse events (SAEs). Pain will be assessed as an AE of interest, during the intervention and 48 hours following the intervention.

The improvement in cartilage quality will be assessed at the 6-month and 12-month follow-ups (previous MRI should not be dated more than 3 months before the intervention) using 3 key MRI-based scoring systems: Area Measurement and Depth and Underlying Structures (AMADEUS) [13], Whole-Organ Magnetic Resonance Imaging Score (WORMS) [22], and Magnetic Resonance Observation of Cartilage Repair Tissue (MOCART) [23].

We initially planned to statistically assess these outcomes at 6 months and 12 months. However, assessment of these parameters at other time points might be subject to exploratory analysis.

The participant timeline is presented in Table 1. The following information will be collected at baseline: age, gender, height, weight, BMI, smoking status, comorbidities, baseline Kellgren–Lawrence grade, current and previous treatments, and posttraumatic etiology. The set of clinical and radiological scores include the VAS, WOMAC, return to work and sports in days, AMADEUS, WORMS, and MOCART.

Table 1. Study assessments and procedures at the study visits.

Procedures	Screening[a]	Baseline	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5
Timing (visit window)	–3 weeks (+3 weeks)	0	1 month (±7 days)	2 months (±7 days)	3 months (±7 days)	6 months (±7 days)	12 months (±7 days)
Informed consent	X	—[b]	—	—	—	—	—
Inclusion/exclusion criteria	X	—	—	—	—	—	—
Baseline characteristics	—	X	—	—	—	—	—
Clinical scores	—	X	X	X	X	X	X
MRI[c]	—	X	—	—	—	X	X
Randomization	—	X	—	—	—	—	—
Lipoharvesting or sham lipoharvesting	—	X	—	—	—	—	—
Intervention[d]	—	X	—	—	—	—	—
PRP[e] injection	—	—	X	X	—	—	—
Concomitant medication	—	X	X	X	X	X	X
AEs[f] and SAEs[g]	—	X	X	X	X	X	X

[a]Screening and baseline visits can be performed on the same day if the patient has been given reasonable time to make a consented decision about participation in the study.

[b]—: not applicable.

[c]MRI: magnetic resonance imaging.

[d]Stromal vascular fraction+platelet-rich plasma (PRP) or PRP-only injection depending on the group.

[e]PRP: platelet-rich plasma.

[f]AEs: adverse events.

[g]SAEs: serious adverse events.

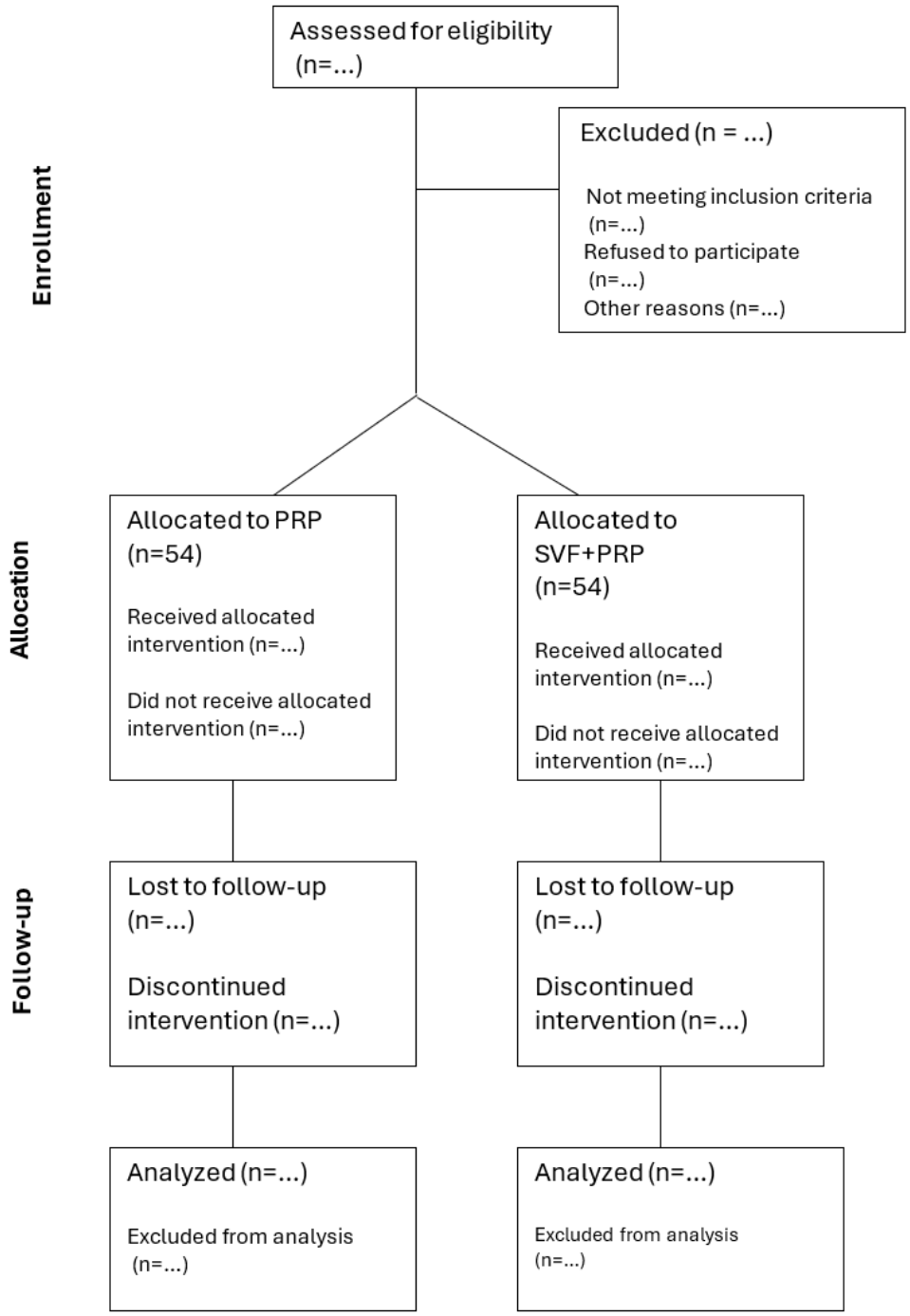
Sample Size

The sample size for this study was calculated using PS software (Vanderbilt University) [24]. We aimed to detect a clinically meaningful difference of 9.1% in the absolute change in the WOMAC function score between the experimental and control groups. The calculation assumed an SD of 13.9%, based on findings from the study conducted by Tubach et al [25].

In their study, Tubach et al [25] evaluated changes in the WOMAC function score in patients with knee osteoarthritis treated with NSAIDs over a 4-week period. They reported an average baseline WOMAC function score of 42.8 (SD 16.1) and an absolute improvement of –11.6 (SD 13.9). These values were used to estimate the variability in absolute changes for our calculation.

With these parameters, a sample size of 108 patients (54 per group) was determined to provide 90% power to detect the specified difference at a 5% significance level using a 2-tailed test. This calculation ensures that our study is adequately powered to detect a meaningful treatment effect based on absolute improvements in functional outcomes. The study will collaborate with health care providers in both study centers to achieve the target sample size. Additionally, potential participants will be contacted through patient registries and referrals. All recruitment efforts will comply with ethical guidelines and prioritize informed consent. Figure 2 shows the CONSORT (Consolidated Standards of Reporting Trials) diagram [26].

Figure 2. CONSORT (Consolidated Standards of Reporting Trials) diagram showing the flow of participants through each stage of the randomized trial. PRP: platelet-rich plasma; SVF: stromal vascular fraction.



Randomization and Blinding

Study participants will be randomized at a 1:1 ratio to either the intervention arm or the active comparator arm using a randomization table and blocked randomization with blocks of 4 patients. Participants will be assigned to specific strata based on age (older or younger than 40 years) and the presence of cartilage defects (partial, full, or full with bone deformation).

The unblinded investigator responsible for the study interventions will perform the randomization shortly before administering the interventions. This study is triple-blinded: (1) Participants will be unaware of their group assignment throughout the intervention and study duration, (2) the investigator performing the intraarticular injection and the outcome assessor will remain blinded, and (3) the statistician will also be blinded. The investigator responsible for preparing the PRP+SVF or PRP-only preparation will be unblinded and will not participate in outcome assessments.

All patients will undergo a venipuncture, either a lipoaspirate or a sham lipoaspirate, followed by an ultrasonographically guided PRP or PRP+SVF injection. It is anticipated that unblinding will not be required to ensure patient safety, as no known adverse effects of the SVF (such as local pain, tenderness, hematoma on donor site, or infection) require

unblinding for clinical management. However, if unblinding becomes necessary due to unexpected circumstances, the unblinded investigator will disclose the allocated intervention for the affected patients.

Data Collection and Management

All data collected in this study will be recorded in standardized electronic case report forms (CRFs; see Multimedia Appendices 1-4). We plan to use Hermes software. Hermes is a tool developed by sponsor-investigator AS, used for a patient registry, and validated by the local ethics committee board (authorization # CERVD AO_2020-00006). Only data with logical numeric variables within the correct ranges or predefined categorical variables can be entered into the electronic CRFs. Data entry for variables of interest is mandatory.

CRFs will be kept current to reflect participant status at each phase during the course of the study. Study-related data will be collected in a coded manner (participants will not be identified in the CRF by name or initials). Identification of patients must be guaranteed at the study site. Patients' identifications will be recorded in a sequential list stored in the local investigator's secured server. At the end of the study, when the database has been checked for completeness and validated by the sponsor-investigator, it will be locked and used for statistical analyses. All "study essential documents" (eg, informed consent form, CRFs) will be archived for at least 10 years after completion of the clinical trial.

Data sharing is not applicable to this article, as, to date, no data sets have been generated nor analyzed.

Statistical Analysis

The WOMAC score will be normalized to a 0%-100% scale, where 0% indicates no symptoms and 100% represents the highest severity of symptoms. This normalization involves converting the raw scores into percentages, facilitating the interpretation and comparison of results across participants and study groups. The absolute difference at 6 months will serve as the primary outcome and will be compared using either the paired Student *t* test or the Wilcoxon signed-rank test, depending on the distribution of the variable, with intention-to-treat analysis. The absolute differences in secondary outcomes (changes from baseline to other time points) between the treatment and control groups will be evaluated with the appropriate statistical test (categorical variables: chi-square or Fisher exact tests; continuous variables: Student *t* or Wilcoxon rank tests). All analyses will include both intention-to-treat and per-protocol analyses. Effect estimates, 95% CIs, and descriptive *P* values will be reported whenever possible, along with corresponding graphs.

A post hoc analysis will attempt to identify variables of interest using the appropriate global linear model.

Since the intervention is considered low risk, no interim analysis is planned. In case of missing primary outcome data, patients will be withdrawn from the analysis. Patients missing secondary outcome data will remain in the study but be excluded from those specific analyses.

Oversight and Monitoring

For quality control of the study conduct and data retrieval, all study sites will have regular monitoring activities performed by appropriately trained and qualified monitors, who are outsourced by the sponsor-investigator. Monitoring activities will consist of on-site monitoring as well as remote and centralized monitoring.

The objectives of a monitoring visit are to (1) verify the informed consent form process for each monitored participant, (2) verify the prompt and accurate recording of all monitored data points and prompt reporting of all safety events, (3) compare collected data with participants' source documents, and (4) ensure investigators comply with the protocol.

The monitors may also inspect the clinical site regulatory files to ensure that regulatory requirements and applicable guidelines (International Council for Harmonisation [ICH] Good Clinical Practice [10]) are being followed.

SAEs will be defined as any untoward medical occurrence that results in death, is life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability or incapacity, or in a congenital anomaly or birth defect. SAEs should be followed until resolution or stabilization. Assessment of causality will be based on the criteria listed in the ICH E2A guidelines [10], and severity will be graded based on the Common Terminology Criteria for Adverse Events Version 5 [27]. All SAEs will be reported immediately and within a maximum of 24 hours to the sponsor-investigator of the study. The sponsor-investigator will re-evaluate the SAE and return the form to the co-investigator. SAEs resulting in death will be reported via the sponsor-investigator to the Swiss Business Administration System for Ethics Committees and to the other ethics committees involved in the trial within 7 days.

Regular audits are not planned. For the purpose of on-site inspection or audit, the competent authorities or ethics committee may require access to all source documents and other study-related records. The sponsor-investigator and local investigators must ensure the availability of these documents at any time.

Ethical Considerations

Ethics Review Approvals

To comply with local regulations in Switzerland regarding clinical trials involving human subjects, this study design is classified as risk category C [28-30].

Therefore, both Swissmedic (the Swiss authority responsible for the authorization and supervision of therapeutic products) and the local ethics committee must review and approve the research protocol. Since both applications require a significant investment, a grant request will be submitted prior to applying to these two institutions. The principal investigator will obtain approval from the competent authority (Swissmedic) before the start of the study. Once the protocol is approved, no changes will be made without prior approval from the ethics committee, except when necessary to eliminate immediate hazards to participants.

Informed Consent

The recruiting investigator will explain the study's nature, purpose, procedures, duration, risks, benefits, and discomforts. Participation will be voluntary, and participants can withdraw at any time without affecting their medical care. Each participant will receive an information sheet and consent form to make an informed decision, with time to consult others and ask questions. Consent will be obtained before any procedures, and the signed form will be kept as part of the records. Participants will be informed that authorized individuals may examine their medical records. The informed consent is available in Multimedia Appendix 5.

Privacy and Confidentiality

The investigator upholds the participant's right to privacy and complies with privacy laws, ensuring anonymity in scientific presentations and publications. Medical information from the study is confidential, and third-party disclosure is prohibited. Participant confidentiality will be maintained using identification code numbers. Authorized representatives, such as those from Swissmedic or the ethics committee, may access relevant medical records for data verification.

Compensation Details

There is no compensation provided for participants in this human subjects research.

Identifiable Features

Identifiable features of research participants in any image or supplementary material will not be visible.

Results

This version of the study protocol presented in this article is ready to be presented to the Switzerland regulatory authorities. A request for funding was submitted to the Swiss Medical Foundation in December 2024, and the study was registered in the portal for clinical trials in Switzerland (number pending).

Enrollment to the study is expected to begin in July 2025 and finish in July 2027. Final end points will be gathered in August 2027, and the results are expected to be published in late 2027. The findings will be shared through conference presentations targeting rehabilitation and sports medicine specialists. The Swiss Medical Network and Switzerland's Physical Medicine and Rehabilitation Network will be engaged through presentations at their yearly research events to help implement findings in clinical settings.

Given the open-access nature of the target journal, all results will be publicly available. To gather feedback, we will use postpublication surveys, interactive webinars, and follow-up interviews with patients and practitioners to discuss the applicability and impact of SVF therapy in practice.

Discussion

This study design intends to assess the potential benefits of SVF injection, an easy-to-use, simple, and noninvasive cellular therapy, on the most frequent joint disease. With this high-quality RCT, SVF will be compared with one of the most commonly used noninvasive therapies in the field of sports medicine, PRP.

Based on available clinical trials, we hypothesize that SVF treatment in addition to PRP may lead to significant clinical and radiological improvement in patients with knee osteoarthritis. The WOMAC and VAS scores are among the most commonly used clinical outcomes in RCTs and meta-analyses for knee osteoarthritis research. For radiological assessment, 3 MRI-based scoring systems—AMADEUS, MOCART, and WORMS—are frequently cited in RCTs. Including these scores as primary and secondary outcomes will facilitate future meta-analyses and allow direct comparison of our trial’s results with those of previous studies

Compared with PRP, cellular therapy with SVF requires more physician training, takes more time, and ultimately incurs higher costs. In other words, it demands greater resources. From the authors’ perspective, patients and caregivers should only invest in these additional resources if clear benefits are demonstrated, which this study aims to establish.

Different techniques have been used to inject or implant cellular therapy with MSCs to the required site, but consensus about the best approach does not exist. However, biologically, some elements support the use of AD-MSCs for nonbone tissue. AD-MSCs would theoretically be more resilient than B-MSCs to the hypoxic articular cavity because they are less dependent on mitochondrial respiration for energy production. From an immunological perspective, AD-MSCs should be preferable to B-MSCs since B-MSCs could induce a higher immunological response due to their higher cell-surface human leukocyte antigen class I expression. AD-MSC highly expresses interleukin-33, which promotes regulatory T cell phenotype proliferation, which would theoretically mean a beneficial effect on anti-inflammatory responses [14].

Han et al [11] compared AD-MSC with B-MSC for knee osteoarthritis and found a superior therapeutic effect of AD-MSC compared with B-MSC on VAS and WOMAC scores. Zhou et al [31] performed a meta-analysis comparing AD-MSC and B-MSC therapies, and they found no statistical differences in clinical scores between the two therapies but did find a higher variability in B-MSC results, suggesting AD-MSCs might be a more reliable therapeutic option. Ude et al [32] found better chondrogenic inductions and gene expressions with AD-MSCs than with B-MSCs.

The therapeutic potential of MSCs is of great interest due to their possible long-term chondroprotective and even chondroregenerative effects. A meta-analysis by Lee et al [19] demonstrated significant improvements in imaging outcomes measured using the WORMS and MOCART scores. WORMS scores improved significantly with SVF therapy compared with controls at both 6 months and 12 months posttreatment (6 months: mean difference [MD]=–18.29, 95% CI – 21.75 to –14.84; 12 months: MD=–26.78, 95% CI –29.95 to –23.61). Similarly, MOCART scores showed notable improvements with AD-MSC therapy at 6 months (MD=24.7, 95% CI 5.92 to 43.48) and 24 months (MD=25.8, 95% CI 5.52 to 46.08), while SVF therapy resulted in significant gains at 6 months, 12 months,

and 24 months (6 months: MD=30.11, 95% CI 26.08 to 34.13; 12 months: MD=36.82, 95% CI 23.95 to 49.68; 24 months: MD=10.60, 95% CI 1.37 to 19.83).

The comparative superiority of SVF over AD-MSCs, or vice versa, remains uncertain, as no RCT has yet directly addressed this question. An observational study [33] suggested the superiority of AD-MSCs, but further evidence is needed.

The meta-analysis by Lee et al [19] showed some differences between both therapies on clinical outcomes. A significant improvement in the VAS score was found at 6 months and 12 months with AD-MSCs (6 months: MD=–1.62, 95% CI –2.46 to –0.79; 12 months: MD=–1.97, 95% CI –3.22 to –0.72), whereas SVF showed significant results only at 12 months (6 months: MD=–2.32, 95% CI –5.15 to 0.52; 12 months: MD=–2.13, 95% CI –3.06 to –1.21). In contrast, functionality measured with WOMAC scores improved significantly 6 months after SVF treatment (MD=–6.12, 95% CI –10.71 to 1.52), while AD-MSC therapy yielded significant improvements only after 12 months (6 months: MD=–1.96, 95% CI –5.36 to 1.45). At 12 months and 24 months, both SVF and AD-MSC therapies produced significant improvements in the WOMAC score (12 months SVF: MD=–9.09, 95% CI –12.67 to –5.51; 12 months AD-MSC: MD=–9.19, 95% CI –12.48 to –5.90; 24 months SVF: MD=–10.71, 95% CI –18.49 to –2.93; 24 months AD-MSC: MD=–6.88, 95% CI –10.24 to –3.52).

The first main strength of our study design is the large sample size. Second, our study population is well-designed and reproducible, with standardized diagnostic criteria and failure of a first-line standardized rehabilitation plan. Third, the multicenter design allows for better reproducibility of patient selection and management, even if interventions are performed at the main study center by a single investigator. This is, however, a study strength, as it will avoid bias related to the intervention techniques.

A sham lipoaspiration procedure with the patient awake is performed to maintain blinding in the control group. Despite all precautions taken to uphold allocation concealment, breaches may occur if the patient diligently questions the procedure. For ethical reasons, if at 6 months, the progression is unsatisfactory, the intervention's nature may be disclosed if deemed clinically relevant, allowing the patient to benefit from SVF infiltration. Consequently, the study may be limited, as the initial 12-month secondary outcomes will not be considered in the final analysis. Finally, the patient selection, clinical follow-up, and rehabilitation plan might differ across the various recruitment centers (multicenter design).

The minimal clinically important difference was chosen as the limit to detect a clinically relevant difference for sample size calculation. From the authors' point of view, even in the case of statistically significant positive effects of the treatment, the generalization of the procedure should be balanced by a complementary cost-effectiveness analysis. Indeed, in case of mild benefits, other procedures such as strengthening, biomechanics adaptation, medication, annual PRP infiltrations, shockwave therapies, or even slight daily activity adaptations might be options of choice. One should be aware that cellular therapies should not be presented to patients as a "magic potion" or "youth elixir." Especially, the authors warn about the recognized risk of financial benefits based on overemphasized clinical promises.

This study will contribute data to establish the clinical relevance of SVF treatment for the most relevant disease of the musculoskeletal system.

Acknowledgments

A request for funding has been presented to the Swiss Medical Foundation.

Data Availability

All data requests should be directed to the corresponding author.

Authors' Contributions

DARC, AS, and TDS established the study design and wrote the draft of the manuscript. CB contributed to the protocol conception and statistical analysis. PD participated in the manuscript writing. All authors read and approved the final manuscript. Data management activities will be conducted by AS and DARC. DARC and AS contributed equally.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Participant Screening Case Report Form (CRF).
[PDF File (Adobe PDF File), 429 KB - resprot_v14i1e62659_app1.pdf]

Multimedia Appendix 2
Participants Enrollment Case Report Form (CRF).
[PDF File (Adobe PDF File), 211 KB - resprot_v14i1e62659_app2.pdf]

Multimedia Appendix 3
Participants Follow-up Case Report Form (CRF).
[PDF File (Adobe PDF File), 354 KB - resprot_v14i1e62659_app3.pdf]

Multimedia Appendix 4
Averse Events and Serious Adverse Events Case Report Form (CRF).
[PDF File (Adobe PDF File), 134 KB - resprot_v14i1e62659_app4.pdf]

Multimedia Appendix 5
Patients informed consent.
[PDF File (Adobe PDF File), 190 KB - resprot_v14i1e62659_app5.pdf]

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Abbreviations

AD-MSC: adipose-derived mesenchymal stem cells
AE: adverse event
AMADEUS: Area Measurement and Depth and Underlying Structures
B-MSC: bone marrow–derived mesenchymal stem cells
CONSORT: Consolidated Standards of Reporting Trials
CRF: case report form
ICH: International Council for Harmonisation
MD: mean difference
MOCART: Magnetic Resonance Observation of Cartilage Repair Tissue
MRI: magnetic resonance imaging

MSC: mesenchymal stem cell
NSAID: nonsteroidal anti-inflammatory drug
PRP: platelet-rich plasma
RCT: randomized controlled trial
SAE: serious adverse events
SVF: stromal vascular fraction
VAS: visual analog scale
WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index
WORMS: Whole-Organ Magnetic Resonance Imaging Score

Edited by A Schwartz, T Leung; submitted 11.06.24; peer-reviewed by CL Shih, QX Ding; comments to author 03.09.24; revised version received 27.12.24; accepted 23.02.25; published 08.04.25.

Please cite as:
Schwitzguebel A, Ramirez Cadavid DA, Da Silva T, Decavel P, Benaim C
Effectiveness of Stromal Vascular Fraction (SVF) and Platelet-Rich Plasma (PRP) in Patients With Knee Osteoarthritis: Protocol for a Phase 3, Prospective, Randomized, Controlled, Multicenter Study (SPOST Study)
JMIR Res Protoc 2025;14:e62659
URL: https://www.researchprotocols.org/2025/1/e62659
doi:10.2196/62659
PMID:

Protocol

Effect of Continuous Positive Airway Pressure or Positional Therapy Compared to Control for Treatment of Obstructive Sleep Apnea on the Development of Gestational Diabetes Mellitus in Pregnancy: Protocol for Feasibility Randomized Controlled Trial

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Abstract

Background: Obstructive sleep apnea (OSA) is a common sleep disorder, and in pregnancy, it is associated with an increased risk of complications, including gestational diabetes mellitus and preeclampsia. Supine sleep may worsen OSA, and in pregnancy, it is associated with an increased risk of stillbirth due to effects on fetomaternal blood flow. Continuous positive airway pressure (CPAP) therapy is considered the gold-standard treatment for moderate to severe OSA, although compliance is frequently poor; positional therapy (PT) is generally less effective than CPAP in nonpregnant patients but may be better tolerated and more accessible during pregnancy. There is limited data on whether widespread, early screening for sleep disorders in pregnant women with symptoms of sleep-disordered breathing or at high risk of metabolic complications and subsequent early intervention with CPAP or PT attenuates fetomaternal risks.

Objective: This study aims to determine the feasibility of conducting a randomized controlled trial to assess improved fetomaternal outcomes in a high-risk pregnant population with OSA, using CPAP or PT, initiated by the 16th week of gestation.

Methods: This study is a randomized, controlled, open-label feasibility study in which pregnant women with an apnea-hypopnea index (AHI) or respiratory disturbance index (RDI) ≥5 are treated with CPAP (auto-titrating and fixed pressure) or positional therapy from early gestation (by 16 weeks) until delivery. The primary outcome is the feasibility of the study protocol and the development of gestational diabetes mellitus by the 28-week gestation period. Secondary outcomes include the development of hypertensive disorders of pregnancy (HDP), maternal weight gain, uterine artery blood flow, glycemic control during pregnancy (in participants who develop gestational diabetes), changes in maternal circulating biomarkers, and neonatal birthweight

complications. Polysomnography at 28- to 32-week gestation period, postpartum polysomnography, therapy compliance, and patient acceptability are also assessed.

Results: The trial commenced on September 30, 2019. The trial is ongoing as of August 6, 2024.

Conclusions: The trial intends to contribute to the growing evidence base to support the need for the identification and treatment of OSA occurring during pregnancy and to assess the feasibility of the study protocol. This will be the first trial to compare the early initiation of CPAP (auto-titrating and fixed pressure) and positional therapy in pregnant women from early gestation, providing alternative therapies for the treatment of OSA in this important population.

Trial Registration: Australian New Zealand Clinical Trials Registry ACTRN12619001530112; https://tinyurl.com/yctdzs4u

International Registered Report Identifier (IRRID): DERR1-10.2196/51434

(JMIR Res Protoc 2025;14:e51434) doi:10.2196/51434

KEYWORDS

obstructive sleep apnoea; OSA; sleep disordered breathing; pregnancy; CPAP; positional therapy; gestational diabetes; GDM; preeclampsia; fetomaternal; maternal; pregnant; fetus; fetal; breathing; apnoea; sleep; respiratory; eclampsia; pregnant women; pregnancy complications; hypertension

Introduction

During pregnancy, physiological changes, including upper airway edema and hormone-related upper airway pressure changes, predispose women to sleep-disordered breathing (SDB) [1]. The prevalence of obstructive sleep apnea (OSA) in pregnancy increases from 3.6% in early pregnancy to 8.3% in midpregnancy and is associated with an independent risk of gestational diabetes mellitus (GDM), preeclampsia, and hypertensive disorders of pregnancy (HDP) [2]. In addition, emerging evidence suggests that the presence of SDB before pregnancy may place women at an increased risk of developing GDM [3]. Supine sleeping in late pregnancy is associated with an increased risk of stillbirth [4], and supine sleep avoidance is recommended from the 28-week gestation period [5].

Treatment options for OSA in non-pregnant adults include continuous positive airway pressure (CPAP), weight loss, positional therapy, mandibular advancement splints, surgery (both upper airway and bariatric), and pharmacological therapies, though not all are suitable for use in pregnant populations. CPAP and positional therapies reduce the occurrence of OSA by reducing the occlusion of the upper airway through pneumatic splinting [6] and repositioning the sleeping persons to reduce collapsibility of the airway [7,8], respectively. Within nonpregnant populations, longer duration CPAP compliance (more than 7 hours) was associated with a reduction in hemoglobin A_{1c} by 1% when CPAP was used for more than 85% of the rapid eye movement stage of sleep during the night [9]. Improvements in blood pressure control have been demonstrated in nonpregnant patients with OSA [10,11], and a small benefit in 24-hour diastolic blood pressure in patients using fixed pressure CPAP compared with auto-titrating CPAP has been reported [12].

In pregnancy, CPAP is recommended as the first line of treatment for OSA [13,14], although alternatives to CPAP may be beneficial but require clinical trials to investigate their utility [14]. In pregnant populations, many studies investigating CPAP treatment have used small sample sizes [15] or initiated therapy in later gestation periods. An early study of 12 pregnant women with OSA at risk of preeclampsia demonstrated no improvement in clinical maternal outcomes [16]; likewise, CPAP failed to demonstrate improvements in glucose levels in obese pregnant women with 2 weeks of CPAP use between 24- and 34-week gestation periods, although compliant use of CPAP in this study demonstrated an improvement in insulin secretion and sensitivity [17]. There are, however, some benefits reported in the literature; a single night of CPAP in a study of 10 pregnant women with preeclampsia and coexisting obesity demonstrated improvements in fetal movements [18], and an improvement in blood pressure control both during sleep and wake was reported in a small study of 7 women, resulting in down titration of antihypertensive medication [19].

Compliant use of CPAP remains a challenge, and in some patients, it may be dependent on clinical support mechanisms, with pre- and postacclimatization phase support improving therapy compliance [20]. Gender-based differences in CPAP compliance have been demonstrated in a large study of nearly 800,000 CPAP users, where women aged 18-30 had the lowest CPAP compliance (51.3%) and were most likely to cease therapy [21]. Barriers to compliant CPAP therapy in pregnant women with OSA are relatively unknown though targeted supports, which have demonstrated improvements in maternal medication compliance, may be beneficial [22]. A recent randomized controlled trial assessed blood pressure outcomes in 340 high-risk pregnant women recruited predominantly during the first trimester, allocated to CPAP or no treatment (control). Despite a mean CPAP compliance of 2.5 hours nightly, and an overall compliance (≥ 4 hours nightly) of 32.7% of participants randomized to CPAP, this reported reductions in diastolic blood pressure and preeclampsia rates [23]. This study additionally presents data on CPAP side effects, and despite rhinitis, mask difficulties, and pressure intolerance reported, there was no significant difference in the reporting of these symptoms between compliant and noncompliant participants, indicating the possibility that these side effects are not barriers to treatment in this special population.

CPAP devices are available in fixed and auto-titrating options and in nonpregnant OSA patients, patient preference has demonstrated mixed results [24,25], although data are lacking in pregnant populations. Furthermore, evidence of the efficacy

of auto-titrating devices through gestation advancement is limited, and despite the availability of auto-titrating devices that attempt to target flow-limited breathing using reduced air pressure in premenopausal women [26], their utility in pregnancy is unknown.

Positional therapy is less effective at reducing apnea-hypopnea index (AHI) and nocturnal oxygen desaturation [7,27] but is effective at reducing supine sleep time [7], which is associated with the worsening of OSA [8]. Positional therapy (PT) in pregnancy is hypothesized to impact outcomes by two potentially independent pathways: first, by addressing SDB, which is typically worse in the supine position, and second, by minimizing compression of the vena cava by the gravid uterus, which may reduce fatal blood flow. A feasibility study using a back-worn positional therapy band for a single night in healthy pregnant women at 32- to 38-week gestation periods showed improvement in maternal oxygenation and reduced fetal heart rate decelerations compared with the controlled night [28].

Given placentation completes around 16-week gestation period, the timing of OSA treatment intervention may be particularly important, as data demonstrates significant benefits of time-specific interventions in pregnancy, for example, aspirin is generally beneficial in preventing preeclampsia if commenced before 16-week gestation period [29]. We thus outline a protocol to determine the feasibility of a parallel group, individually randomized, controlled, open-label trial comparing CPAP or PT to usual care (control). Commencement of therapy by the 16th week of gestation has been chosen to reduce exposure to intermittent hypoxia on the developing placental function during early pregnancy and to establish early compliance to treatment. The use of fixed pressure CPAP after auto-titration of pressure in this trial was determined by factors including access to trial equipment, cost, and absence of evidence of the superiority of auto-titrating over fixed pressure CPAP in pregnancy. This trial aims to determine the feasibility of conducting a larger trial and to obtain preliminary recruitment and efficacy data that may be used to design and power a larger trial. This study may be of interest to others conducting sleep therapy intervention studies in pregnant women.

Clinical Trial Objectives

This study aimed to determine whether CPAP or PT initiated by the 16th week of gestation in pregnant women with a respiratory disturbance index (RDI) or AHI ≥5 results in improved clinical outcomes, particularly in relation to the development of gestational diabetes.

Trial Feasibility Objectives

This study aims to assess the feasibility and acceptability of trial interventions and schedule of visits and determine limitations of trial design, including patient and hospital staff participation.

Methods

All trial primary and secondary outcomes are described in the Australian New Zealand Clinical Trials Registry Trial Registry.

Ethics Approval and Consent to Participate

Overview

Participant recruitment commenced on September 10, 2019. The final patient was recruited in December 2022 and is expected to complete participation in June 2024. The participants affected by product recalls in this trial will be followed up annually for 5 years, if agreeable as per the protocol. Data from participants who choose to withdraw from study participation will be included in the final analysis unless requested by the participant. The trial was registered on November 6, 2019 (ACTRN12619001530112), 7 weeks after the first participant was recruited for the study. The study protocol was not amended during this time.

Human Subject Ethics Review Approvals or Exemptions

The South Western Sydney Local Health District Human Research and Ethics Committee (SWSLHD HREC) approved this study (June 12, 2019, project identifier 2019/ETH00283). The current protocol version 3.1 was approved on November 11, 2022.

Informed Consent

The participants with scheduled antenatal bookings at Liverpool and Campbelltown hospitals will be invited to undertake a screening eligibility preconsent questionnaire, which is presented in Multimedia Appendix 1 by research study staff to determine participation eligibility as described in the eligibility criteria above. Women will be sequentially approached.

Following the screening, study staff will invite eligible participants to provide written informed consent. Multimedia Appendix 2 presents the postconsent baseline information questionnaire, which will be collected at the next trial consent.

The participants will undertake attended polysomnography to determine eligibility in the RCT. Additionally, the participants will be invited to undertake Apnealink Air and Somte at both the baseline and 28- to 32-week gestation periods, in addition to the attended polysomnography as part of a substudy assessing agreement in AHI or RDI scores in the early to mid-gestation period. Sleep studies will be undertaken within a 7-day window, where practicable. Completion of Apnealink and Somte are not required for RCT participation but will be used to determine the validity of these tests for future use in this population. Eligibility for participation in RCT will be determined by polysomnography outcome.

Women who undergo polysomnography by 14-week gestation period and demonstrate OSA as evidenced by an RDI or AHI ≥5 on polysomnography will be invited to participate in the RCT provided exclusion criteria are not met as described above. A second written informed consent will be collected by study staff, and the participants will be randomized to CPAP, PT, or control as described in the randomization section below.

Validation of home sleep testing in this population will be undertaken via a separate substudy. After validation of the home testing method, further recruitment and screening measurements will continue with screening questionnaires and home Apnealink Air only.

Privacy and Confidentiality

Unattended polysomnography, Apnealink Air, and biomarker data will be deidentified, as described in the relevant methods sections below. Patient data are deidentified for the purpose of randomization, as described below.

Participant consent forms, printed results, and other identifying information on hard copy will be stored in a locked cabinet in a security-access area of the Respiratory and Sleep Medicine Research Department at Liverpool or Campbelltown Hospitals. Where possible, study data will be stored separately to participant identifiers. A master list of study ID numbers and participant identifiers will be stored electronically in a password-protected file within a designated electronic folder on the Respiratory Research drive on the secure Liverpool Hospital server. A separate password-protected folder will be designated for any electronic records with results and identifying information.

Compensation

If the participants suffer any harm, they will be compensated as per health authority regulations.

Trial Design

Pregnancy-associated obstructive sleep apnea (POSA) is a 2-center randomized controlled feasibility trial. The participants will be recruited following participation in an observational study by our group that assesses diagnostic validation of Apnealink air and Somte devices and long-term fetomaternal outcomes. The participants will also be approached at antenatal visits or called by telephone to assess eligibility. Recruitment at both study sites will be concurrent, and the participants who meet the eligibility criteria based on AHI or RDI results in the observational study will be approached for participation in the RCT.

The RCT will use a parallel group, individually randomized, open-label design with two interventions and one control group (1:1:1), with minimization allocation among the 3 arms stratified for BMI, previous history of preeclampsia, or gestational diabetes mellitus. A total of 48 participants (16 in each arm) will be recruited. Study visits will occur monthly after randomization until 32-week gestation period and fortnightly thereafter until delivery, as is local routine clinical practice for antenatal visits. Data collection will include demographic, clinical and physical details, sleep questionnaire responses, sleep study data, maternal pathology, fetal scans, birth details, maternal and fetal clinical outcomes, sleep therapy compliance, and therapy acceptance questionnaires.

We used the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) checklist when writing our protocol [30], which can be found in Multimedia Appendix 3.

Trial Setting

POSA will be conducted at Liverpool Hospital (LPH) and Campbelltown Hospital (CTN) public hospitals within the South Western Sydney Local Health District in metropolitan Sydney, New South Wales, Australia. LPH is a tertiary referral center offering comprehensive antenatal services, delivering approximately 4000 women annually, and includes a level 6 neonatal intensive care unit for neonates from a 24-week gestation period in the district and a comprehensive sleep and respiratory service, including a 5-bed sleep laboratory, ambulatory testing, and a comprehensive outpatient service, including clinics for CPAP therapy. CTN delivers approximately 4200 women annually, with a level 4 nursery that cares for neonates from a 32-week gestation period and a general respiratory and sleep clinic, without the capacity to undertake polysomnography. POSA participants recruited from CTN will be referred to LPH for laboratory polysomnography.

Eligibility Criteria

Eligible participants are defined as women aged 18 years of age and older; in early pregnancy (up to 14-week gestation period); at increased risk of metabolic complications defined as one or more of (1) BMI greater than or equal to 35 kg/m^2, (2) previous GDM, (3) previous personal history of preeclampsia (or in mother or sister), (4) underlying renal disease, (5) maternal type 2 diabetes (pregestational), and (6) symptoms of SDB including snoring, witnessed apnea, mild excessive daytime sleepiness (EDS; which does not meet the criteria for severe EDS defined by Epworth Sleepiness Scale (ESS>15), or a fall asleep accident, or near-miss accident in the previous 12 months), or tiredness; and obstructive sleep apnea diagnosed by polysomnography defined as RDI or AHI ≥ 5.

The participants will be excluded if they have (1) a previous diagnosis of OSA on active treatment, (2) confirmed GDM or preeclampsia, (3) maternal type 1 diabetes, (4) multifetal gestation, (5) known fetal chromosomal abnormality, (6) inability to provide informed consent, and (7) severe EDS based on clinical assessment (eg, including a fall asleep motor vehicle accident or near miss, transient sleepiness while driving or at lights or needing to pull over due to sleepiness while driving, or transient sleepiness in any other dangerous situation, ie, cooking, carrying a baby) or ESS of greater than 15.

Interventions

All groups will have antenatal care as usual without restriction during the trial. The participants will be randomized to CPAP, PT, or control, and the participants randomized to intervention (CPAP or PT) will undertake therapy device education at the randomization visit and commence therapy on the day of randomization or as soon as is practicable. The participants will also be encouraged to use their therapy device for all sleep periods (including naps) from randomization until delivery. CPAP and PT devices will be returned following delivery or withdrawal or discontinuation from the study. The CPAP masks used by the study participants may be retained at the end of the study.

All participants will undertake polysomnography at the 28- to 32-week gestation period. CPAP or PT intervention participants will complete polysomnography at a 28- to 32-week gestation period with the device in situ to confirm treatment efficacy. CPAP will be titrated, if required, as described above. In addition, participants will be invited to complete Somte and Apnealink at 28- to 32-week gestation period, as part of the device validation substudies.

CPAP Intervention

The participants in the CPAP intervention group will use a close-fitting facial mask worn overnight during sleep to ensure that the collapsible upper airway is kept patent with a column of air and they will commence on auto-titrating pressure 6-20 cm H_2O (Philips Dreamstation Auto with heated humidification) per clinical practice at the study site. The participants will also be offered a range of CPAP masks to trial with an option to take home multiple masks or sizes if needed. CPAP participants will be educated in device use and troubleshooting by an experienced sleep therapist before commencing therapy. The trial sleep therapist will telephone CPAP group participants on day 3 to gain access to CPAP efficacy data via remote monitoring software (Care Orchestrator, Philips). Pressure will be changed to the 90th percentile pressure in fixed pressure mode, provided compliance data show average usage of CPAP across a period of more than 4 hours (All Days≥4 hours), and treatment efficacy is achieved as determined by residual AHI≤5. The participants with poor compliance or efficacy will be given additional acclimatization time on CPAP, up to 7 days (or as clinically necessary), and changed to the 90th percentile when clinically appropriate. CPAP data will be downloaded via Secure Digital card (SD) data card and reviewed at each study visit and at the return of the device as per the study schedule and interrogated for CPAP compliance, efficacy, and mask leak.

CPAP pressure will be adjusted empirically at scheduled study visits to maintain treatment efficacy (AHI≤5). Polysomnography will be conducted at 28 weeks on the current CPAP pressure. Titration of CPAP pressure will be undertaken if criteria for pressure increase is met per AASM (American Academy of Sleep Medicine) manual titration guidelines, that is, up to 1 increase by 1 cm H_2O per 5-minute period for any of the following: 2 of obstructive apneas, 3 of hypopneas, 5 of the respiratory event–related arousals, or 3 minutes of loud or unambiguous snoring [31]. CPAP pressure changes will be reported in published study findings at the conclusion of the trial.

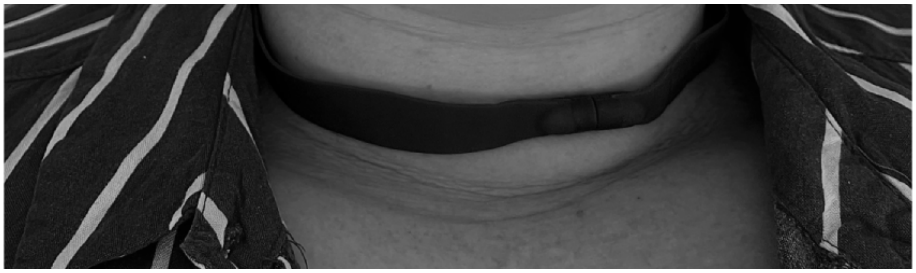
Compliance and efficacy of treatment feedback will be provided to study participants at each visit to encourage compliance. Additional phone or video support will be available, at participants' request, for participants who encounter difficulty with CPAP compliance. To ensure equal therapy support for CPAP and PT treatment arms, remote monitoring of CPAP compliance will not be conducted beyond the acclimatization period. CPAP devices used in this trial have been replaced by the manufacturer in accordance with the Therapeutics Goods Administration device repair or replacement program following product defect correction order RC-2021-RN-01373-1.

Positional Therapy Intervention

The participants in the PT intervention group will use a noninvasive vibratory device (Night Shift Device: Advanced Brain Monitoring, Inc) that is worn around the neck and promotes sleep in the nonsupine position (Figure 1 [source: Frances Clements, Liverpool Hospital, November 10, 2022]). The device provides a vibratory alert to the wearer when the supine position is detected and is secured at the anterior neck with a magnetic closure (Figure 2 [source: Frances Clements, Liverpool Hospital November 10, 2022]).

Figure 1. Nightshift positional therapy device posterior view.

Figure 2. Nightshift positional therapy anterior view.



The participants randomized to PT will be provided education by an experienced sleep therapist before commencing therapy. The device will be fitted by measuring the neck circumference and adjusted to ensure that the device does not slide down the neck. The device will be set with a 15-minute feedback delay, with vibration feedback mode on and the device location at the posterior neck. Downloads of therapy data will be obtained by an experienced sleep therapist at each study visit, where possible, as per the protocol schedule, and at the return of the device, compliance and efficacy data will be interrogated. Recording time, position, patient alert frequency, and snore data will be recorded. Feedback will be provided to study participants at each visit. Additional phone or video support will be available for participants with therapy as requested.

Control Group

Control group participants with significant SDB at polysomnography at the 28- to 32-week gestation period and symptoms of severe EDS (ESS>15) will be identified, withdrawn from the study, and managed according to standard clinical practice under the direction of a sleep physician.

Participant Timeline

The participants will be reviewed monthly until the 32-week gestation period and then fortnightly until delivery, coinciding with scheduled antenatal visits where possible. The trial flow chart is depicted in Multimedia Appendix 4. The flowchart describes the participant's progression through the trial protocol and depicts the timing of the interventions.

Sample Size

There are limited data on this topic, particularly on the estimated risk reduction in event rates. We intend to pilot the RCT with an initial 48 patients. This data will be used to refine the protocol and optimize logistics and will be used to inform a larger RCT.

Randomization, Allocation, Concealment, and Blinding

The participants will be individually randomized via a telephone call to the National Health and Medical Research Council's Clinical Trials Centre at Sydney University, who are independent of the trial, by the study coordinator. Randomization will be based on a minimization method with stratification for previous preeclampsia, personal history of gestational diabetes, and BMI≥35, to either CPAP, PT, or control groups. A maximum imbalance value of 1 between any of the 3 arms will be used in determining whether a forced allocation (ie, to achieve minimization of difference of stratification factor totals) or random allocation is used in a specific subject randomization. Treatment allocation will be unblinded for both study staff and participants.

Data Collection, Management, and Analysis

The complete schedule of study visits, procedures and data collection points is presented in Multimedia Appendix 5, which depicts the trial participant study visits and intervention schedule.

Data Management

Data from Apnealink screening tests, CPAP, and PT will be stored in a deidentified format. Polysomnography data will be stored on the secure hospital network. The system is secured via the Information Management and Technology Division's corporate backup software. Research Electronic Data Capture (REDCap; Vanderbilt University) database [32] will be used for data collection and management. Questionnaires will be completed electronically by participants via an email link where possible or by paper questionnaire where needed. In the event of participant discontinuation from the RCT, long-term fetomaternal outcomes of interest will be collected, where agreed to by participants during consent, in writing.

Data Collection Methods

Blood and Urine Collection

With consent, blood will be collected at 12-16, 16-20, 28 gestation weeks, and 6-12 months post partum by study staff or using hospital pathology collection services in EDTA tubes. The blood will be centrifuged (3000 rpm, 10 min), and plasma will be aliquoted (250 µL). The buffy coat will be collected and stored in approximately 250 µL RNA. Later, all specimens will be snap frozen in liquid nitrogen and stored at –80C at the Ingham Institute of Medical Research (Liverpool, New South Wales, Australia). Biomarkers (sFlt-1 [soluble fms-like tyrosine kinase 1], PlGF [placental growth factor], IL-6 [interleukin-6], TNFα [tumor necrosis factor alpha], and HIF1α [hypoxia-inducible factor 1-alpha]) will be assayed at the conclusion of the study blinded to outcomes.

Urinalysis will be conducted at each study visit using SIEMENS Multistix 10SG Test strips. A score of negative, trace, 30 mg/dL (++), 100 mg/dL (++), 300 mg/dL (++), or >2000 mg/dL (+++) will be recorded. If greater than 1+ protein is detected, a random spot urine sample will be sent to hospital pathology services for measurement of urinary protein adjusted for creatinine excretion.

Fetal Monitoring

Fetal ultrasound will be undertaken at the study site fetomaternal units (FMUs). Uterine artery blood flow (pulsatility index measurements) will be recorded at the randomization visit (12-16-week gestation period), 2-6 weeks later (average 4 weeks

to 16-20-week gestation period), and at 36-week gestation period. Morphology scan (16 weeks) (may be combined with uterine artery blood flow) and growth scan (36 weeks) will be performed. Fetomaternal scans performed at study sites will be performed using ViewPoint 6 (General Electric Healthcare) by experienced sonographers supervised by physician consultants within the FMU.

Questionnaires

ESS [33] and STOP-BANG (snoring, tiredness, observed apnea, high BP [STOP] and snoring, tiredness, observed apnea, high BP-BMI, age, neck circumference, and gender) [34] questionnaires will be used in baseline screening and scored according to standing scoring recommendations (sum of 8 item-scores [ESS] and score 0-8 [STOP BANG]). Functional outcomes of sleep will be assessed using the Functional Outcomes of Sleep Questionnaire (FOSQ-10) [35], which has been validated in pregnancy and scored according to FOSQ-10 marking guidelines [36]. Questionnaires assessing sleep study acceptability, sleep study preference, and therapy acceptability will be undertaken and are presented in Multimedia Appendices 6-13. Questionnaires will be emailed to participants using REDCap or completed in paper hardcopy where the patient is unable to complete electronically. The acceptability questionnaires used in this trial were evaluated on hospital staff unaffiliated with the trial. Feedback was implemented, and questionnaires were redesigned before SWSLHD HREC approval and implementation.

Sleep Study Data Collection

The participants will undergo attended polysomnography (with therapy device in situ for CPAP and PT arms) using Grael v2 (Acquisition System, Compumedics), unattended polysomnography using SOMTE v2 (Acquisition system, Compumedics) and Apnealink Air (Resmed) at 28- to 32-week gestation period at LPH. Laboratory-based polysomnography will be repeated 6-12 months post partum.

Attended and unattended polysomnography will be scored using Profusion PSG 4 auto analysis software (Compumedics) by a single experienced sleep scientist using the 2020 AASM Manual for the scoring of sleep and associated events (Version 2.6 guidelines). Apnealink Air will be automatically scored using Airview (Resmed; AASM 2012, Automatic Scoring) and manually scored by a single experienced sleep scientist using 2020 AASM guidelines (events Version 2.6). All sleep study sets will be reported by the same sleep physician for consistency. Unattended polysomnography and Apnealink Air studies will be scored and reported blindly by sleep scientists and reporting sleep physicians.

Apnealink Air data collection includes airflow (pressure transducer), respiratory effort (abdomen) and oximetry (SpO_2), snoring, and pulse. The participants will complete a self-setup in the home, will be provided with an instruction sheet, and will also manually start study recording as close to anticipated sleep onset as possible and manually stop recording at sleep offset.

Unattended polysomnography data collection included electroencephalography (F3 and F4, M1 and M2), electrooculography (E1 and E2), electromyography (EMG chin [submentalis]), electrocardiogram (modified lead II), airflow (pressure transducer), snoring, airflow (thermistor), respiratory effort (abdomen and thoracic), anterior tibialis EMG (left and right leg), oximeter (SpO_2), and position sensor. The participants will complete a self-setup at home. A comprehensive instruction booklet will be provided, and the participant will be encouraged to watch an instructional video [37]. The participants will have access to phone or video support from experienced sleep staff. Study recording will commence as close to the anticipated sleep onset as possible and manually stop recording at sleep offset.

Attended polysomnography collection includes those in unattended polysomnography as described above, with the addition of electroencephalography (C1 and C2 and O1 and O2), EMG Chin (Chin 1 and Chin 2 and Chin 3), EMG diaphragm, snore (microphone), sound level (dB meter), and digital video (audio and visual). Competent sleep technicians will conduct participant setup.

Outcome Assessment

An oral glucose tolerance test will be undertaken for the assessment of gestational diabetes at 28 weeks (in addition to earlier testing if clinically requested). Collection of fasting blood will be followed by administration of 75 g oral glucose load, with 1 and 2 hours of blood collection. Interpretation will follow the Australasian Diabetes in Pregnancy Society (ADIPS) 2020 guidelines [38].

Blood pressure (BP) will be recorded at each study visit. Diagnosis of HDP will be defined as per the Society of Obstetric Medicine of Australia and New Zealand (SOMANZ) guidelines [39].

Anthropometric measurements (height, weight, and BMI) will be recorded during the randomization visit, and weight will be checked at subsequent study visits by study staff using hospital clinic scales.

Postpartum Follow-Up

RCT participants will be followed up in the clinic at 6-12 months post partum. At this time point, women will be offered repeat polysomnography, an oral glucose tolerance test (if they developed diabetes and have not already undertaken this in the postpartum period), biomarker blood, and urine collection.

Statistical Methods

This trial is a feasibility trial, and as such, no power calculations for the RCT were derived. We prespecified to assess the diagnostic accuracy of the home sleep tests as well as the screening questionnaires following the STARD (Standards for Reporting of Diagnostic Accuracy) guidelines. The accuracy will be assessed at various cutoff points using a receiver operating characteristic curve. The area under the receiver operating characteristic curve and positive and negative predictive values in the patient population will be derived. The first recruitment target will be 50 participants, which provides at least 80% power (α=.05) to detect a C-statistic of 0.7 when the allocation ratio is 1 (ie, 50% prevalence) and 0.75 when the allocation ratio is 2 (ie, 20% prevalence). We will be comparing Apnealink Air and SOMTE unattended PSG to attended PSG. Further exploratory analysis will be undertaken to assess

whether any factors at booking, including the results of the sleep questionnaire, biomarkers, clinical factors, and history in combination with findings of unattended PSG, Apnealink, or attended PSG, are predictive of poor outcomes (either maternal or fetal, as discussed above). A composite of the combined adverse maternal outcomes and combined adverse fetal outcomes will also be assessed as an outcome. Data will be displayed as mean (SD), 95% CIs, and median (IQR) as appropriate based on data distribution. An intention-to-treat analysis will be undertaken for the primary outcome as well as the secondary outcomes. A per-protocol analysis (for primary and secondary outcomes) will also be undertaken, and both data will be presented. A *P* value of <.05 will be considered statistically significant. Where multiple analyses are undertaken, adjustments will be made for multiple comparisons. Longitudinal analysis of repeated measures will be undertaken where measurements are undertaken several times. Where differences at baseline exist between the groups, adjustments will be made statistically. Where less than 10% of any data point is missing, data will be imputed. We have preplanned an exploratory analysis of flow characteristics of all sleep tests to investigate sub-criterion flow changes related to long-term fetomaternal outcomes.

Patient and Public Involvement

The participants were not involved in the design of this study protocol. Participant feedback will be obtained via a series of questionnaires as described above. Members of the public (hospital staff) participated in providing feedback on acceptability questionnaires as described above, and feedback was implemented in the development of the questionnaires.

Data Monitoring

No data monitoring committee has been appointed.

Risk Assessment and Termination of Study

An interim analysis will be performed halfway through enrollment by the safety committee. If there is a convincing signal that either CPAP or PT therapy is associated with adverse outcomes, the study will be terminated immediately, and the SWSLHD HREC will be notified. Significant safety issues and patient complaints will be reported immediately via email to SWSLHD HREC.

Safety Considerations

A safety committee will be established to monitor the safety of participants and to review any potential adverse outcomes. The safety committee will review the outcomes after each of the 4 subjects for the first 16 subjects or if any severe adverse events occur.

Posttrial Care

The participants affected by product recalls in this trial will be followed up annually for 5 years if agreeable as per the protocol.

Results

The trial commenced on September 30, 2019. The trial is ongoing as of August 6, 2024.

Discussion

Principal Findings

Despite the growing interest in the potential for improved fetomaternal outcomes in pregnant women with OSA occurring during pregnancy through the use of CPAP, few large RCTs have been undertaken. In addition, no RCT has compared CPAP and positional therapy for the treatment of OSA occurring during pregnancy. This RCT feasibility study will assess the feasibility of conducting a large RCT to initiate CPAP or positional therapy in pregnant women by the 16th week of gestation.

To date, the largest RCT to investigate the treatment of OSA in pregnant women studied 310 pregnant women with OSA from the first trimester. The primary outcome of the study was BP control during pregnancy and the secondary outcome was the incidence of preeclampsia. The overall CPAP compliance was 2.5 (SD 2.5) hours per night and median use was 1.7 (IQR 0.2-4.5) hours per night, and the authors concluded CPAP therapy reduced the incidence of preeclampsia and demonstrated a reduction in DBP throughout the pregnancy, in high-risk pregnant women with mild to moderate OSA [23]. A recent systematic review assessed the use of CPAP therapy for the prevention of hypertensive-related adverse outcomes in pregnant women with OSA. The authors report risk reduction of gestational hypertension and preeclampsia in the CPAP groups (relative risk [RR] 0.65, 95% CI 0.47-0.89; *P*=.008) and preeclampsia (RR 0.70, 95% CI 0.50-0.98; *P*=.04), which were not correlated with age or BMI. The authors concluded that while the results suggest CPAP therapy as a potential mediator to adverse gestational hypertensive outcomes in pregnant women with OSA, the association remains inconclusive [40].

This feasibility RCT will assist in the understanding of the maternal and health care system challenges in undertaking a CPAP intervention during pregnancy. The therapies in this study will commence by the 16th week of gestation and will be overseen by an experienced sleep therapist to improve CPAP and PT compliance. This is important as many clinical trials involving CPAP are limited by poor compliance of the participants. We will encourage compliance to interventions through an initial education session at randomization by the trial sleep therapist and at each study visit. At these visits, the participants will be provided feedback regarding their therapy compliance and efficacy, and through a series of questionnaires, we will assess barriers to therapy. We anticipate an improvement in fetomaternal outcomes such as improved blood pressure control, reduced incidence of GDM, and preeclampsia in the interventional groups with good adherence to therapy. The learnings from undertaking this work will be important for consideration when expanding to a larger trial. The results of the study will be published in peer-reviewed journals and presented at national and international conferences.

Limitations

Limitations to the trial will be poor acceptability of the trial protocol by the participants and the potential for pregnancy complications to participants in the trial, given the risk of adverse events occurring during pregnancy, particularly in high-risk populations with comorbidities such as obesity and a

history of hypertension and diabetes [41]. Additional limitations to the trial will be the potential for poor CPAP and PT compliance of the participants randomized to these interventions. The use of an experienced sleep therapist in the trial to educate the participants and provide ongoing therapy support during the trial is anticipated to minimize poor therapy compliance but may limit the generalizability of findings.

Conclusions

If this trial protocol demonstrates good overall feasibility, a larger multicenter RCT will be conducted. The results of this feasibility trial will inform a redesign of the protocol for the larger RCT, if required. The use of positional therapy in this trial may provide evidence of the utility of OSA treatment options other than CPAP in pregnant women with OSA. Furthermore, it is anticipated that the follow-up schedule in this trial may inform other study designs involving pregnant women with OSA, ultimately leading to changes to clinical policy in the care of pregnant women.

Data Availability

Data generated during this trial will be available following the completion and publication of the trial from the first and last authors upon reasonable request and approval by the local ethics committee.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Screening eligibility preconsent questionnaire. Participants are invited to complete a Screening eligibility preconsent questionnaire to determine trial eligibility.
[PDF File (Adobe PDF File), 252 KB - resprot_v14i1e51434_app1.pdf]

Multimedia Appendix 2
Baseline information. Participants complete the baseline information questionnaire following trial consent.
[PDF File (Adobe PDF File), 321 KB - resprot_v14i1e51434_app2.pdf]

Multimedia Appendix 3
The checklist presents the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) 2013 checklist.
[PDF File (Adobe PDF File), 210 KB - resprot_v14i1e51434_app3.pdf]

Multimedia Appendix 4
POSA (pregnancy-associated obstructive sleep apnea) trial flow chart. The flow chart describes the participant progression through the trial protocol and depicts the timing of the interventions.
[PDF File (Adobe PDF File), 338 KB - resprot_v14i1e51434_app4.pdf]

Multimedia Appendix 5
Schedule of study visits. The image depicts the trial participant study visits and intervention schedule.
[PDF File (Adobe PDF File), 232 KB - resprot_v14i1e51434_app5.pdf]

Multimedia Appendix 6
Polysomnography (PSG) 28-32 weeks gestation questionnaire. Participants are invited to complete the questionnaire at 28-32 weeks' gestation to assess participant experience following completion of the sleep test.
[PDF File (Adobe PDF File), 89 KB - resprot_v14i1e51434_app6.pdf]

Multimedia Appendix 7
Somte 28-32 weeks gestation questionnaire. Participants are invited to complete the questionnaire at 28-32 weeks' gestation to assess participant experience following completion of the sleep test.
[PDF File (Adobe PDF File), 128 KB - resprot_v14i1e51434_app7.pdf]

Multimedia Appendix 8
Apnealink 28-32 weeks gestation questionnaire. Participants are invited to complete the questionnaire at 28-32 weeks' gestation to assess participant experience following completion of the sleep test.
[PDF File (Adobe PDF File), 126 KB - resprot_v14i1e51434_app8.pdf]

Multimedia Appendix 9
Preferred test questionnaire. Participants are invited to complete the questionnaire to assess participant preference of sleep diagnostic tests.
[PDF File (Adobe PDF File), 44 KB - resprot_v14i1e51434_app9.pdf]

Multimedia Appendix 10
CPAP (continuous positive airway pressure) therapy Questionnaire 16-20 weeks' gestation. Participants randomised to CPAP intervention are invited to complete the questionnaire to assess participant experience of CPAP therapy to 16-20 weeks' gestation.
[PDF File (Adobe PDF File), 163 KB - resprot_v14i1e51434_app10.pdf]

Multimedia Appendix 11
CPAP (continuous positive airway pressure) therapy questionnaire 36 weeks' gestation. Participants randomised to CPAP intervention are invited to complete the questionnaire to assess participant experience of CPAP therapy to 36 weeks' gestation.
[PDF File (Adobe PDF File), 163 KB - resprot_v14i1e51434_app11.pdf]

Multimedia Appendix 12
Position therapy questionnaire 36 weeks' gestation. Participants randomised to positional therapy (PT) intervention are invited to complete the questionnaire to assess participant experience of PT therapy to 36 weeks' gestation.
[PDF File (Adobe PDF File), 163 KB - resprot_v14i1e51434_app12.pdf]

Multimedia Appendix 13
Position therapy questionnaire 16-20 weeks' gestation. Participants randomised to positional therapy (PT) intervention are invited to complete the questionnaire to assess participant experience of PT therapy by 16-20 weeks' gestation.
[PDF File (Adobe PDF File), 163 KB - resprot_v14i1e51434_app13.pdf]

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Abbreviations

AASM: American Academy of Sleep Medicine
ADIPS: Australasian Diabetes in Pregnancy Society
AHI: apnea-hypopnea index
BP: blood pressure
CPAP: continuous positive airway pressure
CTN: Campbelltown Hospital
EMG: electromyography
ESS: Epworth Sleepiness Scale
FMU: fetomaternal unit
FOSQ-10: Functional Outcomes of Sleep Questionnaire
GDM: gestational diabetes mellitus
HDP: hypertensive disorders of pregnancy
HDP: hypertensive disorders of pregnancy
HIF1α: hypoxia-inducible factor 1-alpha
IL-6: interleukin-6
LPH: Liverpool Hospital
OSA: obstructive sleep apnea
PlGF: placental growth factor
POSA: pregnancy-associated obstructive sleep apnea
PT: positional therapy
RDI: respiratory disturbance index
REDCap: Research Electronic Data Capture
RR: relative risk
SDB: sleep-disordered breathing
sFlt-1: soluble fms-like tyrosine Kinase 1
SOMANZ: Society of Obstetric Medicine of Australia and New Zealand
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials
STARD: Standards for Reporting of Diagnostic Accuracy

STOP-BANG: snoring, tiredness, observed apnea, high BP (STOP) and snoring, tiredness, observed apnea, high BP-BMI, age, neck circumference, and gender
SWSLHD HREC: South Western Sydney Local Health District Human Research and Ethics Committee
TNFα: tumor necrosis factor alpha

Edited by A Mavragani; submitted 31.07.23; peer-reviewed by Y Chen; comments to author 23.03.24; revised version received 20.04.24; accepted 17.11.24; published 11.04.25.

Please cite as:
Clements F, Vedam H, Chung Y, Smoleniec J, Sullivan C, Shanmugalingam R, Hennessy A, Makris A
Effect of Continuous Positive Airway Pressure or Positional Therapy Compared to Control for Treatment of Obstructive Sleep Apnea on the Development of Gestational Diabetes Mellitus in Pregnancy: Protocol for Feasibility Randomized Controlled Trial
JMIR Res Protoc 2025;14:e51434
URL: https://www.researchprotocols.org/2025/1/e51434
doi:10.2196/51434
PMID:40215099

Protocol

Interventions to Reduce Serum Per- and Poly-Fluoroalkyl Substances Levels, Improve Cardiovascular Risk Profiles, and Improve Epigenetic Age Acceleration in US Firefighters: Protocol for Randomized Controlled Trial

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Abstract

Background: Occupational cancer and acute cardiac events are the leading causes of death among firefighters. Increased exposure to toxicants on the fire ground, such as polycyclic aromatic hydrocarbons, benzene, and per- and poly-fluoroalkyl substances (PFAS), has been linked to certain cancers, cardiovascular disease, accelerated epigenetic aging, and other adverse health effects. PFAS are a major concern because they are persistent, can bioaccumulate, and are present in several firefighting tools. Compared to the general population, firefighters have elevated serum levels of some types of PFAS. A randomized clinical trial in Australian firefighters found that routine blood and plasma donation for 1 year led to decreased serum PFAS levels, although health outcomes were not directly measured in that study.

Objective: In collaboration with fire service leadership in Arizona, the Firefighter Collaborative Research Project (FCRP) was established to evaluate the effectiveness of 3 interventions in a randomized controlled trial design to reduce serum PFAS levels, reduce cancer and cardiovascular risk, and improve overall health and wellness in US firefighters.

Methods: This study aimed to recruit and enroll up to 1500 active firefighters between August 2023 and October 2024. Between August 2023 and October 2024, active firefighters were recruited and randomized into a study arm based on their eligibility, including serum PFOS levels, for the specific arms. The trial arms include (1) blood and plasma donation, (2) zone 2 physical activity, and (3) intermittent fasting. FCRP outcomes include serum PFAS reduction (arm 1), epigenetic age acceleration (all arms), cardiovascular conditioning (arm 2) and cognitive outcomes (all arms), mental health (all arms), and overall disease risk (all arms). Each study arm includes an intervention and a control group. At enrollment and end of the study, participants provide blood and urine samples and complete a comprehensive questionnaire on their occupational and health history, exposures, and lifestyle behaviors. At the end of the study, participants also participated in a cognitive evaluation. Depending on the study arm,

participants may additionally complete a cardiopulmonary exercise test at baseline and follow-up, a mid-study survey, and a mid-study blood and urine collection.

Results: Participant activities and data collection will conclude by December 2025.

Conclusions: The FCRP is a randomized controlled trial that aims to test the effectiveness of fire service–selected interventions in reducing serum PFAS levels. Study results will contribute to potential interventions that could be used to reduce serum PFAS levels in firefighters.

Trial Registration: ClinicalTrials.gov NCT05869747; https://clinicaltrials.gov/study/NCT05869747

International Registered Report Identifier (IRRID): DERR1-10.2196/67120

(JMIR Res Protoc 2025;14:e67120) doi:10.2196/67120

KEYWORDS

firefighters; PFAS; epigenetics; phenotype; heart disease; cardiovascular disease; CVD; atherosclerosis; occupational health; RCT; cardiovascular; fasting; exercise

Introduction

Occupational cancer and acute cardiac events are the leading causes of death among firefighters [1,2]. The firefighting occupation is classified by the International Agency for Research on Cancer as a group 1 carcinogen due to the direct and indirect exposures to hazards on the job [3]. Firefighters have a significantly higher risk of cancer and cancer mortality when compared to the general population, including skin melanoma, other skin cancers, and prostate cancer, with higher mortality for rectal, testicular, brain and nervous system cancers, and non-Hodgkin lymphoma [4,5]. Increased exposure to toxicants on the fire ground, such as polycyclic aromatic hydrocarbons, benzene, and per- and poly-fluoroalkyl substances (PFAS), have been linked to certain cancers, cardiovascular disease, accelerated epigenetic aging, and other adverse health effects [4,6,7].

PFAS are primary toxicants of concern due to their persistence, ability to bioaccumulate, and associated adverse health effects [8]. Firefighters have additional exposure to these chemicals beyond the general population, with significant sources of PFAS exposure on the fire ground including fluorinated class B aqueous film-forming foam and smoke from burning household materials [6]. A study involving 4 municipal US fire departments located in different states and regions of the country found that firefighters had higher levels of several PFAS chemicals in their blood than the general population [9].

In the human body, PFAS accumulates primarily in the liver, kidneys, and blood. Long-chain PFAS, such as perfluoro octane sulfonate (PFOS) and perfluorooctanoic acid (PFOA), have reported half-lives of several years (3.1-7.4 and 2.1-8.5, respectively) [8]. These chemicals bind strongly to albumin, the most abundant protein in plasma [8,10]. Therefore, these chemicals may be removed from the body through blood or plasma donation. An Australian study among firefighters previously demonstrated the effectiveness of blood or plasma donation to lower serum PFAS levels over 12 months, although no health effects were investigated. Findings from the study revealed that plasma donation was more effective than blood donation at reducing the mean serum level of PFOS at 12 months, while serum PFOS did not significantly change in the control group [11]. Plasma donation reduced PFOS levels by approximately 24% (–2.9 ng/mL, 95% CI –3.6 to –2.3 ng/mL), while blood donation reduced PFOS levels by approximately 11% (–1.1 ng/mL, 95% CI –1.5 to –0.7 ng/mL) [11]. Based on the findings from that study and concern for PFAS exposure, Arizona firefighters requested research to replicate the study and additionally investigate health outcomes such as cardiovascular health and epigenetic age acceleration.

Lifestyle and environmental exposures are associated with DNA methylation patterns, a type of epigenetic alteration. DNA methylation affects gene expression by adding a methyl group to 5’—C—phosphate—G—3’ dinucleotides. These DNA methylation patterns can be analyzed to determine epigenetic age or “biological age” through epigenetic clocks. Previous research has found that accelerated epigenetic age can be a risk factor for cancer, cardiovascular and neurological diseases, as well as death from all causes combined [12]. In addition to the physical health impacts, accelerated epigenetic age has been linked to negative mental health impacts [13]. Studies on firefighters have found differential DNA methylation patterns, or accelerated epigenetic age, potentially as a result of fire ground exposure and increased serum PFAS levels [7,14].

Lifestyle interventions, such as physical activity and dietary restriction or intermittent fasting, may be associated with slowed epigenetic aging [12,15,16]. Findings from the Comprehensive Assessment of the Long-term Effects of Reducing Intake of Energy trial revealed that caloric restriction slowed epigenetic aging [17]. Similar findings have been observed in mice [18]. A recent randomized controlled trial tested the effectiveness of a fasting-mimicking diet (low calorie, low protein, plant-based diet) in improving biological age. After 3 cycles, a cycle being a consecutive 5-day period in a month, biological age was reduced by a median of 2.5 years [19].

Zone 2 physical activity, or continuous, moderate aerobic physical activity corresponding to the near lactate threshold (4 mM blood lactate), shows greater benefits than other types of aerobic physical activity for improving cardiovascular risk factors [20,21]. Common examples of this type of activity include brisk walks, light jogs, and cycling for a continuous interval of time. Occupational health clinicians working with the firefighter community also anecdotally noted that zone 2 physical activity confers the greatest benefits for cardiovascular fitness, although this claim has not been formally tested. Both

types of lifestyle interventions, intermittent fasting, and zone 2 physical activity, have received interest from the firefighter community.

The Firefighter Collaborative Research Project (FCRP) aims to assess the effectiveness of fire service–selected interventions for improving firefighter health. The target population for recruitment is participants enrolled in the Fire Fighter Cancer Cohort Study (FFCCS), a national framework study that collects information on firefighter exposures and works to improve the health of the fire service [22]. Through this randomized controlled trial, we seek to engage our existing cohort of firefighters to evaluate 3 firefighter-identified lifestyle interventions: blood or plasma donation, zone 2 physical activity, and intermittent fasting. The primary outcomes of the study include epigenetic age acceleration, serum PFAS reduction (blood or plasma arm only), and cardiovascular risk reduction (zone 2 arm only). Based on the previously mentioned associations with accelerated epigenetic age and therefore aging and aging-related diseases, secondary outcomes of this study include mental health, sleep quality, and cognitive functioning [12,13].

Methods

Overall Study Design

The FCRP is a community-engaged, randomized controlled trial with the goal of screening 1500 firefighters. The study enrollment period is planned for August 2023-October 2024. Based on eligibility criteria, participants are randomly assigned to regularly donate blood or plasma for 1 year, engage in zone 2 physical activity for 4 months, intermittent fast for 4 months, or serve as a control for the duration of the respective study arm.

We have chosen a community-based approach working with fire service leaders in participating states that are willing to educate firefighters on the importance of the study and encourage participation. Departments designate a liaison who completes training for institutional review board (IRB) approval to distribute study information, coordinate events, and serve as an additional point of contact between researchers and participants. The study team also hosts online informational sessions upon request and actively maintains a study website. Individuals interested in participating in the study are directed to complete a screening survey and to schedule an appointment for an in-person event near them. Both surveys may be accessed through informational materials dispersed by liaisons. Events are hosted regionally, and locations are prioritized based on interest numbers and resources for study activities.

Initially, the state of Arizona was designated as the only state for enrollment for all 3 study arms (blood and plasma donation, intermittent fasting, and zone 2). However, upon interest from other US fire departments, the blood and plasma donation arm of the trial has been expanded to Idaho, California, Washington, Oregon, and Massachusetts. The intermittent fasting and zone 2 arms of the trial will not include non-Arizona fire departments. Given that there are a limited number of volunteer departments with who we have established contacts within these areas, enrollment is focused on career departments. Firefighters of all demographic backgrounds were encouraged to enroll.

Participants

Eligibility Criteria

Individuals interested in participating in the study are directed to complete an online screening survey to assess eligibility. Overall study eligibility criteria include active firefighters enrolled in the FFCCS, with full criteria described in Textbox 1. If participants are not already enrolled in the FFCCS at recruitment, they are given the opportunity to enroll. Individuals currently doing study arm activities at the time of screening are deemed ineligible for participation in the respective study arm. Subjects with conditions that may affect their ability to complete study activities (eg, they do not meet national standard criteria for blood or plasma donation, or have an injury preventing physical activity) are also deemed ineligible for participation in the respective study arm. Individuals who are deemed ineligible for all study arms are thereby ineligible for participation in the overall study. Specific inclusion criteria are detailed in Textbox 1.

Textbox 1. Inclusion and exclusion criteria for the Firefighter Collaborative Research Study (FCRP).

Inclusion Criteria

- Active firefighter (including emergency medical responder and all firefighter subgroups) with either a volunteer or career status
- Individual plans to remain in active service with their current agency for the next 2 years (not planning to retire or resign)
- 18 years of age and older
- Fluently speak and write in English
- All genders, races, and ethnicities
- Enrolled in the Fire Fighter Cancer Cohort Study before enrolling in the FCRP
- Complete a signed and dated informed consent document that indicates the participant has been informed of all aspects of the study before enrollment.
- Agree to avoid participating in FCRP intervention activities outside of their assigned intervention group for the duration of the study.
- Able to comply with scheduled visits, laboratory tests, and other study procedures
- BMI ≥17.5 kg/m^2 and weighing more than 115 pounds

Exclusion Criteria

- Overall
  - Not able to fluently speak or write in English
  - Younger than 18 years
  - Currently a tobacco smoker or vaping (eg, >2 cigarettes or cigars, or incidents of vaping in the past month)
  - Those with planned travel or extended leave (eg, >6 weeks) that would prevent their ability to participate in other interventions
  - Those who are pregnant or become pregnant during study, breastfeeding, or have given birth within the past year
  - Those with a history or diagnosis of any significant metabolic, hematologic, pulmonary, cardiovascular, gastrointestinal, neurological, immune, hepatic, renal, urological disorders, severe injury, or cancer that, in the opinion of the investigator, would potentially put the candidate at risk.
- Blood or plasma
  - Those with any medical contraindication (medical condition or medication) to blood donation, according to Red Cross Guidelines
  - Those who donated blood or plasma in the past 3 months
  - Those knowing they have a condition indicative of levels of hemoglobin, hematocrit, red blood cells, or iron below the lower limit of normal levels
- Zone 2
  - Currently participating in zone 2 physical activity
  - Currently participating in more than 120 minutes per week of aerobic, and cardiovascular training (eg, jogging, cycling, walking, swimming, high-intensity interval training) at >60% of their max heart rate.
- Intermittent fasting
  - Those with a history or diagnosis of diabetes, hypoglycemia thyroid disease, or an eating disorder
  - Those who recently participated in intermittent fasting or Time Restricted Eating
  - Those who recently used antidiabetic medication such as Semaglutide (sold as Ozempic, Wegovy, and Rybelsus) or Tirzepatide (sold as Mounjaro) for the treatment of type 2 diabetes or weight loss will also be excluded from this group.
  - Use of drugs that might affect intermittent fasting or eating behaviors

Interventions

Randomization groups are created at regular monthly intervals and clustered by recruitment region. Participants who have consented to participate in the study are randomized into 1 of the 4 study arms as either an intervention or control, accounting for their eligibility determined during the screening process and baseline serum PFOS concentrations. Upon enrollment into their specific group, participants are provided with instructional materials for assigned activities, activity timelines, and frequently asked questions.

Participants randomized in the blood donation or plasma donation arm include all participants with serum PFOS ≥5

ng/mL, following the previous Australian study [11], while also meeting additional study criteria outlined in Textbox 1. We also included a smaller intervention group of participants with PFOS <5 ng/mL in the plasma arm, to evaluate whether improvements in epigenetic age are independent of baseline PFOS. Participants in the blood intervention arm are expected to donate whole blood every 12 weeks for 12 months, while those in the plasma intervention are expected to donate plasma every 6 weeks for 12 months. Participants are provided with a list of donation centers in their region and acceptable types of donations (eg, whole blood donation is acceptable, but not "Power Red" or platelets). Participants go to donation centers on their own. Controls are asked to refrain from donating plasma or blood throughout the trial period.

Participants randomized into the zone 2 physical activity arm complete a Cardiopulmonary Exercise Test (CPET) before starting their intervention. The CPET uses a mouthpiece and external sensors to measure the heart rate and other cardiovascular health indicators of the individual while they engage in mild exercise on a stationary bicycle. The initial CPET provides a baseline evaluation of cardiovascular fitness, as well as the zone 2 heart rate zone used for the intervention. The calculated range from this exam is provided to participants in their results and they are asked to self-report these results to the study team. The zone 2 heart rate range was based on current American College of Sports Medicine guidelines and corresponded to a lower limit of 40% and an upper limit of 60% of achieved peak VO2 to indicate the anaerobic threshold [23]. Functionally, engaging in zone 2 translates to moderate physical activity, with examples of zone 2 physical activity including hiking up a hill, a light jog, or a moderate cycling session. Participants in the intervention are asked to complete a minimum of 45 minutes of physical activity in their zone 2 range for at least 4 days a week, tracked by a study-provided heart rate monitor watch. Controls are permitted to continue their regular physical activity regimen but are asked to not intentionally engage in zone 2 activity. All participants randomized to the zone 2 physical activity arm are provided with a wrist-worn accelerometer (Garmin Forerunner 45) to passively record their physical activity and sleep data. They are reminded to always wear the device except when it is charging and receive regular compliance checkups from study staff. Participants are also reminded to open the application on their phones at least once a week to allow data to be uploaded to their Garmin account. This data is synced with Fitabase to allow the study team to monitor adherence. Participants in the zone 2 physical activity arm are monitored for compliance through Fitabase and can manually report exercises if they do not wear their wrist-worn heart tracker [24]. At the end of the 4-month period, participants complete a final CPET exam and share their results with the study team to evaluate changes over time.

Participants randomized into the intermittent fasting arm are asked to fast for 14 to 16 hours per day, for at least 4 days a week for the 4-month period. Participants select their own time windows to accommodate firefighter shift schedules. During fasting windows, participants are allowed to consume medications and zero-calorie beverages (eg, black coffee, sparkling water, unsweetened tea). They are not asked to alter their diet in any other manner. Controls are asked to not engage in intermittent fasting throughout the trial period and continue their current dietary regimen. Additional details are provided in Textbox 2.

Textbox 2. Description of study interventions within the firefighter collaborative research project.

Arm 1: Blood or plasma donation

- Blood or plasma donation
  - Participants with perfluorooctane sulfonate >5 ng/mL were prioritized for this arm
  - Blood: 12-month commitment to donating blood every 12 weeks. Each blood donation will take approximately an hour to an hour and 15 minutes each time.
  - Plasma: 12-month commitment to donating plasma every 6 weeks. Each plasma donation will take approximately an hour and 30 minutes to 2 hours each time.
  - Additional surveys administered will involve a time commitment between 30 to 45 minutes.
- Blood or plasma control group
  - 12-month commitment into the control group
  - Additional surveys administered will involve a time commitment between 30 to 45 minutes.

Arm 2: Zone 2 physical activity

- Zone 2 physical activity intervention
  - 4-month commitment to completing a minimum of 45 minutes of physical activity in zone 2 for a minimum of 4 days per week.
  - Cardiopulmonary Exercise Test (CPET) testing before beginning and after completing the zone 2 arm for 4 months.
  - 4-month commitment to wear a wrist-worn heart and health tracker at all times unless it is charging.
  - Additional surveys administered will involve a time commitment between 30 to 45 minutes.
- Zone 2 control group
  - 4-month commitment to wear a wrist-worn heart and health tracker at all times unless it is charging
  - CPET testing before beginning and after completing the participation in zone 2 control group arm for 4 months.
  - Additional surveys administered will involve a time commitment between 30 to 45 minutes.

Arm 3: Intermittent fasting

- Intermittent fasting intervention
  - 4-month commitment. The participant will limit intake of food and calorie-containing beverages to an 8-10 hour window a day and fast for the remaining 14-16 hours on 4 days per week.
  - Additional surveys administered will involve a time commitment between 30 to 45 minutes.
- Intermittent fasting control group
  - 4 month-commitment into the control group
  - Additional surveys administered will involve a time commitment between 30 to 45 minutes.

Data Management

Research activities primarily occur through electronic communications such as email, text, and internet-based surveys, telephone contacts, or postal or express mail. Surveys are self-administered by participants on a computer or smartphone. Should participants be unable or unwilling to access them online, they may be administered by study staff by telephone. Participant information given to study staff via phone or email conversation is entered and stored in the REDCap database [25].

The database for this study is maintained through REDCap, which securely keeps participant identifiers and contact information according to the University of Arizona's standard operating procedures. These procedures operate with respect to cybersecurity, privacy, patient confidentiality, and compliance with applicable patient privacy regulations. All study-related documents and specimens contain a unique identifier for each participant, with any study-related documents with personal identifiers stored in a locked cabinet in lockable offices on campus. Laboratory results are entered directly into the REDCap study database from the study reference laboratory.

Twilio is a cloud-based communications platform that allows for automated text messaging chains to be sent to study participants. It is used to send study survey links to their phones that will take them directly to secure REDCap surveys.

At enrollment and their end-of-study visit, all participants provide biological specimens (blood and urine), and a survey is administered to collect information on occupational history

and exposures, relevant medical history, sleep quality, physical activity information, a food frequency questionnaire, the Center for Epidemiological Studies Depression scale (short form), and environmental exposures (Table 1, and described further in the Outcomes section). Throughout their enrollment period, all participants also receive regular study adherence questionnaires (described below). At end-of-study only, all participants additionally take a cognitive assessment (MindCrowd, described below). Participants assigned to the zone 2 physical activity arm complete a CPET before the beginning of the 4-month intervention and again after the conclusion of the intervention. Once participants in the zone 2 physical activity arm report the results of their first CPET, they are sent a wrist-worn accelerometer (Garmin Forerunner 45) that they are instructed to wear throughout the 4-month period and to return upon completion.

Zone 2 wears their accelerometer every day for the duration of the trial.

Table 1. Participant data collection time points for participants enrolled in the firefighter collaborative research project.

	Baseline	Mid-intervention	End of study[a]
Blood	All	BP[b]	All
Urine	All	BP	All
Questionnaires[c]	All	BP	All
Adherence[d]	N/A[e]	All[f]	N/A
Cardiopulmonary Exercise Test	Z2[g]	N/A	Z2
MindCrowd cognitive assessment (verbal cognition, processing speed)	N/A	N/A	All
Accelerometer	Z2	Z2	Z2
Epigenetics (Infinium MethylationEPIC v2.0 BeadChip)	All	N/A	All
VO2max, resting heart rate, HRV[h], HR[i] recovery	Z2	Z2	Z2
Sleep quality (accelerometer): deep, REM[j], light	Z2	Z2	Z2
Sleep quality (National Health Interview Survey Questionnaire): hours, rested, interruptions	All	N/A	All
Depression (CES-D[k] Short form)	All	N/A	All
Firefighter gear and occupational exposures	All	N/A	All
Dietary quality	All	N/A	All
Self-reported weight	All	All	All

[a]End of the study is approximately 4 months after randomization for zone 2 and intermittent fasting and approximately one year for blood or plasma.

[b]BP: blood/plasma arm.

[c]Questionnaires include diet, depression or mood, physical activity, occupational characteristics, and lifestyle.

[d]Intervention adherence questionnaires are evaluated weekly for IF and Z2, and monthly for blood or plasma.

[e]N/A: not applicable.

[f]All: all arms.

[g]Z2: Zone 2 physical activity.

[h]HRV: heart rate variability.

[i]HR: heart rate.

[j]REM: rapid eye movement.

[k]CES-D: Center for Epidemiologic Studies Depression Scale.

Biological Specimens

All participants provide up to 50 mL of blood via venipuncture at baseline as part of the study screening process and at the completion of assigned study arm activities. Participants in the blood and plasma arm complete an additional collection at mid-study, between 4 and 8 months. Each venipuncture is performed by qualified study staff, phlebotomists, nurses, or paramedic-EMTs at organized study events hosted at participating fire stations or facilities. Upon collection, blood specimens are stored locally in coolers with ice packs for transportation to the University of Arizona, where they are processed within 24 hours, with aliquots stored at –80 °C before testing. Baseline blood specimens for all participants are analyzed for PFAS as the final step in the study screening process and for markers of epigenetic age, such as DNA methylation patterns. At the end of assigned activities, only participants in the blood and plasma arm will have their blood specimens analyzed for PFAS. All blood specimens collected at the end of assigned activities for all study arms will be analyzed for markers of epigenetic age.

Participants are asked to self-collect approximately 80 mL of urine at baseline as part of the study screening process and at

the completion of assigned study arm activities per FFCCS protocol and to be stored for future analyses. Participants in the blood and plasma arms complete an additional collection at mid-study, between 4 and 8 months. Collections take place at organized study events hosted at participating fire stations or facilities. Upon collection, urine specimens are locally stored on dry ice for transportation to the University of Arizona, where specific gravity is measured using the Atago Refractometer (Model PAL-10S, Cat# 4410, Fisher Scientific). The sample is aliquoted and prepared for long-term storage at –80 °C for potential future analyses associated with these interventions.

Adherence to Study Activities and Retention

To determine activity adherence, participants are contacted at regular intervals determined by their intervention via email or secure SMS test messages using Twilio. Each survey asks if the participant has completed their required study activities. Participants randomized to an intervention are asked detailed questions about completing their activities, and participants randomized to control are asked if they engaged in the intervention activities since the last study survey. During the check-in surveys, participants are able to report any adverse events. They will then be contacted by study coordinators, and the events will be reported to the IRB for review to determine any necessary actions to take.

Study coordinators call and email noncompliant participants each week to improve adherence. Participants are contacted if they are due to start study activities but have not completed their baseline survey, have at least 1 week past due for a blood or plasma donation, have not completed a weekly survey for zone 2 physical activity or intermittent fasting in 2 weeks, or have not scheduled an appointment for a follow-up biological collection. Participants may also be contacted if they do not sync their wrist-worn accelerometer (Garmin Forerunner 45) with their mobile application, or if they do not share the results of their CPET with the study team. If the participant does not respond and continues to fall behind on study activities, then the IRB-approved liaison for their department is contacted to engage with the participant and ensure they complete their activities.

Laboratory Methods

Per- and Poly-Fluoroalkyl Substances Concentrations

Serum samples are tested for PFAS by the New Jersey Department of Health Centers for Disease Control method #6304.09 as a reference using Chronos online SPE – uHPLC by Spark Holland coupled with a Sciex 7500 MS/MS. A total of 20 analytes are tested, including perfluorobutanesulfonic acid, perfluorodecanoic acid, perfluoroheptanesulfonic acid, perfluoroheptanoic acid, perfluorohexanesulfonic acid, perfluorohexanoic acid, perfluorononanoic acid, perfluorooctanesulfonamide, perfluoroundecanoic acid, PFOA (perfluorooctanoic acid), PFOS, branched and linear isomers of PFOA and PFOS, 9-Chlorohexadecafluoro-3-oxanonane-1-sulfonic acid, 4,8-Dioxa-3H-perfluorononanoic acid, 2-(N-Ethyl-perfluorooctane sulfonamido) acetic acid, 2-(N-Methyl-perfluorooctane sulfonamido acetic acid), and Hexafluoropropylene oxide dimer acid. Note that total PFOA and total PFOS are calculated as the sum of the branched and linear isomers [26].

DNA Methylation Analysis

DNA methylation analysis of serum samples is conducted at the University of Arizona Genetics Core. After sample accessioning and preparation, genomic DNA is extracted using a Qiagen DNeasy Blood and Tissue Kit (REF: 69581) or similar following the manufacturer's recommendations for whole blood. The extracted DNA is then quantified using promega quantiflor fluorometric dsDNA assay (PN: E2671) and dsDNA quantities are detected using a SynergyHT plate reader (Agilent or Biotek). Samples are then normalized or diluted robotically with HPLC water to the range of 200-500ng in a total volume of 45uL. Following normalization, a bisulfite conversion using the Zymo EZ-96 DNA Methylation Kit (PN: D5004) is performed with the specified thermocycler conditions (95 °C for 30 sec, 50 °C for 60 min for 16 cycles, and Hold" at 4 °C) with 15uL as the final elution volume.

The bisulfite-converted DNA is then input into the illumina infinium methylation EPIC Kit (PM 20087706-8) following the manufacturer's recommendations. Whole genome amplification is then performed on the bisulfite-converted DNA. The amplified DNA is then fragmented and precipitated before being resuspended and hybridized onto the bead chip (v2.0) during an overnight incubation. Unhybridized DNA is washed off before the bead chip undergoes single base extension and staining. Before scanning, the bead chip undergoes a final round of washing and coating to prepare the chip for imaging. Once prepped for imaging, the bead chip is then scanned on an Illumina NextSeq 550 following the manufacturer's recommendations.

Outcomes

The primary outcomes of the study include epigenetic age acceleration, serum PFAS reduction, and cardiovascular risk reduction, with secondary outcomes including mental health, sleep quality, and cognitive functioning. Intervention-specific outcomes include PFAS concentrations (plasma or blood arm), and cardiovascular fitness (zone 2 arm). Urine and blood samples are stored at –80 °C for future biomarker-based outcomes. In total, 20 PFAS types are measured for all participants at baseline and again at end-of-study for participants in the blood and plasma study arm. Participants are provided with a report back of their PFAS concentrations at baseline and again at follow-up if measured. Epigenetic age acceleration will be calculated for baseline and end-of-study samples for all participants using several different clock-based methods, including the Horvath clock, GrimAge, Hannum, SkinBlood, PhenoAge, and Dunedin PACE [26-28]. Epigenetic age acceleration will be calculated using residuals after regressing each clock on chronological age [29,30]. Participants who complete activities required by the study protocol will have their epigenetic age acceleration reported back to them.

Cognitive functioning is measured with the MindCrowd web-based platform created by TGen. MindCrowd measures verbal memory performance using paired associates learning, and processing speed via simple visual reaction time. Both tests

are strongly predictive of age and functional ability across the lifespan, and MindCrowd has been validated in hundreds of thousands of participants across the world [31-33]. To minimize the time burden on enrollment and possible learning effects, MindCrowd is only assessed at follow-up.

Cardiovascular fitness is evaluated with baseline and end-of-study CPETs, and additionally on an ongoing basis with wrist-worn accelerometers. The CPETs produce validated measures of resting VO2 (maximal aerobic capacity), peak VO2, VO2 reserve, and heart rate. The accelerometers from the wrist-worn watch also generate an estimate for peak VO2, and we will assess the progression of this over time as a function of intervention status.

Depression and mood are evaluated at baseline and follow-up using the revised version of the Center for Epidemiologic Studies Depression Scale. Diet quality is measured from a food frequency questionnaire at baseline and follow-up. Sleep quality is measured via the wrist-worn accelerometers for those in the zone 2 arm, and through a modified version of the Centers for Disease Control's National Health Interview Survey's Sleep Surveillance questionnaire for all participants. The National Health Interview Survey sleep survey is slightly modified to account for firefighter's shift work.

Statistical Considerations

Power Analysis

We conducted a power analysis based on the outcomes of changes in PFAS concentrations, as well as changes in epigenetic ages. Following the initial Australian study, to see a change in concentration of 20% PFOS from before and after, we calculated an N of approximately 100 participants per group or 300 total for the blood, plasma, or control groups. However, to observe a change of one year of epigenetic age acceleration, with a standard deviation of 3, we required an N of 141 per group. To account for missingness, we are targeting an N of 150 per group.

Therefore, the targeted sample size for PFOS ≥5 ng/mL is 150 plasma test participants, 150 blood test participants, and 150 shared controls for blood or plasma; and for PFOS <5 ng/mL we are targeting 75 intervention participants; for zone 2 is 150 controls and 150 test participants; for intermittent fasting, sample size is 150 controls and 150 test participants. Thus, the total number of participants that complete the study is targeted at 1120. Randomization of the intervention groups is conducted using R v4.2.0 [34].

Data Analysis

All models will evaluate intent to treat effects, as well as the average treatment effect of the treatment. We will first evaluate characteristics by treatment group to ensure randomization is effective.

To estimate the effect of blood and plasma donation on the reduction of PFAS concentration, mixed effects models with random effects by department or region will be fit to compare changes in PFAS concentration before and after the study among intervention groups. We will report mean differences in the change from baseline to end-of-study measurements by group and adjust for residual confounders. We will also evaluate whether the volume of plasma and blood donated is a significant predictor of PFAS change, and account for adherence in these models. The results of these models will evaluate if there is a statistically significant difference in the change of PFAS concentration from baseline to follow-up, in cases compared to controls, and if there is a dose-response relationship between volume donated and PFAS concentration change.

Linear mixed-effect models will also be used to examine differences between groups in epigenetic age acceleration, cardiovascular fitness, cognitive functioning (measured only at follow-up), mental health, sleep quality, and other measured outcomes. Similar models will be used for zone 2 physical activity and intermittent fasting interventions. Missing data will be assessed and if substantial missing data is identified (greater than 10%), a sensitivity analysis will be conducted using multiple imputations by chained equations.

Ethical Considerations

This study was reviewed and approved by the University of Arizona IRB (STUDY00002462). All participants complete informed consent electronically through the REDCap database system and all collected identifiable data is stored within the database (Multimedia Appendix 1). The research staff verifies that participants fully understand all risks and the necessary study activities that are required of them. Once participants agree to be active participants in the study, the study staff sign the informed consent. All participants receive the results of their PFAS concentrations, measured from the baseline blood collection during the screening process. No monetary compensation is provided to any participant in the study. At the end of study activities, only participants in the blood and plasma donation arm will receive a second set of PFAS results, measured from the blood collection at the end of the study. In addition, following the completion of all study activities, all participants receive the results of their epigenetic clocks.

Any participant information provided in this manuscript is de-identified. Any identifiable information is stored within the REDCap database, which securely keeps participant identifiers and contact information according to the University of Arizona's standard operation procedures. These procedures operate with respect to cybersecurity, privacy, patient confidentiality, and compliance with applicable patient privacy regulations. All study-related documents and specimens contain a unique identifier for each participant, with any study-related documents with personal identifiers stored in a locked cabinet in lockable offices on campus.

Results

This study was funded by the Arizona Board of Regents. Enrollment began in August 2023 and concluded in November 2024. As of January 2025, a total of 916 participants were enrolled in the study and 1893 participants were screened. The conclusion of the blood and plasma interventions is set for December 2025, contingent upon funding. Data analysis will begin once sufficient data has been collected.

Discussion

Overview

All study interventions were selected based on interest from a community-engaged participatory framework with the fire service. Testing the effectiveness of blood and plasma donation in reducing serum PFAS levels in firefighters is a high priority among firefighters, given that this population has been found to have higher serum levels of these chemicals compared to the general population [6,9]. Evaluating all interventions as potential ways to improve epigenetic age acceleration and reduce disease risk is a priority in improving the health of the fire service. A primary strategy for promoting participant adherence to study activities is by reporting the results of their serum PFAS concentrations and epigenetic clock measurements back to them. Newsletters and website updates are also to provide study updates and promote participant engagement.

Strengths

One strength of the study includes measuring the baseline serum PFAS concentrations of approximately 2000 firefighters, leading to a better understanding of the impact of occupational activity history on PFAS. In addition, given that all interventions were requested by fire service leaders, there is more interest and determination to complete study activities. This study will also contribute to research into epigenetic age acceleration and potential interventions to improve it.

Limitations

Our study has some limitations; first, there are significant barriers to plasma donation, including time commitment and distance, which can impede participant adherence. The Australian study being replicated identified an adherence rate of 93.7% to their interventions [11]. All the intervention arms require a time commitment; therefore, compliance is a concern [35]. Finally, not meeting enrollment targets will reduce our study's power to evaluate relationships between the intervention and PFAS levels and epigenetic age acceleration.

Conclusions

The design, enrollment, and research activities of this randomized controlled trial provide an opportunity to observe PFAS interventions in real time and assess their feasibility and benefit.

Acknowledgments

Members of the University of Arizona study team assist with screening and enrollment events, participant contacts, daily operations, and laboratory processing. The University of Arizona team includes Hailey Freeman, Elizabeth Valdivia, Nina Wittmer, Samantha Castro, Danielle Stea, Erin Woods, Joe Mirabito, Elisabeth Hoornaert, Jessica Hlomatchi, Nagateja Yeddulla, Jordan Baker, Dylan Rogers, Alissa Coleman, Mia Huerta, Kylie Lew, and Natalya Mayhew. The Arizona State University team assists with screening and enrollment events in Phoenix and surrounding areas. The Arizona State University team includes Brendan Thomas, Kinta Schott, Avaani Bhalla, Theresa Jorgensen, Alexandra Levendi, Debra Baldauff, Margarita Stirk, Theresa Crain, Hanna Lybbert, Olivia Tilley, and Kyle Reid. Jackie Goodrich of the University of Michigan provided expertise in epigenetics and analyses. A special thanks to our fire service liaisons who assist in recruitment and coordination of events. Our fire service liaisons include Jason Miller, Kane Nixon, Jake Rhoades, McKenzie Hess, Rayne Gray, Dan Jarrett, Jeff McMenemy, Bryon Mabery, Ed Pahl, Orion Godfrey, Brad Pitassi, Jay Evans, Rob Brewster, Stephen Gunn, Blas Minor, Val Gale, David Switzer, Jodi Spargo, Joe Fioresi, Scott Figgins, Clint Steeves, Eric Valliere, Shauna O'Dell, Colt Weddell, Dave Endres, Kevin Montgomery, Kyle Carman, Mark Manor, Rick Olson, Scott Freitag, Adrianne O'Brien, Greg McLaughlin, Chris Sanchez, Elliot Riggs, Jeremy North, Joe Kosiorowski, Robert Corbell, Holger Durre, Jason Heartisan, Dennis Gasrow, Steve Legros, Craig Artrip, Jason Schnase, Rob Mathis, Karyn Barr, Jay Lee, David Hunt, Michael Warmuth, Mark Niemeyer, Heather Fleek, Kirk Carpenter, Derek Biering, Jeff Hughes, Jonathan Hernandez, Doug Menard, Kyle Taylor, Pat McKenna, Paul Lombard, Conor Flaherty, Nick Querzoli, Aaron Guggenheim. The certified testing locations for participant Cardiopulmonary Exercise Tests are 1582 (Rick Hutton) and HeartFit for Duty (Kepra Jack).

Funding for this study was provided by the Arizona Board of Regents to the University of Arizona and Arizona State University (contact information for sponsor: Ken.polasko@azregents.edu) and by NIEHS P30 ES006694.

Data Availability

The datasets generated or analyzed during this study are not publicly available due to participant confidentially, and final datasets are accessible by approved study staff.

Authors' Contributions

JLB, MF, SCB, and KL handled the concept and design. RC and CP managed the drafting of the manuscript. All authors contributed to the critical revision of the manuscript for important intellectual content. JLB, MF, and FW managed funding. KJK, JH, CP, and OH performed data management. MindCrowd Implementation was handled by MH, MF, and CP. JJG and KJ managed Firefighter Research Liaisons. Granting final approval of the version for publication was managed by all authors.

Conflicts of Interest

FW received grants from external partners that were not related to this project, including Arizona Parks and Trails, Pac-12 Health and Wellbeing Initiative, the Collegiate and Professional Sports Dietetic Organization, FrieslandCampina, Standard Process Inc, Kraft Heinz Company, Unilever Corporation, and FEMA. The other authors have no conflicts of interest to report.

Multimedia Appendix 1
Study consent form.
[DOCX File , 123 KB - resprot_v14i1e67120_app1.docx]

Multimedia Appendix 2
SPIRIT Checklist.
[PDF File (Adobe PDF File), 6578 KB - resprot_v14i1e67120_app2.pdf]

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Abbreviations

CPET: Cardiopulmonary Exercise Test
FCRP: Firefighter Collaborative Research Project
FFCCS: Fire Fighter Cancer Cohort Study
IRB: institutional review board
PFAS: per- and poly-fluoroalkyl substances
PFOA: perfluorooctanoic acid
PFOS: perfluoro octane sulfonate

Edited by T Leung; submitted 02.10.24; peer-reviewed by AM Jung, A Bello, RB Ormond; comments to author 28.11.24; revised version received 09.01.25; accepted 25.02.25; published 16.04.25.

Please cite as:
Conner R, Porter C, Lutrick K, Beitel SC, Hollister J, Healy O, Kern KJ, Wardenaar F, Gulotta JJ, Jack K, Huentelman M, Burgess JL, Furlong M
Interventions to Reduce Serum Per- and Poly-Fluoroalkyl Substances Levels, Improve Cardiovascular Risk Profiles, and Improve Epigenetic Age Acceleration in US Firefighters: Protocol for Randomized Controlled Trial
JMIR Res Protoc 2025;14:e67120
URL: https://www.researchprotocols.org/2025/1/e67120
doi:10.2196/67120
PMID:

Protocol

Internet-Based Dementia Prevention Intervention (DementiaRisk): Protocol for a Randomized Controlled Trial and Knowledge Translation

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Abstract

Background: Research has shown that engaging in a range of healthy lifestyles or behavioral factors can help reduce the risk of developing dementia. Improved knowledge of modifiable risk factors for dementia may help engage people to reduce their risk, with beneficial impacts on individual and public health. Moreover, many guidelines emphasize the importance of providing education and web-based resources for dementia prevention. Internet-based interventions may be effective, but few have been studied rigorously or widely disseminated. We created DementiaRisk, an award-winning, web- and email-based education platform for the public focused on modifiable risk factors, featuring multimedia e-learning and email "microlearning" content, to help raise awareness and improve knowledge of actions to reduce dementia risk.

Objective: This protocol describes a randomized controlled trial to (1) evaluate whether exposure to DementiaRisk changes knowledge of dementia risk factors, intention to engage in risk reduction activities, and health behaviors related to dementia risk reduction and to (2) explore qualitative aspects including participants' engagement and satisfaction with the intervention and barriers and facilitators to use.

Methods: Using a sequential explanatory mixed methods design, this study conducts a quantitative analysis followed by a qualitative inquiry to evaluate outcomes and feasibility. In total, 485 participants will be recruited on the web and randomly assigned to 2 groups: one accessing DementiaRisk and the other receiving alternative e-learning on mild cognitive impairment. Assessments will be delivered on the web at baseline (T1), at 4 weeks (T2), and at 2 months after the intervention (T3). Knowledge will be assessed using items from the Dementia Knowledge Assessment Scale, intentions to engage in risk reduction activities will be assessed using items in line with current evidence, and health behaviors related to dementia risk reduction will be assessed using items from the Godin-Shephard Leisure Time Physical Activity Questionnaire along with additional questions related to a range of health status domains. Outcomes and feasibility will be assessed using the Information Assessment Method for patients and consumers. A linear mixed effects model will be used to examine the relationship between each outcome score by group and time point.

Results: This study was approved by the Hamilton Integrated Research Ethics Board on August 24, 2022 (project ID 14886) and received funding in February 2023. Recruitment took place from March 28, 2023, to April 28, 2023, with the final participants completing the intervention by August 18, 2023. Analyses and interpretation of data are ongoing.

Conclusions: DementiaRisk is a readily scalable, technology-enhanced solution for dementia prevention education. It has been designed using evidence-based principles of multimedia learning. It has the potential to scale and spread widely using the open internet, so it may be able to reach a wider audience than traditional in-person educational interventions.

Trial Registration: ClinicalTrials.gov NCT05383118; https://clinicaltrials.gov/study/NCT05383118

International Registered Report Identifier (IRRID): DERR1-10.2196/64718

(JMIR Res Protoc 2025;14:e64718) doi:10.2196/64718

KEYWORDS

web-based intervention; internet; eHealth; dementia risk; dementia prevention; Alzheimer disease; education and training; clinical trial; knowledge translation; public health; health literacy; e-learning

Introduction

Background

Developing a better understanding of how dementia can be prevented and sharing information about how Canadian people can reduce their risk of developing dementia or delay its onset are critical to keeping Canadian people healthy and improving their quality of life. The Landmark Study, which developed evidence-based data modeling to demonstrate the impacts of improving risk reduction efforts to delay onset across the population, suggests that a delay of 1 year could result in nearly 500,000 fewer cases of dementia by 2050 [1]. Additionally, if dementia prevention efforts can delay the onset of dementia by 10 years, then over 4 million new cases of dementia could be avoided by 2050 [1]. Web-based learning about the promotion of brain health is a readily scalable, technology-enhanced solution for dementia risk prevention education. Web-based learning has the potential to reach a wider number of audiences with modifiable risk factors for dementia than traditional face-to-face interventions.

While there have been studies of web-based health information on intentions and behavior change, most of those studies have looked at text-based health information rather than internet-based interventions that have incorporated best practices in instructional design for e-learning. Most of the web-based content about modifying dementia risk factors currently is text based, such as static web pages or pamphlets or booklets. Of the few multimedia e-learning courses available, some require a substantial commitment (eg, weeks long), are synchronous (ie, require real-time participation), are associated with a commercial entity or product for sale, or have a cost associated with them. During the design of our intervention, we could not find any instructionally designed, evidence-based, multimedia e-learning content about dementia risk reduction available in Canada in both languages (English and French). Moreover, very few educational interventions related to dementia risk reduction have been rigorously studied using methods such as randomized controlled trials (RCTs).

While multidomain interventions have been shown to be effective [2], our study will complement those types of more intense, in-person components with a view to expanding awareness of modifiable risk factors to the general population. In addition, while text-based information about risk factors is widely available, DementiaRisk [3]—our instructionally designed, multimedia intervention—is designed to share this knowledge broadly in a way that can improve the understanding of Canadian people. Many interventions about dementia are designed specifically for older adults. However, the development of dementia can begin as early as 20 years before symptom onset or diagnosis [4], so we will be targeting the intervention to all Canadian people of 18 years and older of age to reduce the risk of dementia as early as possible.

A recent EKOS dementia public opinion survey highlighted that there are still many important gaps in the knowledge of Canadian people about dementia risk factors, with only 37% of respondents knowing the link to chronic conditions that affect brain health, such as hypertension, heart disease, and diabetes [5]. Moreover, just over one-tenth believe that hearing loss can increase the risk of developing dementia; and many believe that exposure to toxic chemicals is a risk factor, despite lack of evidence [5].

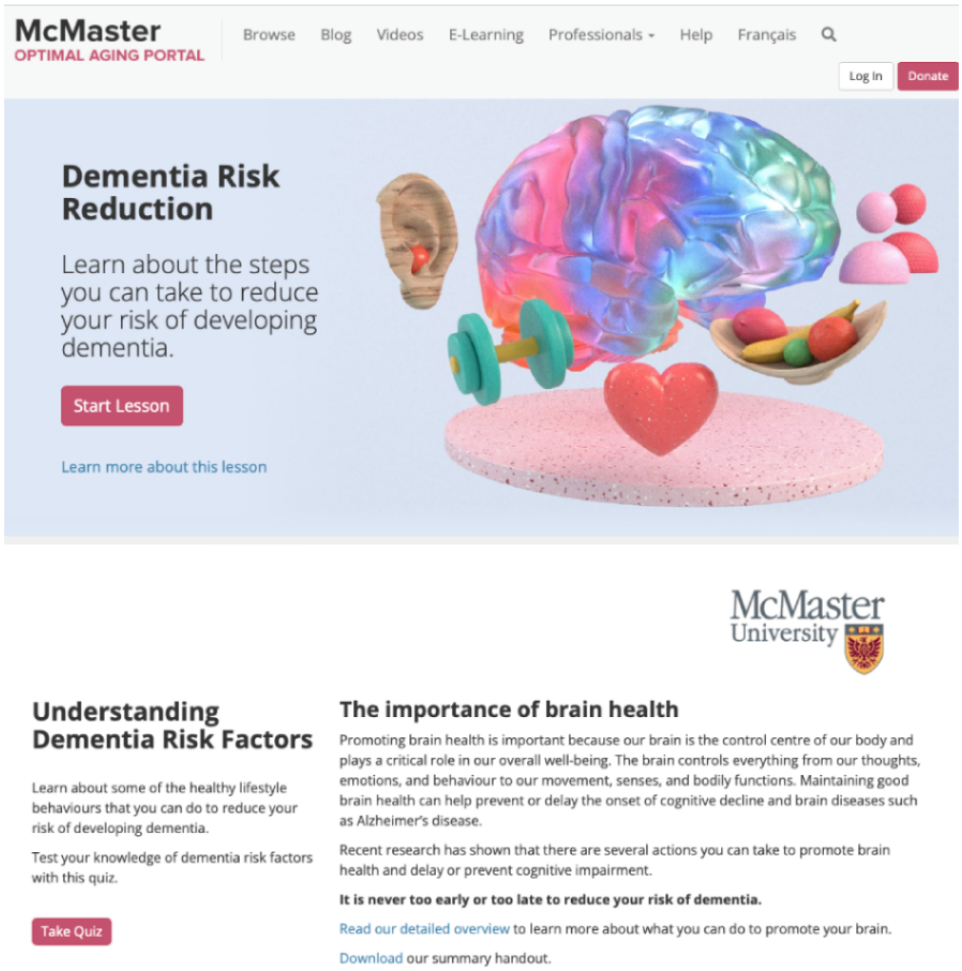
e-Learning Instructional Design

DementiaRisk (Figure 1), when compared to other web-based content, is unique because it uses best practices in multimedia e-learning instructional design, is open-access, and includes asynchronous e-learning with email-based microlearning. To our knowledge, it is also the only asynchronous multimedia e-learning dementia education program with French translation available. Key components of the instructional design include the use of the principles of multimedia learning and audio narration; personalization, including the use of a web-based "coach" or embodied instructional agent; segmenting the content into manageable topics to reduce cognitive load; authentic scenarios and worked examples; review questions; and learner control over navigation [6]. An iterative, participatory instructional design and development methodology—the successive approximation method [7]—was used, with extensive involvement and review from a range of experts in dementia care, including care partners.

In this study protocol, we describe a sequential explanatory mixed methods design RCT comparing the efficacy of DementiaRisk, a high-quality, web- and email-based dementia risk reduction education platform that includes asynchronous multimedia e-learning and email-based "microlearning" content, to our alternative web-based learning program on mild cognitive impairment. This study will be an important contribution to the literature on improving knowledge of dementia risk factors through web-based interventions. These innovations are an important complement to traditional approaches to dementia and brain health education, a key component of quality dementia

care and public health policy. This is the first research study of the effectiveness of DementiaRisk.

Figure 1. DementiaRisk home page.



Research Aim

The overall aim of this study is to explore if and how our dementia risk reduction e-learning influences participants' knowledge, intentions, and health behaviors related to dementia risk factors.

Specific Objectives

The specific objectives of this study are (1) to evaluate whether exposure to the e-learning intervention changes knowledge of dementia risk factors, intention to engage in risk reduction activities, and health behaviors related to dementia risk reduction and (2) to explore qualitative aspects such as participants' engagement and satisfaction with the intervention, as well as barriers and facilitators to use, through surveys.

Research Questions

This study aims to answer the following research questions: (1) Does DementiaRisk increase knowledge of dementia risk factors? (2) Does DementiaRisk increase intentions to engage in risk reduction activities? (3) Does DementiaRisk increase health behaviors related to dementia risk reduction? and (4) Are participants engaged and satisfied with DementiaRisk?

Methods

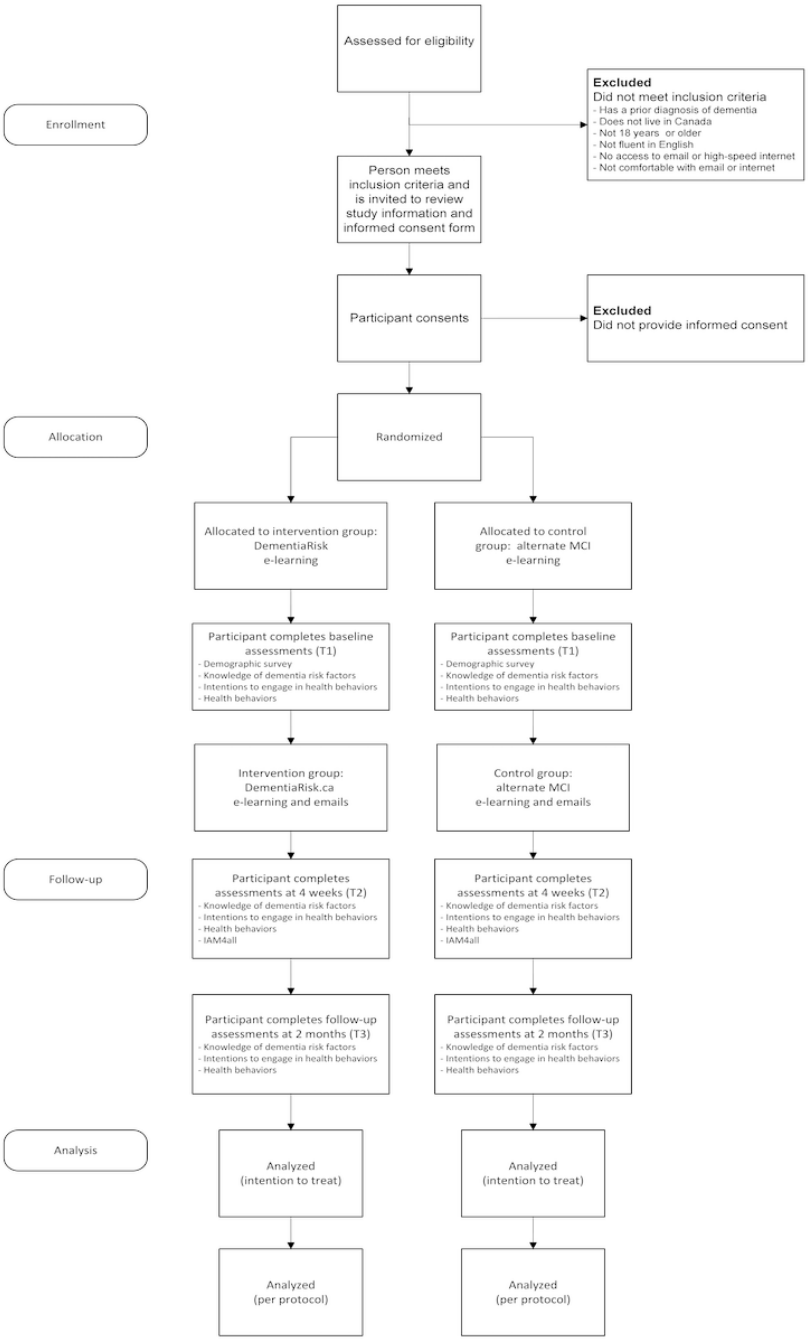
Study Design

A sequential, explanatory, mixed methods design RCT will be conducted to test the effectiveness of DementiaRisk on increasing knowledge, intentions, and behavior change related to modifiable risk factors of dementia. Participants will receive assessments at the following time points: baseline (T1), at 4 weeks (T2), and at 2 months after the intervention (T3; Figure 2). This specific research design offers a valuable approach because it strategically combines the strengths of both quantitative and qualitative research methods.

The underlying philosophy guiding this mixed methods approach is pragmatism, which emphasizes the practical application of research to address real-world problems [8]. This philosophical approach encourages the use of both quantitative and qualitative methods, allowing for more flexibility from other methodological constraints. This flexibility is particularly advantageous in mixed methods research, as it allows us to adapt our approach to capture unexpected findings that may emerge during the study [9]. By incorporating both quantitative and qualitative data, we can gain a more comprehensive and nuanced understanding of the relationship between

DementiaRisk and impacts on knowledge, intentions, and behavior change.

Figure 2. Participant flow through the study. MCI: mild cognitive impairment. For a higher-resolution version of this figure, see Multimedia Appendix 1.



Participants, Setting, and Procedure

Overview

Participants will be recruited using AskingCanadians, a paid panel service that can find representative Canadian participants, including those at increased risk of dementia. AskingCanadians was established in 2005 as a web-based data collection firm, which now allows for access to over 1 million Canadian consumers. The panel will send a copy of our recruitment email to their network where interested participants will be redirected to a survey to identify their eligibility. We will ensure a representative sample of diverse participants with key nonmodifiable and modifiable risk factors for dementia, including a greater percentage of women, some participants with lower level of education, and other risk factors such as hearing impairment, hypertension, smoking, alcohol consumption, and others.

Inclusion and Exclusion Criteria

Participants are eligible to participate, if they meet the following self-reported inclusion criteria: (1) they do not have a prior diagnosis of dementia, (2) they reside in Canada, (3) they are 18 years and older of age, (4) they have a good command of the English language, (5) they have access to email and high-speed internet, (6) they are comfortable using email and

internet, and (7) they have the ability to grant web-based informed consent. Participants are not eligible to participate if (1) they have a prior diagnosis of dementia, (2) they do not reside in Canada, (3) they are not 18 years and older of age, (4) they do not have a good command of the English language, (5) they do not have access to email and high-speed internet, (6) they are not comfortable using email and internet, and (7) they do not have the ability to grant web-based informed consent. Eligibility screening, informed consent, and surveys will be conducted entirely on the web.

Randomization and Allocation Concealment

Participants will be randomized and directed to their assigned group after submitting web-based informed consent using the Division of e-Learning Innovation's research platform. Participants will be randomized using a permuted block stratified randomization, using education and age as the stratification variables. Our stratified block randomization approach will be based on the following components: (1) level of education: we will stratify participants based on educational background or highest level of education completed: "high school or equivalent," "some college or university," and "college or university graduate or graduate degree" and (2) age: we will stratify participants based on ages: "younger than 45 years," "45-65 years," and "older than 65 years."

To ensure a balance between the intervention and the control groups, we will use stratified block randomization with variable block sizes of 4, 6, and 8 (randomly arranged) in a ratio of 1:1. To the best of our ability, efforts will be made to blind participants to their allocation group and study hypotheses. We will ensure that promotional advertisements do not contain logos or direct website links. The informed consent form will not contain the exact outcome measures or the title of the intervention. Allocation concealment will be aided by referring to the intervention as "e-learning related to cognitive impairment and dementia prevention" without biasing participants to study hypotheses or study design.

Sample Size Calculation

Using a conservative estimate of a small effect size (0.16, from a meta-analysis of internet health behavior change interventions), with a power of 0.80 and α of .05, we require a total of 388 participants in the study [10,11]. To allow for a 25% dropout rate, we aim to recruit 485 individuals [10,11]. These recruitment numbers and strategies have been used successfully in similar knowledge translation intervention studies and are a feasible target, given the use of the paid panel [12].

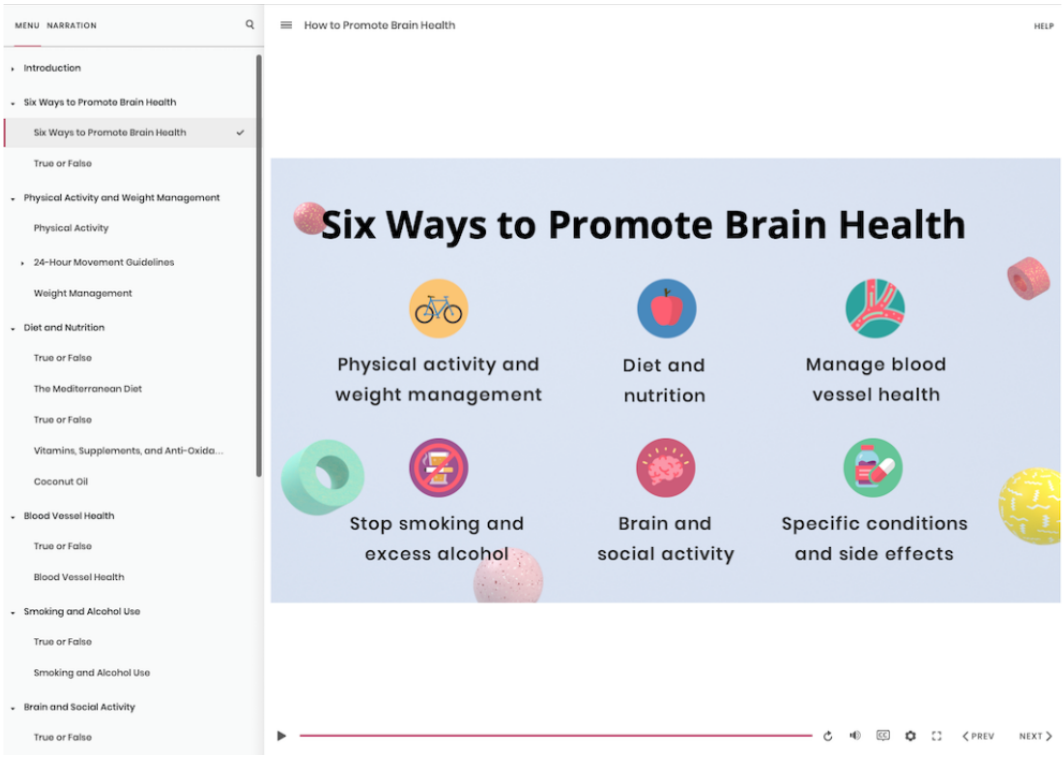
Intervention

Overview

Participants in the intervention group will be provided e-learning about dementia risk reduction and promoting brain health (Figure 3), consisting of the following components: (1) one 35-minute multimedia e-learning lesson on promoting brain health and preventing dementia and (2) a series of 12 "microlearning" emails (3 emails per week) with small segments of content to reinforce the material from the lesson. Participant progress is saved, so they can return to the lesson to complete it at another time. Participants will have 4 weeks to complete the intervention.

The lesson will be delivered through the Division of e-Learning Innovation's learning management system to record participants' access, progress, and completion of the lessons. This allows us to measure the "dose" of educational exposure to the intervention and to provide automated timed reminders to encourage participants to complete the lesson.

Figure 3. DementiaRisk intervention group e-learning lesson.



Microlearning Emails

In addition to the lessons, participants will also receive 3 microlearning emails per week with a small amount of content that reinforces the information from the lessons. This spaced repetition has been shown to benefit knowledge transfer [6]. Content for the emails will be taken directly from the promoting brain health e-learning lesson.

Control Condition

Participants randomized to the control group will be provided e-learning about mild cognitive impairment, consisting of the following components: (1) one 20-minute multimedia e-learning lesson on mild cognitive impairment and (2) a series of 12 "microlearning" emails (3 emails per week) with small segments of content to reinforce material from the lesson.

Outcomes

Overview

Primary and secondary outcomes will be assessed at baseline (T1), at 4 weeks (T2), and at 2 months after the intervention (T3). Qualitative data will be collected at 4 weeks (T2; Multimedia Appendix 2). Participants will access web-based surveys through the password-protected research platform hosted by the Division of e-Learning Innovation. Participants will be required to complete all components of the intervention. Surveys will not be submitted unless the participant completes all questions. Participants will not be able to change their answers after submitting and will not be able to submit multiple attempts.

Primary Outcome

The primary outcome measure of this study is knowledge change related to dementia risk factors. Knowledge of dementia risk factors will be assessed using a custom 15-item multiple-choice assessment aligned with the content of the intervention as well as the risks and health promotion subdomain of the Dementia Knowledge Assessment Scale [13]. Response options are "false," "probably false," "probably true," "true," and "I don't know." The total maximum score for this assessment is 30 (maximum 2 points per question), with higher scores indicating higher levels of knowledge related to dementia risk factors. Individual scoring is as follows: (1) 2 points for answering "true" to a true question, (2) 2 points for answering "false" to a false question, (3) 1 point for answering "probably true" to a true question, (4) 1 point for answering "probably false" to a false question, (5) 0 points for answering "probably false" or "false" to a true question, (6) 0 points for answering "probably true" or "true" to a false question, (7) 0 points for answering "I don't know."

Secondary Outcomes

Secondary outcome measures include (1) intentions to engage in health behaviors in line with evidence will be assessed using a 10-item Likert scale–based survey and a composite score and (2) health behaviors related to behavior change for modifying dementia risk factors will be assessed using the Godin-Shephard Leisure Time Physical Activity Questionnaire along with additional questions related to a range of health status and behavior domains including diet, smoking, alcohol consumption, social activity, traumatic brain injury, blood pressure, depression, air pollution, diabetes, sleep habits, cognitive activity, and hearing to determine a composite score. Where possible, these questions were selected from validated tools (Multimedia Appendix 2). Additional data will be collected on engagement with the web-based intervention throughout the study, including (1) e-learning analytics: progress or completion, login activity, and time on the lesson and (2) email campaign analytics: open rate and click-through rate.

Qualitative Data

Qualitative data will be collected through structured survey questions and open-ended questions. The effectiveness and impact of the intervention will be assessed using the Information Assessment Method for patients and consumers, a validated questionnaire that assesses outcomes of web-based consumer health information [14]. End-of-intervention and poststudy surveys will include open-ended questions to assess participant satisfaction with the intervention, changes in attitudes, beliefs, and behaviors during the study, and feedback on proposed future dissemination methods.

Data Analyses

Overview

All outcome assessors and data analysts will be blinded to participant allocation. The CONSORT (Consolidated Standards of Reporting Trials) extension for randomized pilot and feasibility trials and CONSORT-EHEALTH [15-17] will guide reporting of the study. The 12-item TIDieR (Template for Intervention Description and Replication) checklist was used for the intervention description [18]. Qualitative reporting will adhere to the COREQ (Consolidated Criteria for Reporting Qualitative Studies) [19].

Quantitative Data

All data will be entered into RStudio (version 2022.02.3; Posit PBC) [20-22]. A linear mixed effects model will be used to examine the relationship between total knowledge score and group by time point. The same model will be used to look at health behavior scores and total intention scores. We will look at outcome scores from all 3 time points (baseline [T1], at 4 weeks [T2], and at 2 months after the intervention [T3]). The stratification variables, age and level of education, will be included in all models. Additionally, we will examine possible effect modifiers of age, sex, and education on the relationship between groups and outcomes as well as time point and outcomes. For knowledge scores specifically, we will look at a family history of dementia or having been a care partner of a person living with dementia as a possible effect modifier of the relationship between group and knowledge score and time point and knowledge score. These models will be run for both intention-to-treat and per-protocol participant data.

Qualitative Data

All data will be entered into NVivo (version 14; Lumivero) [23]. Data will undergo a conventional, inductive, content analysis approach [24,25]. Data will be systematically examined by a single analyst; codes and themes will be generated based on the content without relying on preconceived theories. To maintain accuracy and credibility, weekly meetings will be held by the analyst and the research team to discuss developing themes, confirm the coding process, and ensure consistency and depth in the representation of the data.

Ethical Considerations

This study gained Hamilton Integrated Research Ethics Board approval on August 24, 2022 (project ID 14886). Participants were required to provide informed consent and were informed of the length of time of the e-learning, surveys, and email campaign as well as informed about details surrounding data collection, storage, and investigator identities. Participants' identities and confidentiality were maintained throughout the research study. All participant data were deidentified, and all findings will be nonidentifiable. There is no known risk or harm to participating in this study of publicizing its results or findings. Participants were provided with AskingCanadians points that can be redeemed for various gift cards as compensation for participation in the study.

Results

The study received funding in February 2023. Recruitment took place from March 28, 2023, to April 28, 2023, with the final participants completing the intervention by August 18, 2023. Analyses and interpretation of data are ongoing. The analysis is expected to be completed by summer 2024, and the results will be published by winter 2024.

Discussion

Expected Findings

Many Canadian people are not aware of the potential impact of modifiable risk factors with respect to the development of dementia. DementiaRisk represents an important and innovative contribution to consumer health education in the area of promoting brain health and dementia prevention. Specifically, this study aims to explore the impact of DementiaRisk for reducing modifiable risk factors of dementia, specifically through changes in knowledge of dementia risk factors, intention to engage in risk reduction activities, and health behaviors related to dementia risk reduction. Such improvements could contribute to a reduction in the risk of developing dementia, among other benefits [26]. A range of positive effects has been shown for web-based interventions for various target audiences (ie, health care providers and family or friend care partners) on a wide range of outcomes (eg, knowledge, attitudes, burden, stress, and others) [27-34].

Previously, we have shown that e-learning is effective for health professions' learning, and we have also outlined some of the more effective instructional design elements with respect to web-based learning [35,36]. Well-designed e-learning that uses best practices in multimedia such as the use of instructional graphics, audio narration, and personalization has been shown to be more effective than e-learning that does not conform to best-evidence instructional design [6,37]. Interventions delivered through the web have the potential to augment traditional face-to-face or paper-based approaches (so-called "blended delivery"); and web-based interventions may allow for greater access to a multitude of users [34,38], facilitating scale and spread [14,39]. DementiaRisk is based on evidence-based studies of dementia risk factors, including addressing several factors at the same time [2]. In addition to a positive impact on participants in the intervention, we anticipate long-term impacts on the Canadian public as well as a benefit for intervention agents (eg, primary care providers and public health units), given the ease of adoption, "trialability," scale, and spread of DementiaRisk.

Potential Challenges

We anticipate several limitations in this study. First, we anticipate that due to the nature of self-directed web-based interventions, we may encounter higher dropout rates. To mitigate this, we have opted to use AskingCanadians, a paid panel recruitment service that will allow for ensured efficiency of recruitment, potentially higher retention rates, and the ability to attract a diverse and representative sample of Canadian people. Second, many of the instruments for measuring primary and secondary outcomes were custom-created. Although many of the specific survey questions were pulled from validated tools, there is still the possibility that their novelty may influence result validity, which will require cautious interpretation and the use of qualitative data to enrich findings. Third, although the control group will receive e-learning that is related to mild cognitive impairment, and not dementia risk factors, there is the possibility for some contamination or confounding, with some overlap in content domains and the potential for positive outcomes related to the control group content.

Conclusions

Canada's dementia strategy highlights the need to bring awareness to dementia prevention nationally to promote healthy behavior change, in particular, to build the evidence base to inform and promote the adoption of effective risk reduction interventions as well as expand awareness. As the population of older adults living with dementia grows, the demand for high-quality information on dementia prevention is growing as well. Developing a better understanding of how dementia can be prevented and sharing information about how Canadian people can reduce their risk of developing dementia or delay its onset are critical to keeping Canadian people healthy and improving their quality of life. DementiaRisk is a readily scalable, technology-enhanced solution for dementia prevention education. It has the potential to reach a wider number of audiences with modifiable risk factors for dementia than traditional face-to-face interventions.

Acknowledgments

This work was supported by the team at the Division of e-Learning Innovation at McMaster University. Funding was provided by the Public Health Agency of Canada Dementia Strategic Fund. AJL receives support through the John R. Evans Chair in Health Sciences Educational Research and Instructional Development, Faculty of Health Sciences, McMaster University. The authors would like to thank Drs Parminder Raina, Vladimir Khanassov, Wei Wang, Tarek Rajji, and Sid Feldman for their time and participation in this project.

Data Availability

The datasets generated and analyzed during this study can be made available from the corresponding author upon reasonable request.

Authors' Contributions

AJL and SA drafted the original study protocol. AJL, SC, and RW led the intervention. SA drafted the protocol manuscript. All authors have reviewed the manuscript and approved the final version.

Conflicts of Interest

AJL, RS, and McMaster University are co-owners of DementiaRisk.

Multimedia Appendix 1
Participant flow through the study. MCI: mild cognitive impairment.
[PDF File (Adobe PDF File), 59 KB - resprot_v14i1e64718_app1.pdf]

Multimedia Appendix 2
Outcomes questionnaire questions.
[DOCX File , 21 KB - resprot_v14i1e64718_app2.docx]

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Abbreviations

CONSORT: Consolidated Standards of Reporting Trials
COREQ: Consolidated Criteria for Reporting Qualitative Studies
RCT: randomized controlled trial
TIDieR: Template for Intervention Description and Replication

Edited by A Schwartz; submitted 21.08.24; this is a non–peer-reviewed article;accepted 25.11.24; published 27.01.25.

Please cite as:
Levinson AJ, Ayers S, Clark S, Woodburn R, Dobbins M, Duarte D, Grad R, Kates N, Marr S, Oliver D, Papaioannou A, Saperson K, Siu H, Strudwick G, Sztramko R, Neil-Sztramko S
Internet-Based Dementia Prevention Intervention (DementiaRisk): Protocol for a Randomized Controlled Trial and Knowledge Translation
JMIR Res Protoc 2025;14:e64718
URL: https://www.researchprotocols.org/2025/1/e64718
doi:10.2196/64718
PMID:

Protocol

An mHealth Intervention With Financial Incentives to Promote Smoking Cessation and Physical Activity Among Black Adults: Protocol for a Feasibility Randomized Controlled Trial

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Abstract

Background: Black adults in the United States experience disproportionately high rates of tobacco- and obesity-related diseases, driven in part by disparities in smoking cessation and physical activity. Smartphone-based interventions with financial incentives offer a scalable solution to address these health disparities.

Objective: This study aims to assess the feasibility and preliminary efficacy of a mobile health intervention that provides financial incentives for smoking cessation and physical activity among Black adults.

Methods: A total of 60 Black adults who smoke (≥5 cigarettes/d) and are insufficiently physically active (engaging in <150 min of weekly moderate-intensity physical activity) will be randomly assigned to either HealthyCells intervention (incentives for smoking abstinence only) or HealthyCells+ intervention (incentives for both smoking abstinence and daily step counts). Participants will use study-provided smartphones, smartwatches, and carbon monoxide monitors for 9 weeks (1 wk prequit date through 8 wk postquit date). Feasibility will be evaluated based on recruitment rates, retention, and engagement. The primary outcomes include carbon monoxide–verified, 7-day smoking abstinence at 8 weeks postquit date and changes in average daily step count. Feasibility benchmarks include a recruitment rate of ≥5 participants per month, a retention rate of ≥75%, and a smoking abstinence rate of ≥20% at 8 weeks postquit date. Expected increases in physical activity include a net gain of 500 to 1500 steps per day compared to baseline.

Results: Recruitment is expected to begin in February 2025 and conclude by September 2025, with data analysis completed by October 2025.

Conclusions: This study will evaluate the feasibility of a culturally tailored mobile health intervention combining financial incentives for smoking cessation and physical activity promotion. Findings will inform the design of larger-scale trials to address health disparities through scalable, technology-based approaches.

Trial Registration: ClinicalTrials.gov NCT05188287; https://clinicaltrials.gov/ct2/show/NCT05188287

International Registered Report Identifier (IRRID): PRR1-10.2196/69771

(JMIR Res Protoc 2025;14:e69771) doi:10.2196/69771

KEYWORDS

African American; Black; mobile health; mHealth; smartphone app; smoking cessation; physical activity, mobile phone

Introduction

Background

In the United States, tobacco- and obesity-related diseases are among the top 10 leading causes of death in the Black and African American (henceforth Black) population, and these diseases are more common and deadlier among Black adults compared with the overall US population [1-3]. For example, while smoking prevalence is similar among Black and White adults, Black adults are less likely to quit smoking than other racial and ethnic groups [4-6], and rates of lung cancer incidence and mortality are higher among Black male individuals than White male individuals [3]. Likewise, the Black population has high rates of obesity in the United States [7]. Physical inactivity (ie, no physical activity outside of work during the past month), a leading cause of obesity [8,9], is higher among Black adults compared with most other racial groups [8,9]. High rates of smoking (14.2%) [10] and insufficient physical activity (30%) [11] among Black adults are important modifiable health risk factors for cancer and chronic illness [12]. Interventions that simultaneously address these behaviors may promote holistic lifestyle changes, provide significant health benefits, and increase health equity within the Black population [13,14].

Multiple health behavior change (MHBC) interventions are defined as those that promote 2 or more health behaviors and thus have a more comprehensive focus on lifestyle health promotion [15,16]. Smoking and low physical activity are strong candidates for these interventions because people who smoke generally report less physical activity than those who do not smoke [17], and individuals may benefit from replacing smoking with physical activity during a quit attempt [18]. Importantly, engaging in physical activity may increase self-efficacy for quitting and alleviate cigarette cravings during withdrawal [19-22]. Physical activity also improves mood and reduces stress, which are common triggers for smoking relapse [23]. However, numerous studies have shown mixed results regarding the physical activity's effectiveness for smoking cessation [24], in part because adherence to physical activity varies significantly across individuals [23,25,26], with stronger adherence among adults with existing physical activity habits and strong social support, and the type of activity (eg, low-intensity activity vs high-intensity activity) [27].

Low-intensity activities, such as walking, may be more practical and palatable for people trying to quit smoking while still offering benefits for smoking cessation, such as reduced cravings and stress relief [13,19,28]. Low-intensity activities may also promote greater adherence to physical activity because they are accessible, comfortable, and less likely to cause fatigue or injury than high-intensity workouts [29]. Furthermore, low-intensity activities can be included in daily routines, such as walking to a bus stop or church [30]. The inclusivity and ease of low-intensity physical activity may encourage long-term engagement and consistency. Thus, combining low-intensity physical activity with other cessation strategies may synergistically increase the likelihood of smoking cessation and have a greater impact on overall health.

Contingency management (CM) is a simple, powerful, and widely used behavioral strategy where tangible rewards are offered for meeting a prespecified behavior change goal [31-33]. CM is efficacious for improving smoking cessation and physical activity [34-38], but common concerns about CM are intervention costs and maintenance of long-term behavior change once incentives cease [39]. Yet, recent research on smoking and physical activity has shown that CM interventions are cost-effective, and even small financial incentives can lead to long-term changes in smoking and physical activity after incentives are withdrawn [34-38]. Thus, an MHBC intervention that incentivizes behavior change could help Black adults initiate and sustain smoking cessation and adequate physical activity in conjunction with other recommended tobacco treatment components (ie, counseling and pharmacotherapy) [40].

Despite the rapid growth of mobile health (mHealth) technologies, such as smartphone apps, that offer new opportunities to reach and treat at-risk populations, Black adults remain underrepresented in mHealth research [41]. As of 2024, 84% of the Black population owned a smartphone [42]; therefore, app-based interventions have the potential to increase the reach and use of effective treatments for smoking and physical activity within this population. Furthermore, apps combined with sensors and wearables can be powerful tools for self-regulation [42], which is a core component of behavior change [43], and can provide frequent feedback and engagement opportunities. Initial evidence suggests that app-based interventions may be a useful supplement to more intensive behavioral or pharmacological treatments and may even show comparable outcomes to traditional face-to-face interventions in some cases [44-47]. Furthermore, smartphone apps can be used to characterize the behaviors, needs, and outcomes of traditionally understudied and underserved groups.

Research indicates that interventions incorporating culturally relevant content resonate with Black adults, enhancing their motivation and commitment to behavior change [48-53]. Such content has increasingly been incorporated into mHealth interventions targeting smoking cessation and physical activity among Black adults [54-57]. Drawing from publicly available resources such as *Pathways to Freedom*—a short documentary highlighting the historical and cultural ties between the Black community and tobacco use and incorporating health education and culturally relevant messages to motivate Black adults to quit smoking [48,49]—mHealth apps can provide educational content on the historical and social influences of smoking within the Black community. mHealth apps can also provide motivational messages and stress-management techniques grounded in culturally relevant themes, such as prayer and seeking support from family and friends. Furthermore, app-based interventions can deliver education about the purpose and benefits of nicotine replacement therapy (NRT) and debunk myths and misconceptions about NRT that are present in this population [58-60]. Apps can also make it easier for Black adults to create activity goals that reflect their current life circumstances and environment [61,62], and these goals can be adjusted dynamically based on daily performance and feedback, ensuring that goals remain challenging yet attainable. This content can be presented alongside success stories from notable

and relatable Black figures to provide additional motivational support [63-65]. Altogether, when delivered with evidence-based treatment for smoking cessation and physical activity, culturally relevant content may reinforce the quit journey and help address common challenges that Black adults face when quitting smoking and engaging in physical activity.

Objectives

The purpose of this project is to explore the feasibility of an app-based MHBC intervention (HealthyCells) for Black adults who smoke and are insufficiently physically active. In addition to evidence-based tobacco cessation treatment [66], HealthyCells will incentivize daily smoking abstinence, while an enhanced version of the intervention, HealthyCells+, will also include incentives for meeting physical activity goals [36,67]. The inclusion of 2 active study conditions allows for a direct comparison to evaluate the added benefit of financial incentives for physical activity. The central hypothesis is that participants in the HealthyCells+ group will demonstrate greater increases in daily physical activity (measured via step counts) and improved smoking abstinence rates compared to those receiving smoking cessation incentives alone (HealthyCells). HealthyCells will also include an interactive educational e-book experience inspired by the documentary *Pathways to Freedom* [48,49], designed to guide individuals during their quit attempt and provide opportunities to set personalized activity goals, which can be dynamically adjusted daily to reflect current readiness. The primary aim will be to demonstrate intervention feasibility, including recruitment, retention, and adherence metrics, along with rates of carbon monoxide (CO)–verified smoking abstinence and prequit and postquit changes in physical activity.

Methods

Overview

Black adults who smoke and are insufficiently physically active (ie, not meeting physical activity guidelines) [68] will be randomly assigned to 1 of the 2 versions of an MHBC intervention that targets smoking cessation and insufficient physical activity: (1) HealthyCells (incentives for smoking abstinence only) or (2) HealthyCells+ (incentives for both smoking abstinence and physical activity). Both groups will receive a comprehensive tobacco treatment intervention, including 8 weeks of NRT, an initial counseling session to create a quit plan, and 5 weekly counseling sessions (6 sessions in total). Likewise, all participants will receive a study-provided smartphone and intervention app, a Samsung smartwatch to measure daily steps, and a Bedfont iCOquit Smokerlyzer to verify smoking status. Participants will be asked to use their assigned app and equipment for 9 weeks (1 wk prequit date through the eighth wk postquit date).

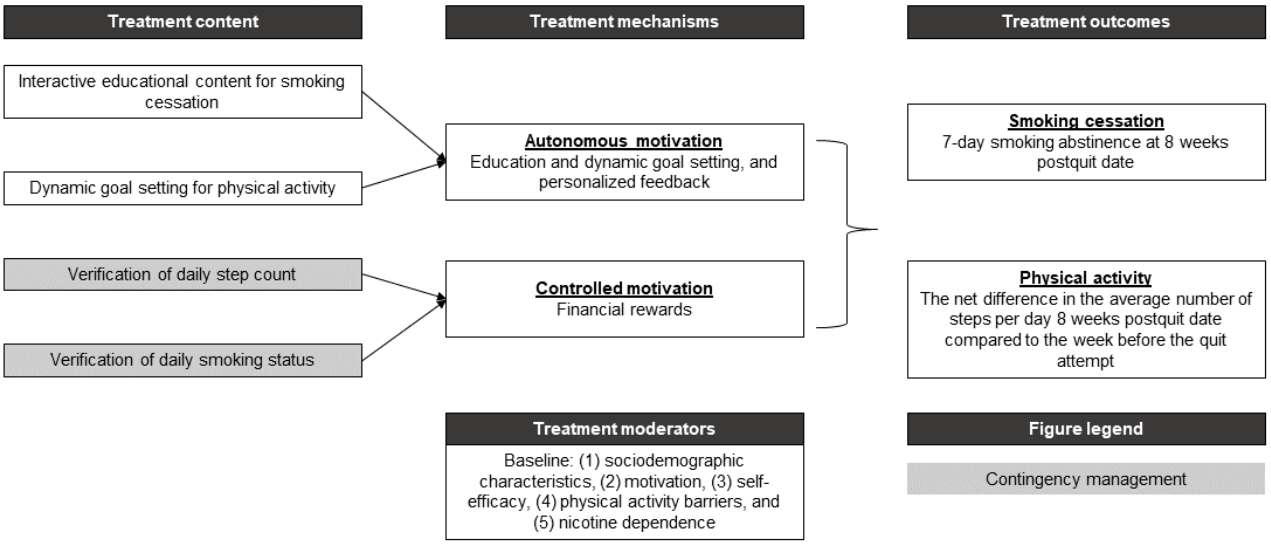
Ethical Considerations

This study was approved by the institutional review board of the University of Oklahoma Health Sciences Center (protocol #14094), and the study was registered at ClinicalTrials.gov (NCT05188287). All procedures involving human participants will adhere to the Declaration of Helsinki and relevant institutional guidelines. Written informed consent will be obtained digitally from all participants before enrollment, and they will be informed of their right to withdraw from the study at any time without penalty. To ensure privacy and confidentiality, participant data will be deidentified and stored on a secure, password-protected server. All breath sample photos and step count uploads will be encrypted, with access restricted to authorized research personnel. Following a structured and transparent payment schedule, participants will receive compensation based on their engagement with study activities, including breath sample submissions, step count verifications, surveys, and interviews (refer to the Study Compensation section). To protect participant privacy, all devices used for data collection, including Samsung smartphones and smartwatches, will be reset to factory settings after study participation has ended for each participant. Any adverse events or deviations from the protocol will be promptly reported to the institutional review board in compliance with ethical oversight requirements.

Theoretical Framework

As shown in Figure 1, this intervention will be guided by self-determination theory principles [69-72]. Self-determination theory posits that two forms of motivation are involved in behavior change: (1) autonomous motivation and (2) controlled motivation [72]. Autonomous motivation consists of engaging in behavior out of curiosity, interest, a sense of challenge, or for its inherent enjoyment. Conversely, controlled motivation involves engaging in a behavior because of external rewards or punishment avoidance [72]. Autonomous motivation is associated with sustained behavior change, whereas controlled motivation is related to temporary change [73]. CM interventions provide financial rewards for immediate behavior change, primarily targeting controlled motivation [74].

Figure 1. The theoretical framework of HealthyCells app, a multiple health behavior change intervention for smoking cessation and physical activity.



Incentives can be paired with resources and activities that cultivate autonomous motivation to sustain long-term behavior change [75]. The research team created an interactive educational e-book experience inspired by *Pathways to Freedom* [48,49] intervention that focuses on several key topics highlighted in Textbox 1, such as the harms of smoking, tobacco marketing, NRT education, and stress management, and includes narratives from several prominent Black individuals who have struggled with smoking, such as the former US President Barack Obama [76]. The research team also developed a personalized activity goal algorithm based on findings from mHealth physical activity interventions [54,77] and qualitative interviews with Black adults [61,78].

Textbox 1. Overview of topics covered in the HealthyCells, Healthy Habit e-book.

Chapters and interactive educational content

- Chapter 1: discusses health and economic harms caused by smoking and the benefits after quitting
- Chapter 2: covers the hidden history of Black adults and the tobacco industry
- Chapter 3: describes how habits are created and why smoking is one of the deadliest habits to break
- Chapter 4: provides an overview of how nicotine reinforces the smoking habit
- Chapter 5: reviews the purpose and benefits of nicotine replacement therapy

Inclusion and Exclusion Criteria

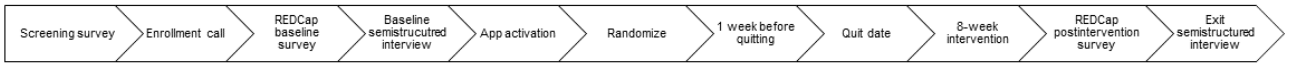
Inclusion criteria for the participants will be as follows: (1) resident of Oklahoma (verified via driver's license or ID); (2) aged ≥18 years; (3) self-identify as *Black* or *African American*, either alone or in combination with other races or Hispanic ethnicity; (4) smoke ≥5 cigarettes or cigarette equivalents per day (ie, cigars and cigarillos); (5) currently (per self-report) engage in <150 minutes of moderate-intensity aerobic physical activity or <75 minutes of vigorous-intensity aerobic physical activity per week [68]; (6) willing to use NRT, a smartwatch, or the study app and able to attend smoking cessation counseling; (7) willing to quit smoking within the next 3 weeks; and (8) exhaled CO level of >6 ppm at app activation.

Exclusion criteria for the participants will be as follows: (1) unwilling to complete the screening survey, (2) unable to understand or speak English, (3) not a US citizen or permanent resident (due to university taxation policies), (4) unwilling to provide social security number, US residency status, or university employee status (to adhere to university reporting requirements), (5) unwilling to abstain from smoking marijuana or cannabis during their quit attempt, (6) unwilling to provide a picture of a tobacco product (to provide initial evidence of current smoking), (7) medical condition (per self-report) that is a potential contraindication for NRT use (eg, uncontrolled hypertension, heart disease, or recent heart attack), or (8) has had a severe allergic reaction or side effect from the use of NRT.

Recruitment

Participants will be remotely recruited and enrolled. No in-person visits are required (Figure 2). Eligible individuals will be identified through the Tobacco Treatment Research Program [79], which offers free tobacco cessation support to adult Oklahomans and assists with study recruitment [38,80-82]. Prospective participants will also be contacted by SMS text messages, email, and phone, and recruitment flyers will be posted in community locations (eg, barbershops and churches) and on social media through a geotargeted campaign focused on Black adults who smoke. Those interested can access a brief web-based eligibility screener via a QR code or direct link.

Figure 2. Participant flow. REDCap: Research Electronic Data Capture.



Study Enrollment

Study staff will contact via phone adults who meet preliminary eligibility to confirm eligibility and discuss study participation. To prevent fraudulent enrollments [83,84], participants will be asked to provide a photo of their driver's license or ID (or other proof of address) and an image of a personal tobacco product to provide initial evidence of smoking status. Eligible and willing participants will be informed about the study and asked to acknowledge their consent with a digital signature. Following enrollment, participants will complete a baseline survey via REDCap (Research Electronic Data Capture; Vanderbilt University) [85] (refer to Multimedia Appendix 1 for a complete list of study measures), and their first semistructured phone interview will be scheduled to discuss their openness to using smartphone apps and to identify potential barriers to mHealth research participation (Table 1). After the interview, participants will receive a welcome packet with study instructions, copies of informed consent, and other signed study documentation, a reloadable Greenphire ClinCard [86], intervention equipment (smartphone, smartwatch, and Bedfont iCOquit Smokerlyzer), and NRT by mail.

Table 1. Overview of qualitative domains covered in each interview.

Domain	Baseline interview	Exit interview
Participation in mHealth[a] research	✓	
Understanding smartphone use and habits	✓	
History of using health apps and Bluetooth-enabled devices	✓	
History of using apps that promote smoking cessation and physical activity	✓	
Understanding preferences for smartphone apps that promote health behavior change within the Black population	✓	✓
History of quitting smoking and the methods used to quit smoking before study participation		✓
Problems with study equipment and smartphone app		✓
Overall impressions of app features		✓
Experiences using smartwatch during study participation		✓
Experiences using NRT[b] during study participation		✓

[a]mHealth: mobile health.

[b]NRT: nicotine replacement therapy.

Upon confirming receipt of the study phone and materials, participants will complete an activation assessment in the study app, independently or with study staff. This will assess their ability to use app features, including viewing images, hearing sounds, reading text, and using the Bedfont iCOquit Smokerlyzer. Participants with an expired breath CO <6 ppm or who cannot use the Bedfont iCOquit Smokerlyzer will be withdrawn before randomization and asked to return the study phone and smartwatch. Participants can keep the NRT and Bedfont iCOquit Smokerlyzer to support their quit attempt and will be transferred to the Tobacco Treatment Research Program for cessation services. Participants who pass the activation assessment will be randomly assigned to the HealthyCells or HealthyCells+ intervention.

Study Randomization

Participants will be stratified according to self-reported sedentary time at baseline (high: >8 h/d, medium: 4-8 h/d, and low: <4 h/d) assessed via the International Physical Activity Questionnaire [87]. Participants (n=60) will be randomized 1:1 in REDCap [85], and research staff will text each new participant a unique code (HealthyCells: 0101 and HealthyCells+: 0202) to access assigned app content.

Standard Care

All participants will receive standard intensive tobacco treatment [66], beginning with a phone counseling session 1 week before the scheduled quit date and continuing weekly through the fourth week after the quit date. Counseling sessions will cover topics, including creating a quit plan, the health impact of tobacco, stress management, adopting lifestyle changes, developing coping strategies, and relapse prevention. In addition, participants will receive 8 weeks of combination NRT (nicotine patches+gum or lozenges) based on package-recommended dosing tailored to baseline smoking and nicotine dependence levels [88]. The first 4-week supply will be mailed, and participants can request the remaining supply through the study app as needed.

MHBC Intervention: App Development and Pilot Testing

Overview

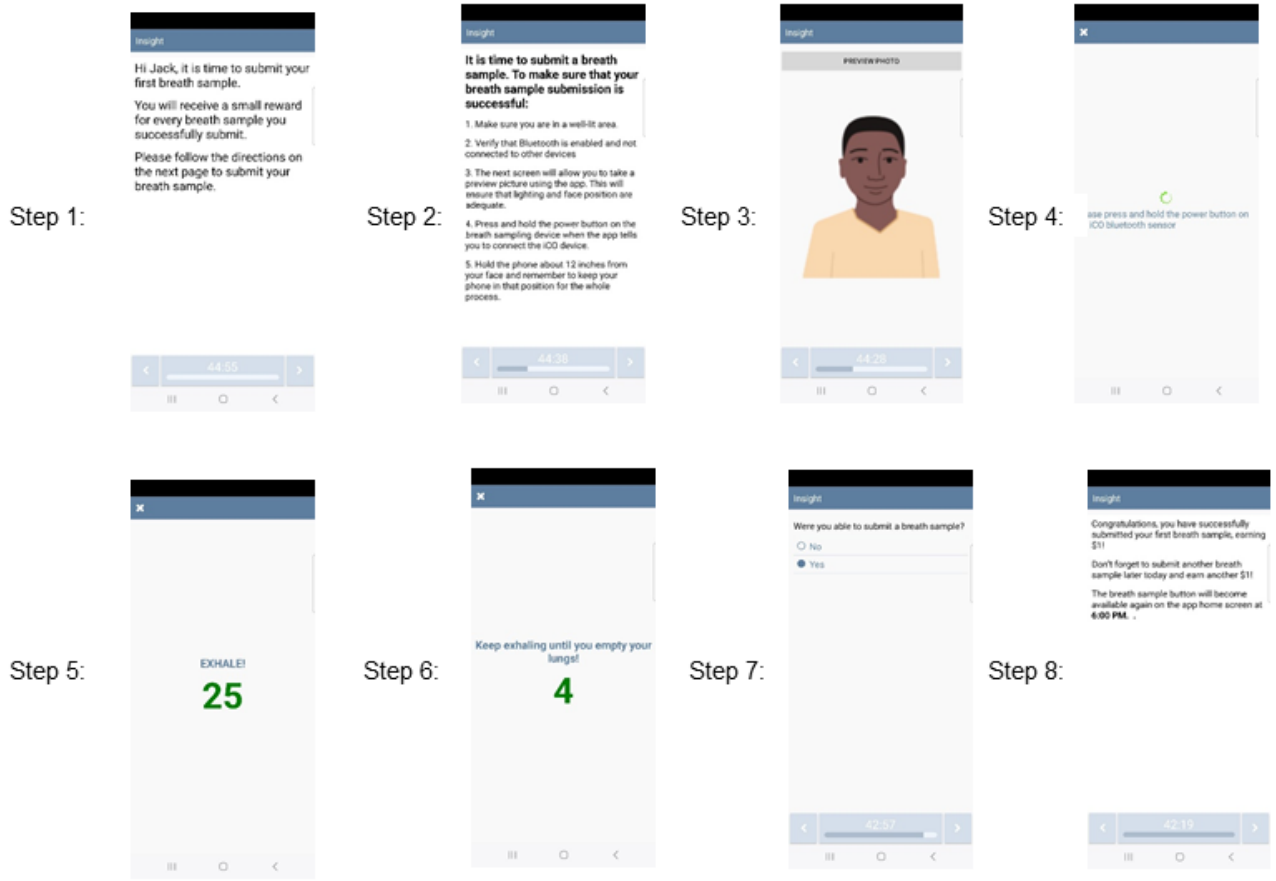
The HealthyCells app was developed using the Insight mHealth Platform [47]. All app content, including breath sample submissions, step count tracking, and interactive educational material, was presented to the African American Cancer Research Community Advisory Board at the Stephenson Cancer Center in November 2024 to solicit community feedback. This meeting was digitally recorded, and the study team reviewed transcripts to identify strengths, weaknesses, and gaps where the app content could be refined. Additional systematic usability testing will be conducted in this feasibility trial to evaluate app engagement, functionality, and acceptability among participants. Findings from this study will inform further refinements to the app in preparation for future large-scale trials to maximize its effectiveness and user experience.

MHBC Intervention: HealthyCells

In addition to all components of standard care described earlier, HealthyCells participants will be able to earn daily financial incentives for CO-verified smoking abstinence each day. Smoking status and identity will be assessed remotely via (1) self-reported daily smoking status, (2) CO breath sample submissions (ie, via the Bedfont iCOquit Smokerlyzer), and (3) Microsoft Azure facial recognition software; each of these assessment types has been successfully integrated into the Insight mHealth Platform [89,90]. Participants will be asked to upload a photo of themselves during the app activation phase, which will be stored as the reference photo for future identity verification. Participants will be instructed to keep their appearance consistent with the baseline photo during breath sample submissions (eg, removing or staying consistent with glasses, hats, and ponytails). During breath sample submissions, 2 photographs will be taken randomly during the exhalation phase to verify identity. Photographs will be encrypted and stored on the study server for later viewing by study staff as needed. A facial recognition mismatch will pause the delivery of incentives and will be flagged for internal review by study staff. Staff will click “thumbs up” or “thumbs down” for an identity match or mismatch, and incentives will be earned on schedule or unearned with incentive levels reset to the starting level.

To earn incentives for smoking abstinence, participants will be instructed to submit 2 breath samples each day (Figure 3). These participant-initiated assessments will appear on the home menu screen, with the first assessment appearing at the beginning of each day (based on participants’ self-reported waking hours) and the second assessment appearing 8 hours after the initial evaluation is completed. Participants will earn US $1 for each breath sample submission regardless of current smoking status. The incentive schedule used in this study is an adaptation of a low-cost incentive schedule the investigators have used in their previous and ongoing work with adults who are socioeconomically disadvantaged [38,89-91]. Participants who demonstrate abstinence (ie, self-reported abstinence that day, CO ≤6 ppm, and identity verification) on both breath sample submissions on their scheduled quit date will receive US $20 to reinforce the initiation of the quit attempt strongly. After that, abstinent participants will be rewarded US $4 per day, increasing by US $0.50 per week until US $5.50 per day is reached during the fourth week postquit date. Participants who are nonabstinent (or who do not provide a sample) will not earn an incentive that day, though they may begin earning incentives for abstinence again the next day. However, the amount will reset to the starting level of US $4 per abstinent day. Participants will earn US $7 per abstinent day during the eighth week postquit date. To gain the maximum incentives for smoking cessation (US $325), participants must report daily smoking abstinence and submit 2 breath samples each day (CO ≤6 ppm) with identity verification during all eligible assessment weeks (ie, wk 1-4 and the eighth wk postquit date).

Figure 3. An example of a breath sample submission to verify smoking status.



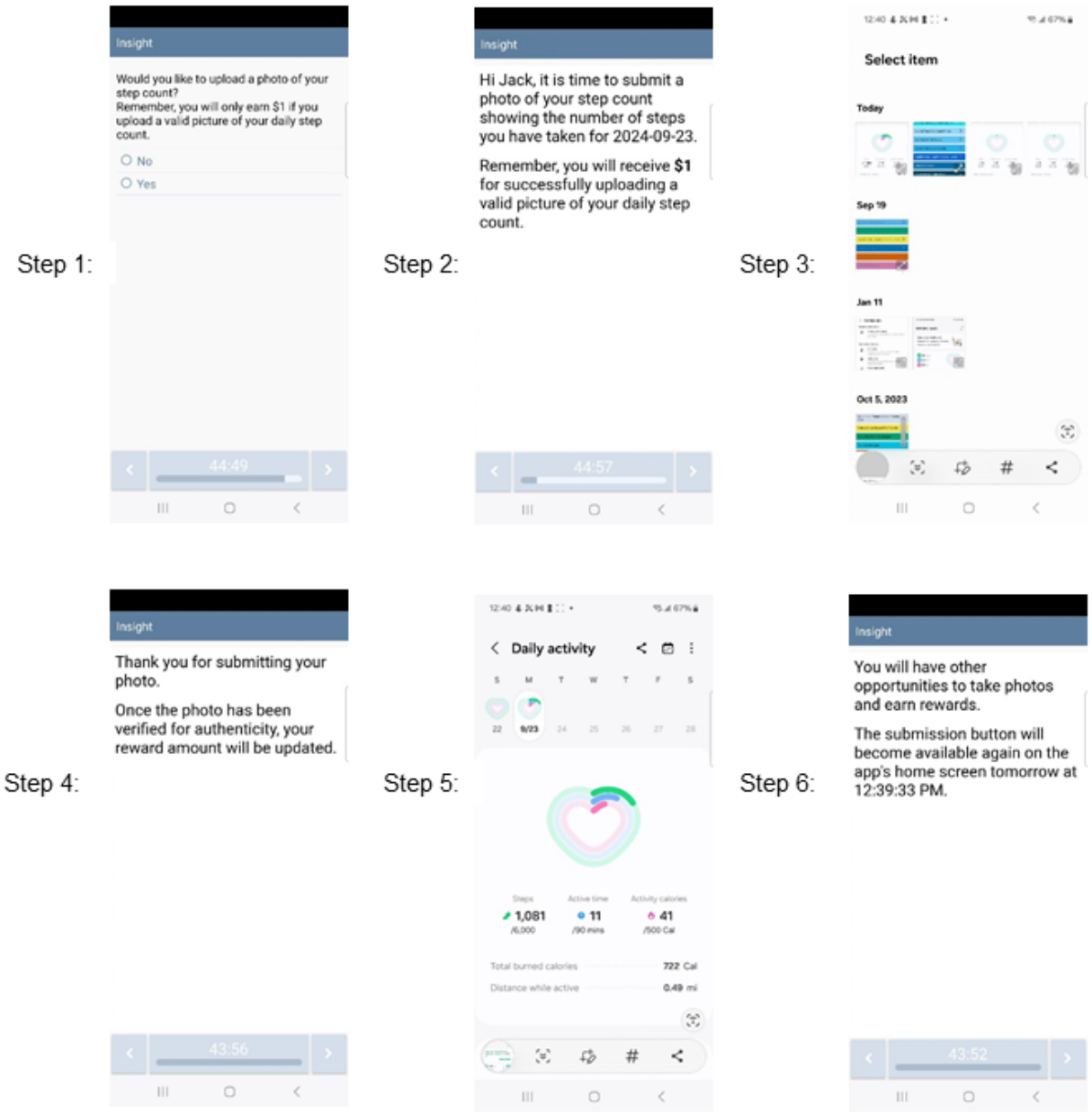
HealthyCells intervention participants will receive a Samsung smartwatch to track their activity and a daily SMS text message about the benefits of increasing physical activity via the app (refer to the Daily Smoking Cessation Progress Report section). They will also have access to content and features that provide strategies for engaging in physical activity to aid their quit attempts (refer to the Set and Review Activity Goals section). However, HealthyCells intervention participants will not receive incentives to increase their physical activity.

MHBC Intervention: HealthyCells+

In addition to the small financial incentives earned for biochemically verified abstinence, HealthyCells+ intervention participants will earn small incentives for increasing physical activity (ie, daily step count) during their quit attempt. Starting on their scheduled quit date, participants will be rewarded US $0.50 per 1000 steps for every step >4000 daily steps, and they will receive a US $2.50 bonus if they walk at least 6000 steps a day. These criteria were set based on research showing Black adults walk about 4000 steps per day on average [92]. Providing incentives above this threshold will ensure the incentive protocol will not reinforce a sedentary lifestyle, and a bonus for meeting the 6000-step per day goal will reinforce higher levels of daily physical activity and greater positive health benefits [92-100]. Participants will not be incentivized beyond 10,000 steps per day, consistent with previous research showing limited additional health benefits [93,95-100]. Therefore, the maximum amount participants can earn per day for daily steps will be US $5.50 (ie, US $3.00 for 10,000 steps +US $2.50 for step goal bonus), an amount that parallels the amount participants can earn at the fourth week postquit date for daily smoking abstinence.

Participants will self-report their daily step count via an assessment on the app home menu at the end of each day (based on self-reported typical time to bed). This assessment will also ask participants to upload a picture of their step count (captured by the smartwatch; Figure 4). To promote compliance, participants will receive US $1 for each successful photo upload (up to 7 submissions/US $7/wk). Participants will not earn incentives for their self-reported step count total if an image is not uploaded. Consistent with the incentive schedule for smoking cessation, participants will earn these incentives for increasing physical activity starting on the scheduled quit date up to 4 weeks postquit date. Incentives may also be earned during the final 7 days of the intervention period (eighth wk postquit date). To gain the maximum incentives for increasing physical activity (US $255.5), participants must submit all step count photos and take 10,000 steps daily during all eligible assessment weeks (ie, wk 1-4 and the eighth wk postquit date).

Figure 4. An example of a valid photo upload of activity data to verify daily step count.



App Features

Overview

Several app features will be available to help participants earn incentives for abstinence and increase physical activity (Table 2 and Figure 5). Multimedia Appendix 2 provides a complete list of features and a detailed description. A summary of each feature is presented in Table 2.

Figure 5. Home screens for HealthyCells (left) and HealthyCells+ (right) apps. NRT: nicotine replacement therapy.

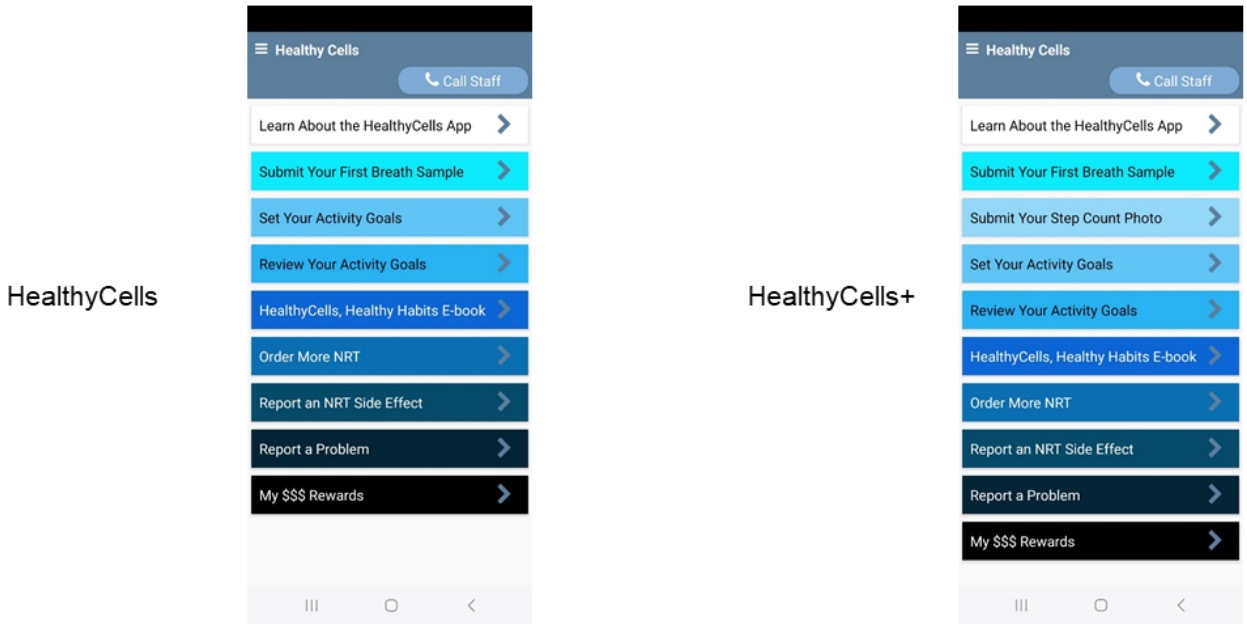


Table 2. Overview of app features.

App features	HealthyCells	HealthyCells+
App Instructions: provide participants with an app overview and study instructions	✓	✓
HealthyCells, Health Habits e-Book: interactive information about smoking and smoking cessation	✓	✓
Breath Sample Submission: submit breath samples using an Bedfont iCOquit Smokerlyzer to verify smoking status and facial recognition software to verify participant identity	✓	✓
Set Activity Goals: set daily steps, active time, and caloric goals	✓	✓
Review Activity Goals: review activity goals and receive feedback to adjust goals for the next day	✓	✓
Submit Step Count Photo: upload an image of activity data for independent verification of step count goals		✓
Report an NRT[a] Side Effect: report side effects from NRT and receive assistance from study staff	✓	✓
Order More NRT: request more NRT during a quit attempt	✓	✓
Track My Rewards: displays the amount of compensation received for completed study assessments	✓	✓
Report a Problem: report a problem with study equipment or assessments	✓	✓

[a]NRT: nicotine replacement therapy.

Learn About the HealthyCells+ App

This feature will be accessible on the home screen at any time during the intervention and will provide an overview of the study apps and instructions for accessing them on their phone.

HealthyCells, Healthy Habits E-Book

Participants can access a short e-book to help them prepare for their upcoming quit attempt. Textbox 1 gives an overview of the topics covered in each chapter. On days 3 to 7 of the prequit week, participants will be informed 1 hour before self-reported typical bedtime about the availability of e-chapters. The entire e-book will be accessible on the home screen at any time after the participant's scheduled quit date.

Set and Review Activity Goals

This feature will be accessible on the home screen at the beginning of each day, allowing participants to set activity goals. If a participant inputs a step goal below the recommended amount needed to receive health benefits or incentives, the app will notify them that they have selected an amount below the recommended threshold. Participants can adjust their goals

before confirming. Once the participant has set their step goal, this feature will be removed from the home menu screen until the next day.

A total of 8 hours after setting their goal, an option to review their progress will appear on the app home screen. Participants self-report their current step count as indicated on their smartwatch, and the app will automatically calculate whether the participant has met their step goal set earlier in the day. The app will ask participants to rate how challenging it was to meet their current step goal, and their feedback will be used to adjust their step goal for the next day. We created a simple algorithm to set new goals based on the participant's response dynamically: if they rate their current step goal as "not challenging," the next day's step goal will increase by 10%; if "just right," it will increase by 5%; and if "very challenging," it will decrease by 10%. For example, if a participant's goal was 6000 steps and they found it "not challenging," their new suggested goal would be 6600 steps. Once they review their activity progress, this feature will be unavailable on the home menu until the following day.

Report an NRT Side Effect

This feature will be accessible on the home screen at any time, and participants can select from a list of side effects associated with NRT that they experienced during the intervention. Only serious reported side effects will be sent to the study staff and research team via an encrypted email.

Order NRT

This feature will be accessible on the home screen at any time, and participants can order up to 4 weeks of additional NRT, which will be sent directly to the participant's current mailing address.

Track My Rewards

Any time during the intervention, participants can track their rewards for submitting breath samples and activity photos (refer to the Study Compensation section) from the app home screen.

Report a Problem

From the app home screen, at any time during the intervention, participants can report any issues they have encountered during study participation via an encrypted email sent directly to the research team.

Return Study Materials

This menu option will appear on the app home screen after the participant has submitted their final breath sample and uploaded the final photo of their smartwatch activity data to verify their step count. Participants can access instructions about returning their study equipment via study-provided shipping materials.

Daily Smoking Cessation Progress Report

Each day during the intervention, participants will receive a notification from their study app 30 minutes after their self-reported wake time to complete a "Daily Smoking Cessation Progress Report." The app will alert participants visually and audibly for 30 seconds, with a 15-minute snooze option available up to 5 times; after the fifth snooze, the assessment will be marked as missed. The assessment provides feedback on whether smoking status assessments were completed during the previous day, and participants will be asked to self-report confidence in using the Bedfont iCOquit Smokerlyzer and facial recognition. Participants will receive a reminder to use nicotine patches and gum or lozenges daily (or as needed). Participants will also be reminded to wear their smartwatch and set daily activity goals. In addition, participants will be asked to respond to 5 questions assessing sleep quality, mood, stress, energy, and focus.

Study Compensation

Participants will earn up to US $650 in the HealthyCells condition and up to US $905.5 in the HealthyCells+ condition by earning incentives and completing various study activities (Table 3). Upon completing the enrollment call (ie, the participant is fully eligible and agrees to join the study), participants will receive US $25. Completing the baseline survey (US $50) and interview (US $50) within 72 hours will qualify them for a US $25 bonus, totaling US $125. During the intervention, participants will earn US $1 per breath sample submitted twice daily, with additional bonuses if both samples indicate smoking abstinence (CO <6 ppm), for a possible total of US $325. HealthyCells+ intervention participants will earn US $1 daily for submitting step count photos, with bonuses for exceeding 4000 steps (up to 10,000 total steps) and meeting a 6000-step goal, potentially totaling US $255.5. Completing the postintervention survey at the end of the intervention will offer US $50 and an additional US $50 for participating in the exit interview. If these 2 activities are completed within 72 hours, participants will earn a US $25 bonus, totaling US $125. Participants who return study materials will receive US $25, with an additional US $25 bonus if returned within 7 business days, totaling US $50.

Payments will be delivered via a reloadable GreenPhire ClinCard [86] once per week, with the first payout occurring after the baseline interview and the final payment after study materials are returned. This structured payment system encourages consistent engagement and ensures the timely return of valuable study materials by tying the final payment to their return. Participants can also track their earnings in real time through the app (refer to the Track My Rewards section), which adds transparency to the process.

Table 3. Compensation amount and payment schedule for completed study activities.

Activity	Compensation (US $)	Bonus condition	Total compensation (US $)	Study condition	
				HealthyCells[a]	HealthyCells+[b]
Study enrollment[c]	25	None	25	✓	✓
Baseline survey	50	Complete both the baseline survey and interview within 72 h (US $25)	Up to 125	✓	✓
Baseline interview	50	Complete both the baseline survey and interview within 72 h (US $25)	Up to 125	✓	✓
Breath sample submission	1 per sample (2 samples/d)	Not smoking when completing breath samples (up to US $20)	Up to 325	✓	✓
Step count photo Submission	1 per photo (1 upload/d)	Per step above 4000 steps (maximum 10,000 steps; US $3); meeting 6000 step goal (US $2.50)	Up to 255.5		✓
Postintervention survey	50	Complete both the postintervention survey and baseline survey within 72 h (US $25)	Up to 125	✓	✓
Exit interview	50	Complete both the postintervention survey and baseline survey within 72 h (US $25)	Up to 125	✓	✓
Return study materials	25	Return study materials within 7 business days (US $25)	Up to 50	✓	✓

[a]The total compensation was up to US $650.

[b]The total compensation was up to US $905.5.

[c]Participants only earn US $25 if they successfully enroll in the study.

Postintervention Assessment and Treatment Outcomes

At the eighth week postquit date, participants will complete a postintervention assessment via REDCap [85], answering questions similar to those in the baseline assessment to track changes in physical and mental health and health behaviors and to assess app impressions (Multimedia Appendix 1). A final semistructured interview will gather feedback on the app and suggestions for improvement (Table 1). The primary outcome for smoking cessation will be CO-verified, 7-day point prevalence smoking abstinence at 8 weeks postquit date, which will be assessed via smartphone-based self-report and a corroborating CO assessment. Expired CO is a valid indicator of smoking and cessation and compares favorably with cotinine and other biochemical measures [101]. Daily abstinence will be examined as a secondary outcome and defined as self-reported abstinence within the day combined with 2 breath CO sample submissions <6 ppm and identity verification. The number of days and consecutive days of CO-verified abstinence will be explored as additional outcomes. The other primary outcome will be the net change in average daily steps during the eighth week postquit date compared with average daily steps the week before the quit attempt (HealthyCells+ group only). Second, we will explore the number of total and consecutive days that ≥6000 steps were achieved as additional outcomes [102]. A valid day of observation for daily steps will be defined as (1) a smartwatch that was worn for at least 10 waking hours with (2) ≥500 steps taken within a day [103].

To ensure accurate, objective measurement of step count, study staff will pair each participant's Samsung smartwatch with a Samsung smartphone and create a unique Samsung Health account before shipping the study materials. The Samsung Health app integrates seamlessly with the smartwatch, allowing continuous step count tracking. These data sync automatically from the watch to the app, enabling real-time data capture. Throughout the intervention, the research team will periodically access each participant's Samsung Health account to securely export step data, which will be saved as a file for analysis. Once participants return the phone and smartwatch, the study team will directly extract step data from the smartwatch to verify and complement the app-synced step data. This dual extraction process enhances data reliability, ensuring comprehensive and objective measurement of participants' physical activity [102]. After this extraction, the phone and smartwatch will be reset to factory settings to prepare them for use with another participant, ensuring privacy and consistency across participants.

Feasibility and Engagement Outcomes

We will assess several metrics to gauge the feasibility of evaluating the intervention in a larger-scale trial. Key metrics include completion rates for surveys and interviews (retention and engagement), instances of lost or damaged phones or

watches (technology use barriers), and participant engagement with app features, such as completing the e-book for smoking cessation and setting and reviewing daily step goals. We will also characterize the frequency of photo uploads of daily step counts, completion of daily smoking status assessments, NRT adherence, completion of counseling sessions, and duration of smartwatch wear. These feasibility metrics will also be explored qualitatively by interviewing participants about their experiences with the intervention (ie, exit interview), such as their engagement with app features, ease of completing assessments, and any challenges encountered with study equipment.

Sample Size Justification

The sample size of 60 participants was chosen based on recommendations for feasibility trials [104,105], which prioritize assessing study processes, recruitment, retention, and intervention engagement rather than detecting statistically significant effects. This sample size is sufficient to evaluate key feasibility metrics, such as recruitment rates (target: ≥5 participants/mo), retention (≥75% completion), and adherence to intervention components, which are critical for planning a fully powered randomized controlled trial. In addition, this sample size allows for preliminary comparisons between the HealthyCells and HealthyCells+ groups to explore trends in CO-verified smoking abstinence and changes in daily step counts.

Analytic Plan

This analytic plan will focus on describing intervention feasibility. Feasibility indicators will include enrollment of all study participants within 12 months (≥5 adults enrolled/mo), retention of at least 75% of the participants at 8 weeks postquit date, achieving 20% smoking abstinence at 8 weeks postquit date (consistent with NRT and behavioral support standards) [104,105], and observing a meaningful 500 to 1500 [106,107] average daily step increase at eighth week postquit date. SAS (version 9.4; SAS Institute) [108] will be used for all statistical analyses, generating descriptive statistics to compare demographics, smoking status, and physical activity levels by treatment group. Group comparisons on participant characteristics and outcomes will use 2-tailed *t* tests for continuous variables and chi-square tests for categorical variables. Given the small sample size and pilot design (N=60), we will report all potential group differences with the α set at $P<.20$, following recommendations for pilot studies [109].

Smoking cessation will be analyzed in two ways: (1) an intention-to-treat analysis with missing data classified as smoking and (2) a completers-only analysis excluding participants with missing data. For physical activity outcomes, specifically the change in average daily step count from the baseline week to the eighth week postquit date, *t* tests will evaluate pre-post differences between groups. Days with <500 steps or <10 hours of watch wear time (indicating nonwear time or recording error) will be excluded. Participants must have at least 4 days of valid step count data to be included in the analyses.

Exploratory analyses will examine the association between physical activity and smoking cessation success using continuous and categorical approaches, with 6000 steps as the threshold for categorical analyses. Logistic regression analysis will evaluate the impact of average daily step count based on all postquit assessment weeks (5 wk in total) on CO-verified 7-day point prevalence abstinence at 8 weeks postquit date. In addition, participants will be categorized based on achieving a daily average of ≥6000 steps, allowing us to evaluate whether higher activity levels (≥6000 steps) are associated with greater cessation success. Finally, we will explore additional metrics, including the number of consecutive abstinent days and the frequency of meeting daily step goals. The analysis will examine these metrics as continuous and categorical variables to assess their association with smoking cessation rates.

Qualitative Analysis Plan

The baseline and exit interviews will be evaluated separately to comprehensively understand participants' experiences and impressions at different stages of the mHealth intervention. Transcripts from both interviews will be analyzed in NVivo (version 12; Lumivero) using an inductive thematic approach [110,111]. A codebook will be developed collaboratively by coding a subset of interviews, with iterative refinements to ensure reliability before the lead author's independent coding of the remaining transcripts. Periodic team reviews will resolve discrepancies.

The baseline interview will assess participants' initial perspectives and familiarity with mHealth tools, which may inform their engagement with the intervention. Key focus areas will include motivation for participating in mHealth research, smartphone use habits, and previous experiences with health apps and Bluetooth-enabled devices. By examining these factors, the analysis will capture participants' baseline comfort levels with digital health tools, previous exposure to apps for smoking cessation and physical activity, and any initial preferences for culturally tailored health behavior interventions within the Black population. Insights from these domains will provide context for interpreting participants' engagement with the intervention and potential barriers that could influence adherence.

The exit interview will assess participants' experiences with the intervention, focusing on perceptions of the cultural tailoring and usability of the intervention components. A central focus will be feedback on the e-book modeled after *Pathways to Freedom* [48], with analysis capturing participants' impressions of its cultural relevance, clarity, and perceived impact on smoking cessation. Participants' feedback on which sections resonated, any challenges encountered, and suggestions for improvement will provide insights into enhancing this culturally tailored component. Further domains in the exit interview will evaluate participants' overall impressions of the app features, experiences with the smartwatch, adherence to NRT, and any technical issues encountered with study equipment. This analysis aims to identify strengths and weaknesses of the intervention from the user perspective, including insights into specific app features that supported or hindered engagement and practical challenges with using the devices.

We will synthesize findings from the baseline and exit interviews to identify overarching themes related to engagement, cultural resonance, and barriers to adherence. This holistic

analysis will reveal how initial expectations and previous experiences influenced participant experiences and how the intervention can be refined to improve acceptability and effectiveness for larger-scale studies. Examining recurring themes across interviews may provide actionable insights for enhancing intervention design, especially regarding cultural tailoring, usability, and support for behavior change.

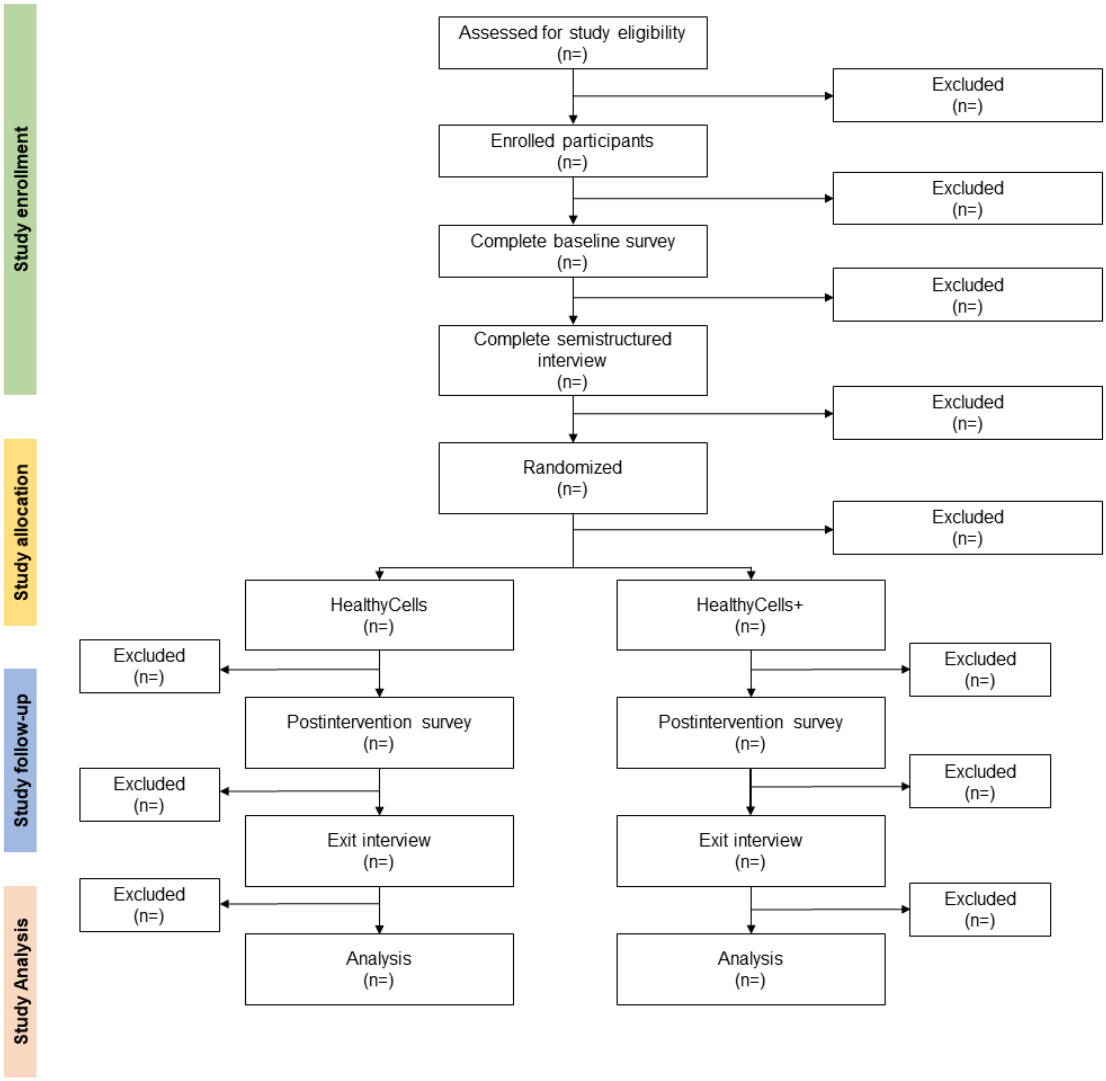
Integration of Study Findings

We will use a mixed methods approach to capture a holistic view of intervention feasibility and participants' experiences [112]. Quantitative data will provide intervention outcomes and milestones, and qualitative findings will uncover insights into participants' expectations, experiences, and perceptions regarding the intervention. Triangulation will occur through a systematic comparison of quantitative metrics with qualitative themes [112,113]. For example, if quantitative results indicate high smoking cessation rates, qualitative data will be examined to identify participant-reported factors that facilitated this success. Conversely, if step count improvements are minimal, qualitative insights may help reveal barriers to physical activity engagement or limitations within the app that could be addressed in future studies. This combined approach will provide information about feasibility and generate participant-driven insights, increasing the likelihood that future interventions will be effective and tailored to meet community needs.

Results

This study was reviewed and funded by the National Institute of Minority Health and Health Disparities (Multimedia Appendix 3). This study was approved by the institutional review board of the University of Oklahoma Health Sciences Center (protocol #14094) on 12/10/2021. Data collection is expected to start in February 2025 and finish in September 2025 (Figure 6 depicts the CONSORT [Consolidated Standards of Reporting Trials] diagram). Primary data are expected to be analyzed by October 2025. The preparation of manuscripts on primary and secondary outcomes is expected to start in late 2025 and early 2026.

Figure 6. Participant recruitment, allocation, intervention adherence, and follow-up in the feasibility randomized controlled trial evaluating the HealthyCells interventions for smoking cessation and physical activity promotion (CONSORT [Consolidated Standards of Reporting Trials] flow diagram).



Discussion

Principal Findings

This study evaluates the feasibility of the HealthyCells intervention, an app-based mHealth approach integrating financial incentives for smoking cessation and physical activity promotion among Black adults. We anticipate that participants in the HealthyCells+ group, who receive incentives for both smoking abstinence and physical activity, will achieve greater increases in daily step counts and higher rates of CO-verified smoking abstinence compared to the HealthyCells group, who are incentivized for smoking abstinence only. Feasibility metrics, including recruitment, retention, and participant adherence, are expected to demonstrate strong engagement and acceptability of the intervention over the 9-week study period.

Comparison to Prior Work

This study builds upon previous MHBC mHealth interventions, such as See Me Smoke-Free [114] and PhoS [115], which showed potential to promote behavior change but were limited by reliance on self-reported outcomes and low adherence rates [46,116,117]. In contrast, HealthyCells incorporates objective measures of behavior (eg, CO breath samples for smoking abstinence and step counts verified by smartwatches), addressing these limitations. In addition, culturally relevant content, such as that inspired by *Pathways to Freedom* [48,49], distinguishes HealthyCells from other interventions by tailoring messages to resonate specifically with Black adults. This study also advances CM research by combining financial incentives for multiple behaviors, a strategy that has shown promise in previous studies [34-38].

Strengths and Limitations

A key strength of this study is its focus on a population disproportionately affected by tobacco- and obesity-related health disparities. By leveraging mHealth technology and CM, this intervention offers a scalable and accessible approach to behavior change. Objective tracking of outcomes ensures data reliability, and the inclusion of culturally tailored content enhances the potential for participant engagement.

However, this study has limitations inherent to feasibility trials. The sample size (n=60) is small and not powered to detect statistically significant differences in outcomes. In addition, the absence of a control group limits conclusions about the intervention's effectiveness. Despite these limitations, this study will provide critical pilot data for a fully powered randomized controlled trial.

Future Directions

Findings from this feasibility study will guide the refinement of the HealthyCells intervention for larger-scale trials. Future research will explore the effects of long-term interventions, the maintenance of behavior change after incentives are withdrawn, and the scalability of interventions to other underserved populations. In addition, further refinements to the app based on participant feedback will aim to enhance usability and engagement. Ultimately, this research has the potential to contribute to health equity by addressing smoking and physical inactivity in high-risk populations using innovative, culturally tailored, and technology-driven strategies.

Acknowledgments

This work was supported by the Oklahoma Tobacco Settlement Endowment Trust (STCST00400_FY25), the OU Health Stephenson Cancer Center through a National Cancer Institute Cancer Center Support Grant (P30CA225520), and the National Institute on Minority Health and Health Disparities (1K01MD015295-01A1). The Mobile Health Shared Resource at the Stephenson Cancer Center provided programming and technological support.

Data Availability

The datasets generated and analyzed during this study will be made publicly available in a suitable data repository following the publication of all primary and secondary analyses. Until that time, the data will be available from the corresponding author on reasonable request.

Authors' Contributions

AA designed the intervention and formulated the research questions and hypotheses. AA prepared the first draft of the manuscript. All authors revised it and approved the final draft.

Conflicts of Interest

MSB is one of the inventors of the Insight mHealth Platform and receives royalties related to the use of this platform by investigators external to the University of Oklahoma Health Sciences Center. All other authors declare no conflicts of interest.

Multimedia Appendix 1
Overview of study measures across each assessment type.
[DOCX File , 21 KB - resprot_v14i1e69771_app1.docx]

Multimedia Appendix 2
Overview of scheduled assessment and menu options available in both study apps.
[DOCX File , 21 KB - resprot_v14i1e69771_app2.docx]

Multimedia Appendix 3
National Institute of Health peer-review report.
[PDF File (Adobe PDF File), 162 KB - resprot_v14i1e69771_app3.pdf]

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Abbreviations

CM: contingency management
CO: carbon monoxide
CONSORT: Consolidated Standards of Reporting Trials
MHBC: multiple health behavior change
mHealth: mobile health
NRT: nicotine replacement therapy
REDCap: Research Electronic Data Capture

Edited by A Schwartz; submitted 09.12.24; this is a non–peer-reviewed article;accepted 30.12.24; published 31.01.25.

Please cite as:
Alexander A, Businelle M, Cheney M, Cohn A, McNeill L, Short K, Frank-Pearce S, Bradley D, Estrada K, Flores I, Fronheiser J, Kendzor D
An mHealth Intervention With Financial Incentives to Promote Smoking Cessation and Physical Activity Among Black Adults: Protocol for a Feasibility Randomized Controlled Trial
JMIR Res Protoc 2025;14:e69771
URL: https://www.researchprotocols.org/2025/1/e69771
doi:10.2196/69771
PMID:39888657

Protocol

Effect of Medication Management at Home via Pharmacist-Led Home Televisits: Protocol for a Cluster Randomized Controlled Trial

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Abstract

Background: Older adults are more likely to have multiple chronic conditions, be prescribed multiple medications, and be more susceptible to adverse drug reactions (ADRs) to their medications. In addition, older adults often use over-the-counter medications and supplements, further complicating their medication regimens. Complex medication regimens are potentially harmful to older adults. Interventions aimed at reducing medication discrepancy in the ambulatory clinic setting, such as reviews of medication lists and the implementation of "brown bag" reconciliation, continue to be challenging, with limited success. Pharmacist-led interventions to improve appropriate medication use in older adults have demonstrated effectiveness in reducing ADRs. Video visits have the potential to provide direct visualization of medications in older adults' homes, thereby reducing medication discrepancy and increasing medication adherence. Pharmacist-led management of older adults' medication regimens may improve appropriate medication use in older adults.

Objective: The objective of this study is to examine the effect of pharmacist-led medication through home televisits compared to usual care on appropriate medication use, medication discrepancies, medication adherence, and ADRs.

Methods: We will conduct a 2-site cluster randomized controlled trial (RCT). The intervention will be a pharmacist-led home televisit including medication reconciliation and assessment of actual medication use. The cluster RCT was iteratively adapted after a pilot test. The primary outcome of medication appropriateness of the intervention will be measured using the STOPP (Screening Tool of Older Persons' Prescriptions) criteria for potentially inappropriate medications (PIMs) at 6 months. Medication lists obtained will be compared against electronic medical records (EMRs) by a clinician to establish discrepancies in medications. The clinician will review medications using the validated Medication Appropriateness Index (MAI).

Results: This project has been peer-reviewed and selected for support by the Veterans Affairs (VA) Health Services Research Service. The pilot phase of the study was completed December 2021 with 20 veterans and was primarily informed by the Steinman model of the prescribing process adapted to include system- and provider-level factors. The last date of enrollment was August 6, 2021. We anticipate the completion of the ongoing trial in spring 2025. The first results are expected to be submitted for publication in 2025.

Conclusions: The cluster RCT will provide evidence on medication management through televisits. If found effective in improving the use of medications, the intervention has the potential to impact older adults with multiple chronic conditions and polypharmacy.

Trial Registration: ClinicalTrials.gov NCT04340570; https://clinicaltrials.gov/study/NCT04340570

International Registered Report Identifier (IRRID): PRR1-10.2196/65141

(JMIR Res Protoc 2025;14:e65141) doi:10.2196/65141

KEYWORDS

older adults; medication management; televisit; polypharmacy; adverse drug reaction

Introduction

Polypharmacy in Older Adults and the Importance of Medication Reconciliation

The US population is aging rapidly; the population aged 65 years and above is projected to be doubled by 2050. The most rapidly growing segment is the population of older adults aged 85 years and above, which will more than triple from 5.9 million in 2012 to 18 million in 2050 [1,2]. Older adults aged 65 years and above often have multiple chronic diseases—more than 60% have 2 or more chronic diseases [3], and 17% have 4 or more chronic diseases [4]. Older adults with multiple chronic comorbidities often require multiple medications for management, particularly with guideline-based management of chronic diseases [5,6]. The use of multiple medications in older adults is common, with almost 20% of older adults aged 65 years and above taking 10 or more medications [7,8]. Multiple-medication use in older adults is associated with a lower adherence rate and increased use of inappropriate medications [9,10]. The use of multiple medications increases the risk for potential drug interactions, leading to undesirable adverse drug reactions (ADRs), which could also contribute to lower medication adherence. In particular, older adults are more susceptible to ADRs due to the changes in their physiology, clearance, and reserves [11], particularly with polypharmacy [9,12] Based on the phycological changes in the older population, knowing the drug regimens with older adults is an important feature in order to provide medication safety and make adjustment to their regimen accordingly to ensure appropriate medication use. The START/STOPP (Screening Tool to Alert to Right Treatment/Screening Tool of Older Persons' Prescriptions) criteria [13-15] and American Geriatrics Society (AGS) Beers criteria [16,17] for potentially inappropriate medications (PIMs) were developed to provide evidence-based guides to signal clinicians about medications that are potentially inappropriate and to enhance medication appropriateness. These medications include those with strong anticholinergic properties, which may disproportionately affect older adults and are linked to adverse outcomes of ADRs, and other medications that are demonstrated to have significant side effects in older adults.

Use of Telemedicine to Improve Medication Use in Older Adults

Telemedicine is a modern visit option enabled by advances in telecommunications technology [18]. The use of telemedicine in older adults has been examined in prior small studies that have demonstrated feasibility, acceptability, and user satisfaction [19-22]. Extending televisits to patients' homes has the potential to impact many aspects of care that rely on patient self-management, such as medication use. Although telephone-based pharmacist interventions have the potential to impact medication use at home [23,24], they still rely on accurate information reported by older adults over the phone without a mechanism for confirmation. The addition of video has the potential to further enhance the visit [25,26] by (1) visual ascertainment of actual medications taken by patients, (2) visual demonstration of the patients' actual use of medications, and (3) education of patients on proper use. Although in-person home-based reconciliation has the potential to improve accurate appraisal of medication use and reconciliation, it is not feasible for wide adoption as it is resource intensive. The study proposed here will examine the impact of home televisits by pharmacists on patients at high risk for ADRs (ie, with polypharmacy and multiple chronic conditions).

Methods

Research Design Overview

This study is designed as a mixed methods hybrid type 1 effectiveness implementation study [27], where we will test the health impact of pharmacy televisits, while also collecting data on the implementation process to facilitate subsequent scale-up efforts [28]. As older adults have higher rates of chronic conditions and polypharmacy, we included veterans aged 65 years and above in this study. The inclusion criterion of 5 or more medications is based on prior literature on polypharmacy and findings of increased risk for drug interactions and ADRs. The enrollment criteria are consistent with and exceed the criteria set in fiscal year 2019 by the Center for Medicare Services for provision of medication therapy management in Medicare Part D [29]. Among patient characteristics, polypharmacy (≥5 medications) and multiple chronic conditions

are considered important risk factors for ADRs and are highly prevalent among frail older adults at risk for ADRs [30].

The intervention for the cluster randomized controlled trial (RCT) was iteratively adapted after a pilot test with 20 veterans [31]. Home televisits, where pharmacists conducted medication reconciliation and management, were refined, after which a formative evaluation [32] was conducted, guided by the Consolidated Framework for Implementation Research (CFIR) [33]. Data were gathered in several ways: (1) enrolled veterans (n=20) were observed by study staff present within the veterans' homes during the clinical pharmacist home televisit, and (2) study staff administered a postencounter questionnaire with the goal of improving the veteran-based technical experience and clinical encounter. The data points were used to adapt and make changes to the intervention for the cluster RCT.

The cluster RCT is registered on ClinicalTrials (NCT04340570). The intervention will be a pharmacist-led home televisit including medication reconciliation and assessment of actual medication use. Pharmacists will review medication appropriateness using evidence-based criteria and provide recommendations for change of medication use to the patients' primary patient-aligned care team (PACT). PACTs provide team-based care and consist of a primary care provider (PCP), a registered nurse, a medical assistant, and, often, either a social worker or a pharmacist. In the control group, participants will receive usual care in which medication reconciliation and review will be conducted in clinics by primary care teams. As a primary outcome, we will examine the effect of the intervention on the number of veterans with PIMs, as determined using evidence-based criteria. As secondary outcomes, we will determine the number of PIMs, medication discrepancy using data from record reviews and interviews, and medication appropriateness using validated instruments at 6 months after the intervention. We will also compare the intervention's effects on the incidence of ADRs using data from record reviews and interviews. To assess the potential for future implementation of the intervention, we will administer postintervention questionnaires to key stakeholders, including veterans and PACT clinicians, to examine implementation barriers to and facilitators of the intervention.

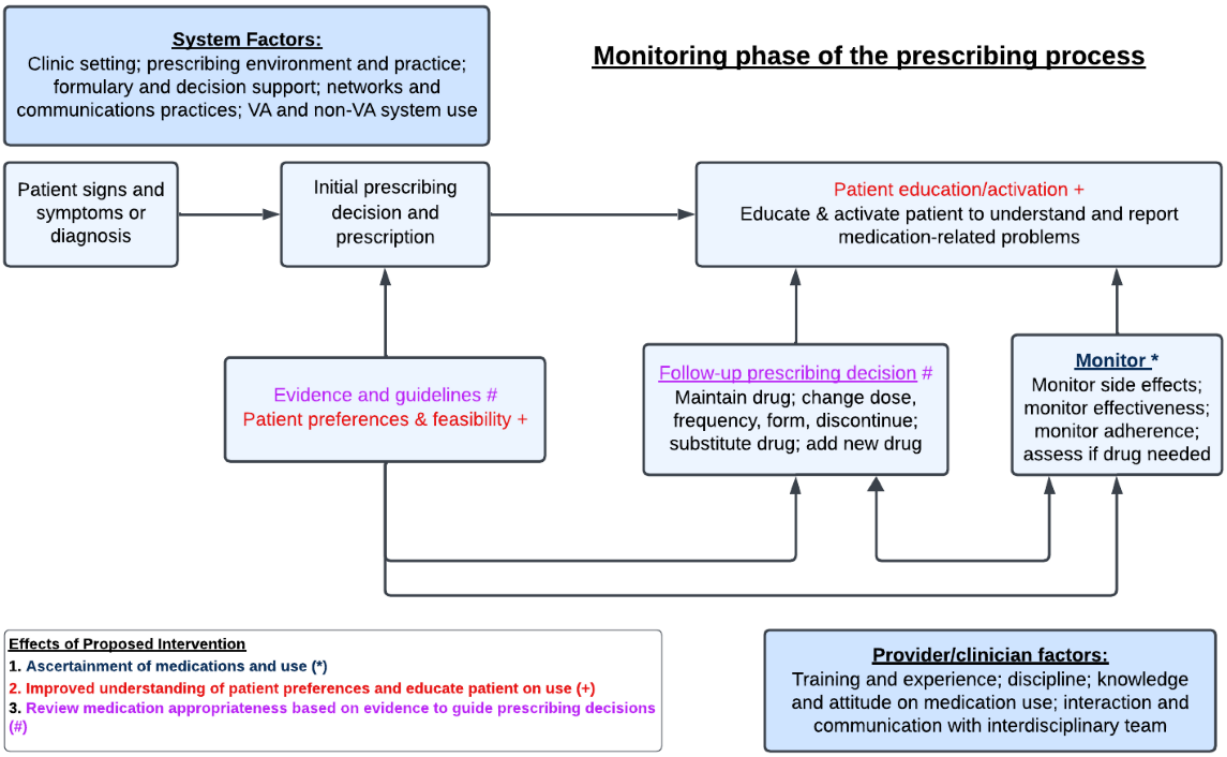
Ethical Considerations

This study was approved by the Veterans Affairs (VA) Central Institutional Review Board (CIRB; IRBNet ID 1612635). To obtain participants' informed consent, a research assistant (RA) will determine whether eligible patients have the capacity to provide informed consent to participate in the study using a screening questionnaire that assesses the 4 elements required for capacity understanding of study procedures, appreciation of what will happen if enrolled, communication of a choice to enroll or not, and demonstration of a rationale for that choice. Recruitment and written informed consent will take place in a location that ensures privacy and convenience for the patient.

Conceptual Framework of Medication Prescribing in Older Adults

Our conceptual framework is informed by the CFIR [34] and Steinman et al [35] on prescribing and prescription monitoring processes. The pilot phase was primarily informed by the Steinman model of the prescribing process adapted to include system- and provider-level factors. The system-level factors include the Veterans Health Administration (VHA) policy on medication management (including non-VA care use), facility-level prescribing environment and practices, and decision support systems. In designing our proposed intervention, we considered the potential effect of home televisits by pharmacists to ascertain the medication regimen and use, identify discrepancies and educate patients on use, and review medication appropriateness, thereby enhancing steps in the monitoring phase of the prescribing process (Figure 1).

Figure 1. Conceptual framework of prescribing and prescription-monitoring process. Modified from Steinman et al [31]. VA: Veterans Affairs.



Cluster Randomized Controlled Trial Patient Recruitment

The inclusion criteria include the following: (1) the veteran must be a PACT patient in a Bronx VA or Bedford VA geriatrics or primary care clinic; (2) be 65 years or older; (3) have 2 or more chronic conditions; and (4) have 5 or more medications listed on the VA medication record continuously in the previous 6 month. Patients fulfilling these criteria will be approached for study enrollment through letters of invitation after approval by human subjects' committees.

Cluster Assignment by PACT

We will randomize patients by PACT to prevent a team from having participants in both treatment and control groups and to reduce contamination. Prior to initiating enrollment, the project coordinator will assign PACTs to intervention and control groups using lists of computer-generated random numbers in a 1:1 ratio, with separate lists for the Bronx VA and the Bedford VA, in order to maintain balance in both groups within each study site. There are 69 primary care and geriatric PACTs in the Bronx VA and 14 in the Bedford VA, and each PACT will keep the group assignment for the duration of the study.

Study Flow

After enrollment, veterans who agree to participate in the study will be interviewed by a trained research coordinator using survey instruments that will include data elements listed in Table 1. Veterans will receive the televisit intervention, or not, based on the PACT team they belong to, as discussed earlier. The detailed procedure for control and intervention groups is described later. To observe what occurs at follow-up appointments with the PACT provider, after the first follow-up appointment postintervention, participants will be asked about whether medication use was discussed during the appointment, whether medication reconciliation was performed and how, and what, if any, medication changes were made. Electronic charts will be reviewed for documentation of medication reconciliation and management during the visit. Primary outcomes will be ascertained at 6 months after study enrollment and are described in Table 1, including the subject survey and chart review. The subject survey for outcome assessment will be conducted by a research coordinator trained to take the subject's medication history, and the chart review will be conducted by a clinician blinded to the study assignment. The subject survey will include confirmation of medications participants are currently taking, including names, dosages, and frequency. Participants will be asked to list medications that they take, including over-the-counter drugs and supplements. A clinician rater blinded to the study assignment will review medication data from the subject survey and chart review to determine medication discrepancies and appropriate use of medications.

Table 1. Data elements and instruments.

Data elements	Source	Instruments or measurements
Outcomes		
Primary: PIM[a] use	Chart review, interview	STOPP[b] criteria, assessment of medication list by blinded clinical reviewer [14]
Secondary: medical discrepancies	Chart review, interview	Medication discrepancies (omissions, duplications, additions)
Medication appropriateness	Chart review, interview	MAI[c] [36]
Patient satisfaction, self-efficacy, and adherence	Interview	CAHPS[d] item pertaining to medication use [37], MUSE[e] [38]
Health-related quality of life	Interview	EQ-5D-5L [39]
ADRs[f]	Chart review, interview	ADRs determination by clinical reviewer
Baseline covariates		
Sociodemographics	Baseline survey, chart review	Gender, age, race, ethnicity, education, income, Medicare, Medicaid
Chronic illness burden	Patient interview, chart review	Modified RAND index [40]
Medication list	Chart review, patient interview	Number and type of medications, source (VA[g], non-VA, over the counter)
Medication use	Interview, chart review	Number and type of medications, method of administration, presence of refill gap (>90 days)
Patient's self-efficacy on medication use	Patient interview	MUSE
Health literacy	Patient interview	Short Test of Functional Health Literacy in Adults (S-TOFHLA) [41]
Cognitive function	Patient interview	MoCA[h] [42]
Physical function	Patient interview	Katz Activities of Daily Living (ADL) index/Lawton Instrumental Activities of Daily Living (IADL) scale [43,44]
History of acute care use (hospitalization, emergency department)	Patient interview, chart review	Days prior to enrollment for most recent hospitalization and emergency department visit, number of episodes in the previous year
Health-related technology use attitude, self-efficacy, and comfort	Patient interview	Self-reported comfort and confidence in using technology [45]

[a]PIM: potentially inappropriate medication.

[b]STOPP: Screening Tool of Older Persons' Prescriptions.

[c]MAI: Medication Appropriateness Index.

[d]CAHPS: Consumer Assessment of Healthcare Providers and Systems.

[e]MUSE: Medication Understanding Use and Self-Efficacy Scale.

[f]ADR: adverse drug reaction.

[g]MoCA: Montreal Cognitive Assessment.

Intervention

Patients assigned to the intervention will have a pharmacist televisit appointment made and coordinated. Participants will be asked whether they have a device at home capable of supporting televisits, including home computers with cameras, tablets, smartphones, and a broadband or 4G connection. Participants who do not have appropriate devices will be provided with VA-issued internet-enabled tablets on which to conduct the visits. On the scheduled day of the visit, the research team will coordinate with the participants over the phone to facilitate the initialization of the televisit by the pharmacist. The content of the televisit is described next, in the *Design of the Televisit Intervention* section, and has been adapted through the pilot phase with direct observation of the televisit at home. Subsequent to the televisit, the pharmacist will document the visit content in the electronic medical record (EMR) to note discrepancies noted during the televisit, a review of medications with START/STOPP criteria, and recommendations based on the criteria-based review for PCP review and concurrence for adjustments of medications. Recommendations will be communicated to the PCP electronically through secure email or an electronic note or over the phone or through a face-to-face discussion if preferred by the PCP. Adjustments in the medication regimen will be noted at 7 days in the EMR after recommendations are made. If recommendations are not

adopted, the pharmacist will communicate with the PCP electronically to request reasons for not adopting recommendations. Participants will then continue follow-up primary care with their PCP.

Design of the Televisit Intervention

We plan to use the VA video connect (VVC) capability introduced in fiscal year 2018 to conduct televisits between clinical pharmacists located at the VA medical centers and participants at home. An appointment will be scheduled with each participant for time to conduct the home televisit. The devices, EX90s or web cameras, used at the clinician side will be located at the Bronx VA or the Bedford VA and at the participants' side will be their choice of computer, tablet, or smartphone with an internet connection and webcam capability or a VA-provided tablet if they do not have a device or home internet capabilities. Because the experience of the televisit may differ with different participant devices, various devices were tested in phase I of the study, and their strengths and pitfalls and modes of connecting were identified.

After establishing a video connection, the pharmacist will conduct home-based medication reconciliation by asking the participants to show and explain the use of each of their medications. The pharmacist will also include a brief medication-focused functional assessment, including asking the participants to read aloud and interpret 1 or more of their prescription bottles and to demonstrate the ability to open the bottles. Before ending the visit, the pharmacist will educate the participants regarding possible side effects or interactions between their medications. The pharmacist will also solicit and answer any questions the participants have about the medications. The pharmacist will note the medications used and compare them against the list of medications on each participant's EMR to note discrepancies and then generate a note in the EMR to notify the primary care team of the review and information obtained. If the pharmacist finds that patients are taking medications differently, they will clarify the correct usage of the medications.

Pharmacist Review of Medications

After the televisit is completed, the pharmacist will conduct a medication review using the START/STOPP criteria to review the indication of each medication (see Table 2). They will also review whether there are medications prescribed beyond the recommended duration of each medication, where the treatment duration is well defined. The pharmacist will use evidence-based guidelines to inform follow-up prescribing decisions (maintaining, adjusting the dose, or stopping the medication); see Figure 1. Medications noted to be inappropriate or those that do not have an indication will be flagged for consideration of deprescribing. Duplication of drug class prescriptions will also be noted. Other disease-specific criteria will be reviewed based on the criteria [13-15]. Recommendations generated from the medication review based on START/STOPP criteria will be communicated to the PCP for consideration of modification of the medication regimen. Final decisions on medication modification will be made by primary care clinicians in consultation with their patients as it usually would be in a clinical setting.

Table 2. Scope of pharmacist-led intervention televisit, laying out the steps, content, and approximate duration of each step.

Step	Content and sample questions	Approximate duration (60-75 minutes total)
Setup	Establish a connection, preparation for the visit.	5-10 minutes
Introduction	Identify individuals in the visit and discuss the purpose of the visit.	5 minutes
Identification of the medication regimen and visualization of medications	• What medicines do you currently take? • How about over-the-counter medicines? How about vitamins and supplements? • Where do you keep your medications? Can you show me?	15 minutes
Description and visualization of how to take medications	• What do you take this medicine for? • When do you take this medicine? • Can you show me how much you take each time?	15-20 minutes
Clarify medication instructions	If medications are taken incorrectly, ask why. Educate and use the teach-back method to confirm understanding.	15 minutes
Questions and closing	Answer the patient's questions, if any. Discuss the next steps of review and communication with the PCP[a].	5-10 minutes

[a]PCP: primary care provider.

Control Arm (Usual Care)

After baseline MoCA and technology comfort assessment, medication reconciliation and management will be conducted by the control primary care teams in the manner they usually do. PACTs are guided by the VHA Directive on Medication reconciliation [46], which includes in-clinic assessment of medication information provided by patients via lists, recall or actual medication reviews, comparing information obtained to the VA EMR to note discrepancies, and educating the patient on updated medications. PACT PCPs may also request assessment of medication regimens by pharmacists embedded in their clinic based on clinical decisions regarding the needs of the individual patient and the availability of such services. The prescription of a new medication may trigger a review by a VA pharmacist guided by EMR-based interaction alerts. We

considered using an active control group with pharmacist review (in-clinic or chart review); however, the intervention with pharmacist-led home televisits informing medication review represents a bundled intervention, and the study will examine the effectiveness of the intervention as an enhancement of care to what currently occurs (usual care). This design involving participant interviews and chart reviews will also allow us to characterize current usual medication management for older adults in PACTs.

Outcomes

Primary Outcome

PIM use, which is the primary outcome, will be assessed by the blinded clinical reviewer based on the medication data obtained from home visit surveys using the STOPP criteria [14]. Proportions of participants with PIMs in the intervention group will be compared with proportions of participants with PIMs in the control group.

Secondary Outcomes

Medication lists obtained through subject surveys will be compared against the EMRs by a clinician to establish discrepancies in medications. Discrepancies will be characterized as "no potential harm," "monitoring or intervention potentially to preclude harm," or "potential harm," similar to prior approaches to assess potential clinical impacts [32]. In addition, the clinical reviewer will assess the medications using the validated Medication Appropriateness Index (MAI) [36]. Each medication will receive a score based on the 10-item tool to determine its appropriateness. Patient satisfaction will be ascertained using an item pertaining to medication use from Consumer Assessment of Healthcare Providers and Systems (CAHPS) version 3.0 [37], a 7-item, 5-point Likert scale on medication management by pharmacists adapted from a validated instrument [33,47]; self-efficacy on medication use will be assessed using the Medication Understanding Use and Self-Efficacy Scale (MUSE) to assess change from before and after the intervention [38]. Health-related quality of life will be assessed using the EQ-5D-5L instrument, a brief validated instrument with good test-retest reliability [39,48].

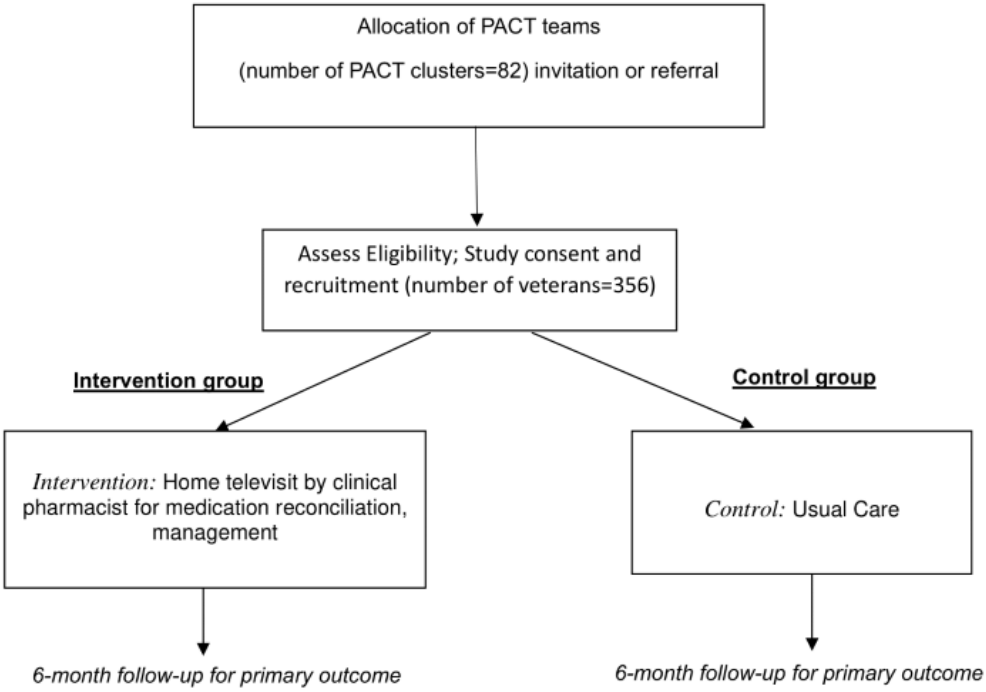
Implementation Factors

Postintervention questionnaires will be administered to key stakeholders, including veteran participants and PACT clinicians, to assess the potential for future implementation of the intervention. This will allow us to examine implementation barriers and facilitators. An invitation to complete the postintervention questionnaires will be emailed to PACT providers in the intervention arm. To ensure we understand PCP decisions on pharmacist recommendations, we will track PCP adoption of recommendations provided by pharmacist reviews and examine PCP reasons for adoption or nonadoption of recommendations, as well as provider factors that can influence those decisions. Patient and clinician interviews and questionnaires will identify perceived barriers and facilitators on a Likert scale. The knowledge and attitude on prescribing for older adults will also be obtained using validated Likert questions, although the attitude and behavior in clinician communication with pharmacists will be gathered using the Home Medicines Review Inventory (HMRI).

Results

The study flow is summarized in Figure 2. The pilot phase of the study was completed December 2021 with 20 veterans and was primarily informed by the Steinman model of the prescribing process adapted to include system- and provider-level factors. This project has been peer-reviewed and selected for support by the VA Health Services Research Service. The last date of enrollment was August 6, 2021. We anticipate the completion of the ongoing trial in spring 2025. The first results are expected to be submitted for publication in 2025.

Figure 2. Study design showing specific steps included in intervention and control groups. PACT: patient-aligned care team.



Discussion

Summary

The complex medication regimens of many older adults contribute to increased risk for drug interactions, ADRs, and other poor health outcomes. A number of studies have found that the use of PIMs is associated with adverse outcomes, such as falls, acute care use, and other negative outcomes [49,50]. Improving medication prescribing using START/STOPP criteria has been found to reduce adverse effects and improve patient outcomes in a number of studies, although mostly in institution-based settings (acute care hospitalization, nursing homes) [50]. Pharmacist-led interventions have been demonstrated to have beneficial effects [51,52] but often do not reach the majority of those who would most benefit from them. Leveraging the advances of telemedicine, clinicians can provide medication management services to older veterans at home. The televisit intervention with pharmacists in medication management has the potential to bridge the current gaps in older adult care and provide a scalable solution to improve medication use in older adults.

The study's pilot phase refined the procedure for pharmacists to conduct home televisits. It is possible that veterans will consider televisits to home cumbersome or invasive and that VA primary care staff will consider tailoring medications for older adults an additional task burden that competes with other mandated tasks. Our prior experiences of home televisits suggest that they are well accepted, and our hybrid effectiveness implementation study will enable us to identify potential implementation challenges and thus can inform future implementation. To ensure we understand PCP decisions on pharmacist recommendations, we will track PCP adoption of recommendations provided by pharmacist reviews to identify PCP reasons for adoption or nonadoption of recommendations, as well as provider factors that can influence those decisions.

The older adult population has increased the use of technology, allowing the VA to use technological advances for VA televisits, overcoming previous barriers, and we expect future changes in technology will further facilitate use. Our study design will allow us to observe older adults using technology at home to enhance our understanding of the barriers to use, and qualitative interviews with clinicians and patients will further identify factors to guide future implementation. We have elected to use 2 separate sites in the RCT phase in order to enhance our understanding of contextual issues and external validity.

Strengths and Limitations

This study design includes both a pilot phase trial and a hybrid effectiveness implementation trial, which ensures that we would observe and be able to address challenges prior to the RCT, although the results of the hybrid implementation effectiveness trial would allow us to determine its effectiveness, while preparing us to spread the intervention, if effective, in the health system. We aim to limit crossover contamination for providers with cluster randomization. Lastly, the standardized intervention and structured pharmacist protocol will ensure consistency and reliability.

The study design also has a few limitations. One is that the study will be conducted in urban and suburban settings, which may limit generalizability Another limitation is that the pilot phase was conducted during the COVID-19 pandemic, which introduced unique challenges in recruitment due to factors such as travel restrictions and increased risk for participants; however, the study team tackled those challenges and completed the pilot phase of the study despite limitations introduced by COVID-19. This study will contribute toward the literature on pharmacist-led medication management through home televisit procedures, as

well as interventions aimed at improving medication use in older veterans.

Conclusion

This study design will demonstrate how medication management will be beneficial through televisits. The implementation effectiveness trial will show how it can improve the use of medications and interventions related to the potential impact on older adults with multiple chronic conditions and polypharmacy. Clinicians can offer older veterans medication management services at home by using telemedicine's advancements. The use of pharmacists in televisit medication management interventions has the potential to close existing gaps in older adult care and offer a scalable way to enhance older adults' medication use.

Acknowledgments

This study is funded by the Veterans Affairs (VA) Health Systems Research, VA Office of Research and Development. The content is solely the responsibility of the authors and does not necessarily represent the official views of the VA Office of Research and Development or those of the US government. The funding body did not participate in designing the study or in writing this manuscript.

Data Availability

No data sets will be generated or analyzed during this study.

Authors' Contributions

LRM, WWH, SRH, ANS, MBM, JLB, KSB, ALS, CZ, CEH, MDV, MZ, MR, and BCB contributed to the intervention concept and design and to the writing and preparation of the manuscript. Generative artificial intelligence was not used in the preparation of this manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer review from the HSR-6 Post-acute and Long-term Care - Department of Veterans Affairs Office of Research and Development - Health Services Research and Development Service (USA).
[PDF File (Adobe PDF File), 86 KB - resprot_v14i1e65141_app1.pdf]

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Abbreviations

ADR: adverse drug reaction
CAHPS: Consumer Assessment of Healthcare Providers and Systems

CFIR: Consolidated Framework for Implementation Research
EMR: electronic medical record
MAI: Medication Appropriateness Index
MoCA: Montreal Cognitive Assessment
MUSE: Medication Understanding Use and Self-Efficacy Scale
PACT: patient-aligned care team
PCP: primary care provider
PIM: potentially inappropriate medication
RCT: randomized controlled trial
START: Screening Tool to Alert to Right Treatment
STOPP: Screening Tool of Older Persons' Prescriptions
VA: Veterans Affairs
VHA: Veterans Health Administration

Edited by T Leung; submitted 06.08.24; this is a non–peer-reviewed article;accepted 25.11.24; published 05.02.25.

Please cite as:
Hossain SR, Samant AN, Balsamo BC, Hawley CE, Zanchelli MC, Zhu C, Venegas MD, Robertson M, McCullough MB, Beizer JL, Boockvar KS, Siu AL, Moo LR, Hung WW
Effect of Medication Management at Home via Pharmacist-Led Home Televisits: Protocol for a Cluster Randomized Controlled Trial
JMIR Res Protoc 2025;14:e65141
URL: https://www.researchprotocols.org/2025/1/e65141
doi:10.2196/65141
PMID:

Protocol

Stress and Hypertension Among African American Female Family Caregivers of Persons Living With Alzheimer Disease and Related Dementias: Protocol for a Pilot Internet-Based Randomized Controlled Trial

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Abstract

Background: Caregivers of persons with Alzheimer disease and related dementias (ADRD) neglect their health, including by ignoring stress levels. African American women are vulnerable and susceptible to hypertension. Chronic caregiving stress and hypertension place them at high risk for cardiovascular disease. Addressing stress reactivity or resilience is vital in lessening their caregiving stress, enhancing their quality of life (QOL), and fostering healthy blood pressure (BP) self-care behaviors.

Objective: This pilot study aims to investigate the feasibility and acceptability of implementing the Mindfulness in Motion (MIM) plus the Dietary Approaches to Stop Hypertension (DASH) intervention in this population and to evaluate its effect on ADRD caregivers' stress and QOL. Additionally, it explores the mediation of stress reactivity or resilience between interventions and self-care behaviors.

Methods: A small randomized controlled trial pilot study will recruit 28 African American or Black female caregivers aged 40 years diagnosed with hypertension and on an antihypertensive medication. Participants will be randomly assigned to either the MIM DASH or the Alzheimer's Association caregiver training group (attention control). Trained facilitators will deliver both interventions over 8 weeks through 1-hour, group, internet-based sessions, via video or telephone. After completion, both groups will receive coaching calls over 9 months, beginning with 8 weekly calls followed by 4 monthly calls to encourage use of the educational materials. Primary outcome measures include feasibility (recruitment and retention) and acceptability (attendance). Secondary measures assess caregiver stress (Perceived Stress Scale), QOL, and self-care behaviors (Food Frequency Questionnaire and self-reported physical activity). Data collection occurs at baseline, 3 months, and 9 months. Quantitative data will be analyzed using descriptive statistics, CIs, and mediation models.

Results: This study was approved by the institutional review board in April 2022 and funded in May 2022. The first data were collected in January 2023, and the last data were collected in September 2024. The completion of all aims' data analysis is anticipated in spring 2025. The participants' mean age was 62.4 (SD 7.98) years, with a mean baseline systolic BP of 128 (SD 19) mm Hg and diastolic BP of 79 (SD 10) mm Hg. Participants reported that MIM DASH was acceptable (at a mean score of 59.08, SD 7.38, compared to 60.83, SD 5.56 for caregiver training). Regarding feasibility, as reflected in attendance, MIM DASH participants had a mean attendance of 6.3 (SD 2.3) sessions, and the caregiver training group had 4.9 (SD 2.9) sessions.

Conclusions: This study's findings demonstrate the feasibility of conducting an internet-based intervention (MIM DASH) for African American women with hypertension who also care for families living with ADRD. These results will inform the design of a larger randomized controlled trial to evaluate the intervention's efficacy and scalability further.

Trial Registration: ClinicalTrials.gov NCT05721482; https://clinicaltrials.gov/study/NCT05721482

International Registered Report Identifier (IRRID): DERR1-10.2196/66975

(JMIR Res Protoc 2025;14:e66975) doi:10.2196/66975

KEYWORDS

African American women; high blood pressure; stress reactivity and resilience; caregiving; hypertension; stress; Alzheimer disease; dementia; lifestyle and healthy self-care behaviors

Introduction

Background

Family caregivers of individuals with Alzheimer disease and related dementias (ADRD) provided an estimated 18.4 billion hours of unpaid care, valued at nearly US $350 billion [1]. The prevalence of ADRD is higher among African American individuals, leading to a disproportionately more significant share of the family caregiving burden. Approximately one-third of these caregivers of individuals living with dementia acknowledge postponing or neglecting their health due to their caregiving role [1]. Given African American individuals' heightened risk of ADRD, particularly vascular and mixed dementia, this problem disproportionately affects African American family caregivers [1].

Although African American caregivers generally express positive feelings about caregiving and report cultural justification for providing care [2,3], they nonetheless endure the adverse effects of chronic caregiver stress—increased cortisol levels, hypertension [4,5], and consequently, cardiovascular disease [6]. Compounding their risk, African American women face a heightened danger of uncontrolled hypertension and cardiovascular disease [7]. No demographic group is more at risk for the double jeopardy of caregiving stress and hypertension than African American women caring for a family member who has ADRD.

Hypertension is the leading cause of cardiovascular disease among African American women, affecting 56.7% of this group [8]. Numerous studies recommend lifestyle changes such as stress management, reducing sodium intake, increasing the intake of fruits and vegetables, weight management, and engagement in regular physical activity to manage hypertension [9,10]. Researchers have hypothesized that African American individuals face excess chronic stress that makes adopting healthy self-care behaviors difficult [11,12].

One of the underlying mechanisms behind adopting healthy self-care behaviors is stress reactivity or resilience—the body's psychological and physiological response to stress [13]. Understanding these factors can contribute to more effective and sustainable behavior changes such as healthy eating, stress management, and physical activity.

Only a few studies have explored the stress and resilience associated with healthy self-care behaviors among African American caregivers. No research to date has used an interdisciplinary methodology to examine the intricate relationship between stress and resilience in this demographic. This protocol paper describes a mind-body intervention designed to address the complex interplay of stress and hypertension in African American caregivers.

Purpose

This randomized controlled pilot study examines the feasibility and acceptability of Mindfulness in Motion (MIM) combined with Dietary Approaches to Stop Hypertension (DASH) to promote hypertension self-care in African American women who are family caregivers of people living with ARD.

MIM uses gentle yoga stretches and teaches mindful awareness skills, while the DASH program promotes a diet rich in vegetables, fruits, whole grains, and lean proteins [14,15]. These interventions combined provide a comprehensive strategy for stress management and hypertension reduction. The control group will receive the Alzheimer's Association's caregiver training [16-19].

Study Aims

This study aims (1) to determine the feasibility and acceptability of MIM DASH and caregiver training for African American female caregivers with hypertension; (2) to compare the influence of MIM DASH on caregiver stress and quality of life (QOL) with the influence of caregiver training; and (3) to investigate the potential mediation effects of stress reactivity or resilience between each program and self-care behaviors.

Theoretical Models

Of MIM

Developed in 2004, MIM was based upon the ideas of Urie Bronfenbrenner's Socio-Ecological Model, which highlights the multilevel influences on behavior [20]. The Socio-Ecological Model has been extensively researched and is an effective way to structure multilevel interventions to aid in the long-term adoption and sustainability of programming [21]. MIM's combination of dietary education and experiential mind or body practices aligns with the multilevel Socio-Ecological Model of change. MIM was first implemented in 2009 as a small, randomized controlled trial with 48 employees [22]. Guided by the question of "Is MIM effective?" the program was tested in various additional studies with medical center faculty, staff, residents, and patients [23-30]. These trials showed significant stress and burnout reduction results with improved resilience.

Of DASH

The 8-week DASH education uses a critical thinking model of behavior change and culturally appropriate approaches to emphasize eating vegetables, fruits, whole grains, fat-free or low-fat dairy choices, fish, poultry, beans, and nuts and using vegetable oils [31]. Additionally, it limits foods high in saturated fat, sugar-sweetened beverages, and sweets. Critical thinking provides individuals with the tools for reasoning, empowerment, problem-solving, and making sound decisions [16]. The DASH eating plan decreases cardiovascular outcomes, including subclinical injury and systematic inflammation biomarkers, and improves blood pressure (BP), especially among African American individuals [32]. The critical thinking approach allows individuals to analyze information and their behavior to make fully informed decisions in the best interest of African American individuals; it also provides opportunities for reflection.

MIM and DASH

MIM and DASH both address health behaviors but from different perspectives. MIM integrates mindfulness practices, while DASH emphasizes critical thinking and heart-healthy dietary choices. Together, they contribute to holistic well-being and improved health outcomes.

Study Timeline

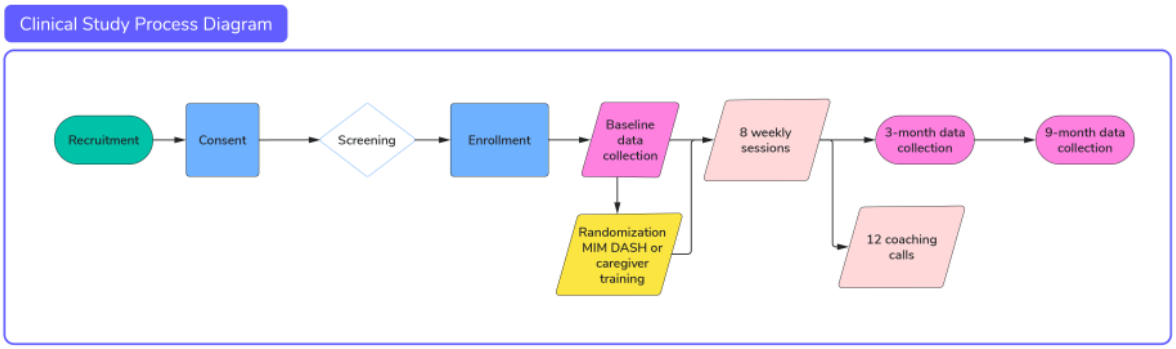
The participants will be tracked for 9 months in the 2-year funded trial. Data will be collected at baseline, at 3 months, and during a 9-month follow-up.

Methods

Design

In this randomized controlled trial, 28 community participants will be enrolled and randomly assigned to MIM DASH (n=14; intervention group) or caregiver training (n=14; attention-control group). This study's team will use REDCap (Research Electronic Data Capture; Vanderbilt University) to deliver informed consent to prospective participants via an online check box. Figure 1 provides a flow chart for this study.

Figure 1. Flow Chart for the Study: The figure visually represents participants' enrolment and randomization into training or intervention programs, followed by their sessions and data collection phases.



Recruitment

Participants will be recruited from clinics, the African American Alzheimer's and Wellness Association, the Central Ohio Alzheimer's Association, local churches, the Research Match registry, and social media. Additionally, study flyers will be displayed in places potential participants are likely to frequent, such as libraries, beauty salons, health provider offices, and senior centers. To maintain confidentiality, the list of all potential participants will be securely kept separate from the documentation and tracking spreadsheet in the REDCap. Basic demographic information and reasons for refusal will be noted for eligible individuals who decline participation. Enrollment and screen failure data will be tracked using the National Institutes on Aging (NIA) Common Data Screening, and enrollment forms will be reported to the NIA once every month (NIA Clinical Research Operations & Management System) [33].

Eligibility

Study participants will be adults aged 40 years and older who self-identify as Black or African American women and as family caregivers to someone living with ADRD. Inclusion criteria include the following: (1) have a diagnosis of hypertension that is treated with an antihypertensive medication; (2) have a score of two or greater on the eight-item Informant Interview to Differentiate Aging and Dementia [34]; (3) provide unpaid care for a person living with ADRD at least 10 hours per week and assist a person living with dementia with at least 1 instrumental activity of daily living (eg, bill paying, medication management, or transportation); (4) speak English; and (5) have access to a telecommunications device such as a desktop computer, laptop, tablet, smartphone, or telephone, to enable participation. Exclusion criteria include the following: (1) expect to move out of the area within nine months; (2) have a diagnosis of resistant hypertension (BP that remains above goal despite concurrent use of a diuretic or water pill and at least two other antihypertensive medications of different classes), or (3) are actively participating in a mindfulness or yoga program.

Randomization

All caregivers who enroll in this study and complete the baseline assessment will be randomly assigned into either the intervention group (MIM DASH) or the attention-control group (caregiver training). The rationale for an attention-control condition is to strengthen this study's design and minimize the chance that differences between the groups could be related to receiving social support from interacting with others [14]. Once one of

this study's staff members has completed the baseline data collection, the statistician will randomly assign this study's participants using a randomization table generated from the statistical software in the REDCap database. Trial participants will be blinded to this study's hypotheses.

MIM DASH (Intervention Group) Delivery

A trained MIM facilitator and a dietitian will deliver the intervention in eight 1.5-hour (~45 minutes for MIM and ~45 minutes for DASH) sessions via Zoom (Zoom Video Communications, Inc) with telephone access. Participants will receive session materials such as PowerPoint (Microsoft Corp) slides to follow along by phone or the Zoom videoconferencing app. Table 1 provides a list of the topics.

Table 1. Weekly topics for MIM[a] DASH[b] (intervention group) and caregiver training (attention-control group).

Week	MIM DASH	Caregiver training
1	• Introduction to MIM • What African American individuals should know about hypertension and its consequences	Healthy brain and body
2	• Mindful sleep • Understanding blood pressure overview	10 warning signs
3	• Vision of self • Clearing up myths about hypertension	Dementia conservations
4	• Mindful eating • Basics of the DASH diet	Effective communication
5	• Balance through movement • Be a DASH detective: sodium is the culprit	Understanding behaviors
6	• Sensation • DASH: throughout your day—breakfast, lunch, and dinner	Safety and driving
7	• Clarity and release • DASH: when eating out	Physician's visits
8	• Staying grounded and moving forward • DASH: diet is only part of the story	Money and legal

[a]MIM: Mindfulness in Motion.

[b]DASH: Dietary Approaches to Stop Hypertension.

Each MIM session will consist of mindfulness-related material—the somatic mind and body connection, relaxation, yoga, meditation, self-awareness, and bodily cues relating to emotional reactivity. Group interaction will center on sharing ideas toward effective practice and practical daily challenges to being mindful. Each class will begin with a prompt for participant contemplation during the session that references a unique weekly theme, which will be reiterated in the session materials. Then, the participants will be led through a body scan, gentle stretching, yoga, progressive relaxation, and mindful eating meditation, ending with formal meditation. Each participant will receive a new weekly link to online video mindfulness practice recordings. The workbook has a diary section to document study activities. The diary is personalized and retained by the participant. Participants will be instructed to perform mindfulness video meditations at least 5 times weekly and record the time in their diary.

The DASH portion focuses on education to increase intakes of vegetables, fruits, and whole grains and decrease intakes of fat, sodium, sugar-sweetened beverages, and sweets. The education includes adapting traditional "soul" food dishes to meet the DASH dietary guidelines. Participants will be provided practical tips on incorporating DASH into their daily lives. They will receive an individual MyPlate (United States Department of Agriculture Center for Nutrition Policy and Promotion) displaying serving sizes and food groups comprising a balanced meal and a home BP monitor. Principal investigator KDW will provide training on using the BP monitor and American Heart Association infographics and video [35,36]. Repetition of key concepts will be embedded throughout the sessions to increase critical thinking and problem-solving [17]. After completion of the 8-week sessions, the MIM DASH participants will receive 8 weekly and then 4 monthly coaching calls to review sessions and support the adoption of self-care behaviors. Our team has successfully delivered the MIM DASH intervention for older African American individuals with hypertension [14].

Caregiver Training (Attention-Control Group)

A study team member trained by the Alzheimer's Association will deliver the caregiver training. Participants in this group will attend eight 1.5-hour group lessons via Zoom for 8 weeks (Table 1). The training uses the Alzheimer's Association caregiver topics listed in Table 1. The Alzheimer's Association

materials are based on the latest scientific evidence of dementia researchers and practitioners in partnership with various community-based, academic, and health care organizations [37].

As with the MIM DASH group, participants will receive educational materials to follow along using Zoom videoconferencing or phone. Participants will have group discussions and role-play using a case study scenario. After completing the 8-week sessions, participants will receive 8 weekly and then 4 monthly social calls to encourage them to maintain their involvement and enhance study retention for subsequent data collection [14].

Fidelity

To maintain the fidelity of the intervention, a detailed protocol manual will be developed for MIM DASH and caregiver training. The MIM facilitators will be enrolled in 8 weekly 1-hour sessions as participants and attend a half-day workshop with return demonstrations. Before leading an MIM session independently, the facilitators will observe an 8-week MIM course and be the designated fidelity checker [38]. During each weekly session, the facilitator will show MIM educational and practice videos created by coinvestigator MDK. For the DASH component, the registered dietitian, also a coinvestigator IKRA, will develop a training plan and materials. Coinvestigator IKRA will deliver the DASH component and train others if needed. The materials for DASH will include a scripted facilitator manual. The principal investigator will also be trained to deliver MIM DASH as a backup facilitator. A study staff member will use a fidelity checklist for MIM DASH to observe the facilitators.

Sample Size and Power Analysis

Our sample size of 28 participants (14 participants per arm) conforms to the recommended sample size rules of 20-30 for pilot studies, as there are diminishing returns for precision, particularly over sizes of 12 per group (“rule of 12s”) [39-41]. Further, a sample of 28 is considered a sufficient pilot sample to determine variance in a main trial powered to 80% to detect an effect of 0.4 [41]. In line with pilot studies, the sample size lacks the power to detect a small-to-medium effect size for aim 3. Therefore, our mediation analysis will not emphasize statistical significance but report point estimates, 95% CIs, and effect sizes.

Measurements

Data collection measures consist of surveys, systolic and diastolic BP, the Pittsburgh Stress Battery, a Food Frequency Questionnaire, and the collection of a hair sample for cortisol analysis. Study staff were trained and observed before independently collecting data. Table 2 provides a data collection timetable, including the constructs, measures, and brief psychometrics provided in validation studies. These data will be collected in the treatment and attention-control groups at baseline, 3 months, and 9 months. Each study visit is estimated to take 2 hours. Maximum flexibility is critical to engage busy caregivers in research. Our team offers several options for data collection. Study visits may be conducted at the participant’s preferred time, day, and location. For example, participants may select the visits at their home, a dedicated research study office, or a private room at a local library. Study visits can take place outside of traditional office hours and workdays. The participant may have this study visit broken up into two 1-hour visits if needed. In these cases, the research staff will prioritize the collection of data that requires an in-person visit (eg, BP and hair collection) and offer to meet again in person or via telephone or Zoom to collect the remaining data.

Table 2. Data collection variables, measures, and psychometrics.

Construct and measures	Psychometrics			
	Baseline	3 mo	9 mo	Reliability and validity
Pre-enrollment screening				
AD8[a]	✓			The area under the curve is 0.908 (95% CI 0.888-0.925)
Biologic				
Age in years	✓			N/A[b]
List of comorbidities	✓			N/A
Measure of health literacy				
Newest Vital Sign	✓			α=.74
Self-care behaviors				
Stress management practices survey part A	✓	✓	✓	α=.71
Healthy Eating Index: Block FFQ[c]	✓		✓	Test-retest reliability, *r*=0.59
DASH[d] index: Calculated from the Block FFQ	✓		✓	The mean correlation coefficient between frequencies of intake of 55 foods assessed by 2 FFQ 12 months apart=0.57
Medication list and BP[e] log	✓	✓	✓	C statistic=0.704
Krousel-Wood medication adherence	✓	✓	✓	C statistic=0.704
Systolic and diastolic BP	✓	✓	✓	κ=0.68
Stress reactivity or resilience				
Daily inventory of stressful events	✓	✓	✓	κ ranged from 0.66 to 0.95
Pittsburgh Stress Battery	✓	✓	✓	Heart rate α=.93; systolic BP α=.92; and diastolic BP α=.93
Stress or QOL[f]				
Perceived Stress Scale (caregiver stress)	✓	✓	✓	α=.83
Folkman 1 question regarding what is most stressful	✓	✓	✓	α=.83
Discrimination in the health care setting consists of 7 questions on a Likert scale to measure the stress of discrimination in the health care setting as a result of age and ethnicity	✓	✓	✓	α=.89
Hair cortisol (chronic stress proxy)	✓		✓	Correlation with 30-day saliva (*r*=0.42, *P*=.04)
WHO-5[g] (QOL)	✓	✓	✓	Sensitivity 0.93; specificity 0.83
Depression-PHQ-9[h]				
PHQ-9 has 9 questions to evaluate mild, moderate, or severe depression	✓	✓	✓	PHQ-9 α=.90
Generalized anxiety disorders				
GAD-7[i] is a 7-item instrument that is used to measure or assess the severity of generalized anxiety disorder	✓	✓	✓	GAD-7 α=.92
Revised memory and behavior checklist				
32-item checklist that assesses activities of daily living and problem behaviors in people living with ADRD[j]	✓	✓	✓	α=.84
Credibility				
The credibility scale has 5 questions		✓		α=.86
Acceptability				
Acceptability of participant preferences has 13 questions		✓		N/A

[a]AD8: 8-item Informant Interview to Differentiate Aging and Dementia.

[b]N/A: not applicable.
[c]FFQ: Food Frequency Questionnaire.
[d]DASH: Dietary Approaches to Stop Hypertension.
[e]BP: blood pressure.
[f]QOL: quality of life.
[g]WHO-5: World Health Organization-5.
[h]PHQ-9: Patient Health Questionnaire-9.
[i]GAD-7: Generalized Anxiety Disorder Assessment.
[j]ADRD: Alzheimer disease and related dementias.

Pre-Enrollment Screening

We will screen potential participants using the Informant Interview to Differentiate Aging and Dementia. The survey is a dementia screening interview that differentiates typical signs of aging from dementia [42]. The instrument contains 8 items to examine memory, orientation, judgment, and function. The instrument demonstrated strong discrimination in a validation study (area under the receiver operating characteristic [ROC] curve=0.834) [42]. A score of 2 or greater indicates that cognitive impairment is likely present.

Biologic

Age in years and a self-reported list of comorbidities will be obtained at baseline.

Measure of Health Literacy

At baseline, we will administer the 6-item Newest Vital Sign (Pfizer Inc) to assess functional health literacy [43]. The data collector will ask the participants to read a food label for a pint of ice cream. Then, participants will be asked questions regarding serving size, calories, carbohydrates, saturated fat, and food allergies. Scores range from 0 to 6, with lower scores indicating lower health literacy. Scores of less than 4 indicate the possibility of the respondent experiencing low literacy. The scale was initially validated in a sample of 492, including English- and Spanish-speaking adults residing in the United States. Our study will use the English version of Newest Vital Sign that has adequate internal consistency (α=.76) and excellent discrimination (area under the ROC curve=0.88) [4].

Self-Care Behaviors

Four measures will be used to assess self-care. First, the stress management practices will be measured using the Measure of Current Status (MOCS) Part A [44]. MOCS is a list of 13 statements, such as “I am able to use muscle relaxation techniques to reduce any tension I experience,” to which participants respond using a Likert scale (0=I cannot do this at all to 4=I can do this extremely well). This scale also has 4 subfactors: relaxation, awareness of tension, having needs met, and coping confidence. Scores will be summed and range from 0 to 52, with higher scores indicating a more significant use of stress management strategies. Reported internal consistency (α) across MOCS Part A was .71, .77, .86, and .89 [44].

Second, the Block Food Frequency Questionnaire will be used as a validated measure with a food and beverage list that includes 127 items, plus supplementary questions to adjust fat, protein, carbohydrate, sugar, and whole grain content. The questionnaire also includes self-reported physical activity [45]. The questionnaire assesses the frequency with which the respondent generally consumes each food or beverage. It has 9 continuous responses ranging from “never” to “every day” for most foods. The Block Food Frequency Questionnaire provides a Healthy Eating Index score for diet quality (range 0-100) [46]. The DASH index will be calculated using the resulting data and a quintile system to score foods related to the DASH diet. All components are equally weighted. Vegetable, fruit (including fruit juice), nuts and legumes, and whole grains intake are scored from 1 (lowest quintile) to 5 (highest quintile). The overall DASH component scores range from 8 to 40.

Third, we will obtain a list of medications from participants. Finally, the Krousel-Wood Medication Adherence scale captures 4 domains of medication adherence behavior. It was developed to identify low adherence to medication refills in older adults [47]. The scale has reported adequate discrimination (area under the ROC curve=0.704). Scores range from 0 to 4, with a score of 1 or greater indicating lower adherence to medication refill behavior.

Stress Reactivity or Resilience

Systolic and diastolic BP is measured 3 times, starting with a 5-minute rest [35]. Stress resilience and reactivity will be assessed using 2 measures. First, the Daily Inventory of Stressful Events was identified from the Science of Behavioral Change research network list of instruments recommended to assess stress reactivity or resilience**.** The instrument is a semistructured interview in which participants report whether specific stressful events had occurred within the past 24 hours. This instrument categorizes scores for each reported stressful event by examining (1) content classification of the stressor, for example, work overload, argument over housework, or traffic problem; (2) who was the focus of the event; (3) threat type experienced (eg, loss, disappointment, or frustration); (4) objective and subjective severity of stressors; and (5) primary appraisals (eg, areas of life that were at risk because of the stressor). Scores range from 0 to 27. This instrument will be distributed and the data will be collected via an automated text link from the Mosio app. Research staff will call participants who prefer not to use Mosio to deliver the inventory daily to gather the data. Second, the Pittsburgh Stress Battery is a test of stress reactivity. It measures BP response during stressful tasks. The tasks include the Stroop color matching test, mirror tracing, and mental mathematics. For example, during the mental math task, participants will be given 3 trials of fundamental arithmetic problems lasting 1 minute per trial. Participants who score 60% or greater will advance to the random-medium level; those who do not will repeat the easy level. Before the third trial, the data collector

will place the BP cuff on the participant's left arm unless contraindicated. At the 30-second mark of the third math trial, the data collector will use an automatic BP machine (clinician grade) to measure systolic BP, diastolic BP, and heart rate. CN is a neuropsychologist who will assist in the interpretation of data. The Pittsburgh Stress Battery was identified as a valid measure of stress reactivity by the Science of Behavior Change Research Network [48].

Stress or QOL

We will use the Perceived Stress Scale, which has 10 items rated on a Likert scale with a reference range of 0-40 regarding stress over the past month, with higher scores indicating higher stress [49]. The scale was validated across 3 samples, 2 made up of college students and 1 from a smoking cessation program. Internal consistency across the 3 samples was 0.84, 0.85, and 0.86. Further, the scale correlated well with measures of stress symptoms (correlations ranged from 0.52 to 0.76), and the measure is appropriate for multiple applications. The Everyday Discrimination Stress in the Healthcare Setting Survey is a 7-item scale adapted for use in a medical setting from the Everyday Discrimination Scale [50]. The survey questions load to a single factor [51]. Using this scale, we will examine the respondents' experiences and frequency of race-based mistreatment while accessing health care. The scale has a reported internal consistency of α=.89 and a test-retest reliability of 0.58. Further, the scale correlates well with the Krieger Experiences of Discrimination (r=0.51), a measure of societal discrimination.

Hair cortisol will be used as a proxy for chronic stress. To collect the hair samples, approximately 25-75 mg of hair (approximate width of shoelace tip when bunched) will be cut from the posterior vertex region of the scalp as close to the scalp as possible. The posterior vertex has the lowest variation in cortisol levels, making it the preferred area for sampling. To prep for assay, the hair sample is cut, washed twice with isopropanol, and dried over 1-3 days. A total of 10-75 mg of hair is placed into a microcentrifuge tube, minced, and then ground in a Retsch 400 Mill. A total of 1.1 mL of high-performance liquid chromatography–grade methanol is added to the ground sample and incubated for 18-24 hours at room temperature with constant agitation. The tubes are centrifuged at 5000 g for 5 minutes at room temperature to pellet the powdered hair. The entire amount (~1 mL) of supernatant is transferred to a clean microcentrifuge tube, and the methanol is removed by evaporation using a stream of air for 6-8 hours at room temperature. The cortisol extract is reconstituted in 100 µL of Salimetric immunoassay cortisol analysis diluent buffer. Samples are assayed in duplicate inter- and intra-assay coefficients of calculated variation. Hair cortisol levels are expressed in hair as picogram per milligram and generally logged due to skewed distributions as needed. Participants will be surveyed on corticosteroid use, as these medications may suppress cortisol levels, and hair care practices, such as frequency of washing, chemical treatments, and hair product use [52]. Hair samples will be collected at baseline and 9 months.

We will use the World Health Organization-5, a short questionnaire consisting of 5 Likert scale statements of well-being over the past 2 weeks [53]. Scores range from 0 to 25, with higher scores indicating greater well-being. The measure is adapted from more extended versions (10 items and 28 items) and is approved for use in diverse populations by the World Health Organization [53].

Depression and Anxiety

The Patient Health Questionnaire (PHQ-9) is a widely used measure of depression symptoms and severity. The questionnaire's 9 items describe conditions that the respondent may be experiencing and how frequently they experience those specific conditions. Each item is scored on a scale of 0-3, with 0=not at all and 3=nearly every day. Items are summed with total ranges of 0-27; scores of 5-9 are mild depression, 10-14 are moderate depression, 15-19 are moderately severe depression, and 20 are severe depression. The measure was initially validated by administering the questionnaire to 6000 patients in 15 clinics [54]. The PHQ-9 demonstrated 88% specificity and 88% sensitivity for a score ≥10. The Generalized Anxiety Disorder Assessment (GAD-7) is based on 7 items scored from 0 to 3. Like the PHQ-9, the GAD-7 asks respondents about the frequency of feelings and behaviors, with 0=not at all and 3=nearly every day. The score is then summed up with totals ranging from 0 to 21, with cutoff scores for mild, moderate, and severe anxiety symptoms being 5, 10, and 15, respectively. The GAD-7 was tested in a sample of 1184 patients and demonstrated strong reliability with both internal consistency (α=.92) and test-retest (0.83) [55].

Memory and Behavior

The Revised Memory and Behavior Problems Checklist assesses the psychological comorbidities of the caregiver and the health status of the person living with ADRD [34]. It consists of 24 items that evaluate activities of daily living and problematic behaviors in people living with ADRD. Factor analysis has 3 distinct subscales related to memory, depression, and disruptive behavior. Scores range from 0 to 96, with higher marks indicating more behavioral problems in the care recipient. Overall, the measure demonstrated good internal consistency (α=.84), with subscale internal consistency ranging from 0.67 to 0.89.

Feasibility and Acceptability

We will track the feasibility of recruitment by counting the number of participants screened per month, the number who are eligible, the number enrolled per month, the average time delay from screening to enrollment, and the completion of data collection [56]. We will track treatment-specific preference ratings (pre- and postintervention) for acceptability. The participants will complete the Acceptability of Participant Preferences 13-item Likert-type survey ranging from 1 (strongly disagree) to 5 (strongly agree). Interventionists will keep detailed intervention session records describing participant responses to the intervention. For the MIM DASH group, we will collect data regarding the usage of self-care equipment (home BP monitor and MyPlate) from follow-up coaching calls. We will use a credibility scale for both groups regarding the expectation of benefits of this study. The Credibility Scale (α=.86) measures attitudes toward the treatment condition and the participants'

expectation of benefit once the treatment has been explained [57,58]. The scale consists of 5 questions rated 0 (not at all confident) to 10 (very confident). Higher scores, up to 45, will indicate greater credibility of the treatment condition. This will also aid in determining participants' willingness to be randomized for future studies.

Data Analysis Plan

To assess data quality, we will check biweekly data for completeness, accuracy, timeliness, and consistency. These checks will be completed by examining frequencies and descriptive statistics, summarizing participant characteristics, and examining variable distributions. Once identified, data anomalies will be fully investigated, and remediation strategies will be considered as appropriate.

We acknowledge potential confounders, such as health literacy and problem behaviors that the care recipient exhibits, that could influence participation in the intervention and outcomes. As this study's sample size is small, we are limited in the number of covariates that can be used in the analysis. Therefore, we will control for the participant's health literacy and the participant's report of problem behaviors of the care recipient.

To address aim 1, determining the feasibility and acceptability of MIM DASH and caregiver training for African American female caregivers with hypertension, we will conduct descriptive data analyses to report findings related to feasibility and acceptability. These analyses will include a summary of participant background characteristics, including age, educational attainment, relationship to the individuals they care for, and baseline health measures. Descriptive analysis will include frequency counts and percentages for categorical variables and mean, median, range, and SD for continuous variables.

Next, we will use descriptive statistics to examine the feasibility and acceptability of the MIM DASH intervention and caregiver training, including (1) the approach-to-enrollment ratio, (2) the proportion of participants that complete all 8 sessions of the assigned intervention arm and attention control arm, (3) frequency of completion of the follow-up calls, and (4) proportion of sessions that the interventionist deviates from the delivery of the intervention protocol. Further, we will report the mean rating of the MIM DASH intervention from participants and the proportion of participants rating the MIM DASH intervention positively (4 or above). We will report point estimates along with 95% CIs to indicate the precision of these estimates. Based on our previous experience enrolling African American participants in studies, feasibility will be defined by (1) enrolling at least 40% of potentially eligible patients and (2) completing at least 75% of the assigned intervention. Acceptability will be determined by an average rating of 4 or higher and at least 80% of participants rating the intervention positively.

To address aim 2, comparing the influence of MIM DASH on caregiver stress and QOL with the influence of caregiver training, we will conduct an intention-to-treat (ITT) analysis. Thus, all outcomes for enrolled participants will be included regardless of the intervention dosage. The Perceived Stress Scale will be used to measure caregiver stress, and the cortisol level extracted from hair will be a proxy measure of chronic stress. The World Health Organization-5 will be used to measure QOL. The data will be collected in person and documented in REDCap at baseline and 3 and 9 months after the intervention. Descriptive statistics, including mean and SD, will be used to summarize each primary and secondary outcome. We will also report mean differences, 95% CIs, and effect sizes for both within- and between-group differences at each visit. The fixed effect of MIM DASH intervention will be examined by mixed-effects models with measurements nested within persons.

To address aim 3, investigating the potential mediation effects of stress reactivity or resilience between each program and self-care behaviors, we will conduct a mediation analysis with self-care as the outcome (y), participation in MIM DASH as the predictor (x), and stress resilience or reactivity as the mediator (m). We hypothesize that heightened stress reactivity will diminish the relationship (between x and y). In contrast, heightened stress resilience will enhance the relationship between MIM DASH (x) and adopting self-care behaviors (y). To quantify these variables, we will use the Daily Inventory of Stressful Events and the Pittsburgh Stress Battery to measure stress reactivity or resilience. Self-care behaviors will be calculated using the Stress Management Practices survey and the DASH eating index by the Block Food Frequency Questionnaire. The data will be collected in person and by online surveys at baseline and 3 and 9 months after the intervention. We will report descriptive statistics for each of the measures. Finally, we will conduct a mediation analysis to examine if stress resilience or reactivity explains a significant amount of the relationship between MIM DASH participation and self-care behavior. The estimated effects of the mediation and 95% CIs will be reported.

Ethical Considerations

This study has received ethical approval from the Ohio State University Behavioral and Social Sciences institutional review board (IRB; approval 2022B0031) and conforms to the World Medical Association's Declaration of Helsinki requirements. All participants were provided written informed consent before their inclusion.

This study will use descriptive data through surveys and objective measures that include computer tasks while measuring BP, heart rate, and hair samples for cortisol level. The research has minimal risk, as the Ohio State University Behavioral and Social Sciences IRB deemed. There may be no direct benefit to the participant. However, their participation may provide data that will provide insight into ways African American women can reduce their BP and improve their overall health. Autonomy and rights will be given to participants, including the right of refusal at any time, without penalty or loss of benefits to which they are otherwise entitled. If a participant is a student or employee at Ohio State, their decision will not affect their grades or employment status.

The consent and study staff will also describe the use of Mosio for 2-way communication via text messaging. The restricted website associated with Mosio will contain the participant's cell phone and study ID numbers, which the designated study

staff member assigns. The participants can choose not to use the Mosio system at any time. Participants will be informed that there are no costs related to participation. They will not incur any additional charges related to text messages to and from Mosio over and above what they normally have.

All participants will receive the BP categories flyer from the American Heart Association and be instructed to consult their provider if they have a systolic BP higher than 180 mm Hg or a diastolic BP higher than 120 mm Hg. The participant will be instructed to seek immediate assistance or contact their provider. The data monitoring plan is in place and consists of a physician, nurse scientist, and a biostatistician who will review data and any unexpected events at least once per year. Participants will receive US $50 after completing each data collection point, including the home BP monitor, for a total of US $150.

Study staff will be carefully trained to protect participant confidentiality. They will work with participants to devise a plan for contacting them by phone, email, text messaging, or some other means determined by the participant and decide if messages may be left. Participants will be assigned a study ID number, and a master log will be created associating participant names and study numbers. The master log will be stored separately from the College of Nursing's secure server. Only the primary investigator and designated study staff will have access to the master log, which will be destroyed at the end of this study. Study staff's access to study data will be determined based on the relevance to their responsibilities. Only aggregate data will be reported for the dissemination of study findings. Duo Mobile authentication and Zscaler cloud security are used to access REDCap and the College of Nursing secure server.

To mitigate the risk that participants violate the privacy and confidentiality of others in their group sessions, we will ask that those participants (and their family or support person) refrain from discussing with other participants outside the group. Likewise, they will be asked not to acknowledge meeting if they encounter each other elsewhere. These steps are not foolproof, and participants will be informed of the associated risks at the time of consent.

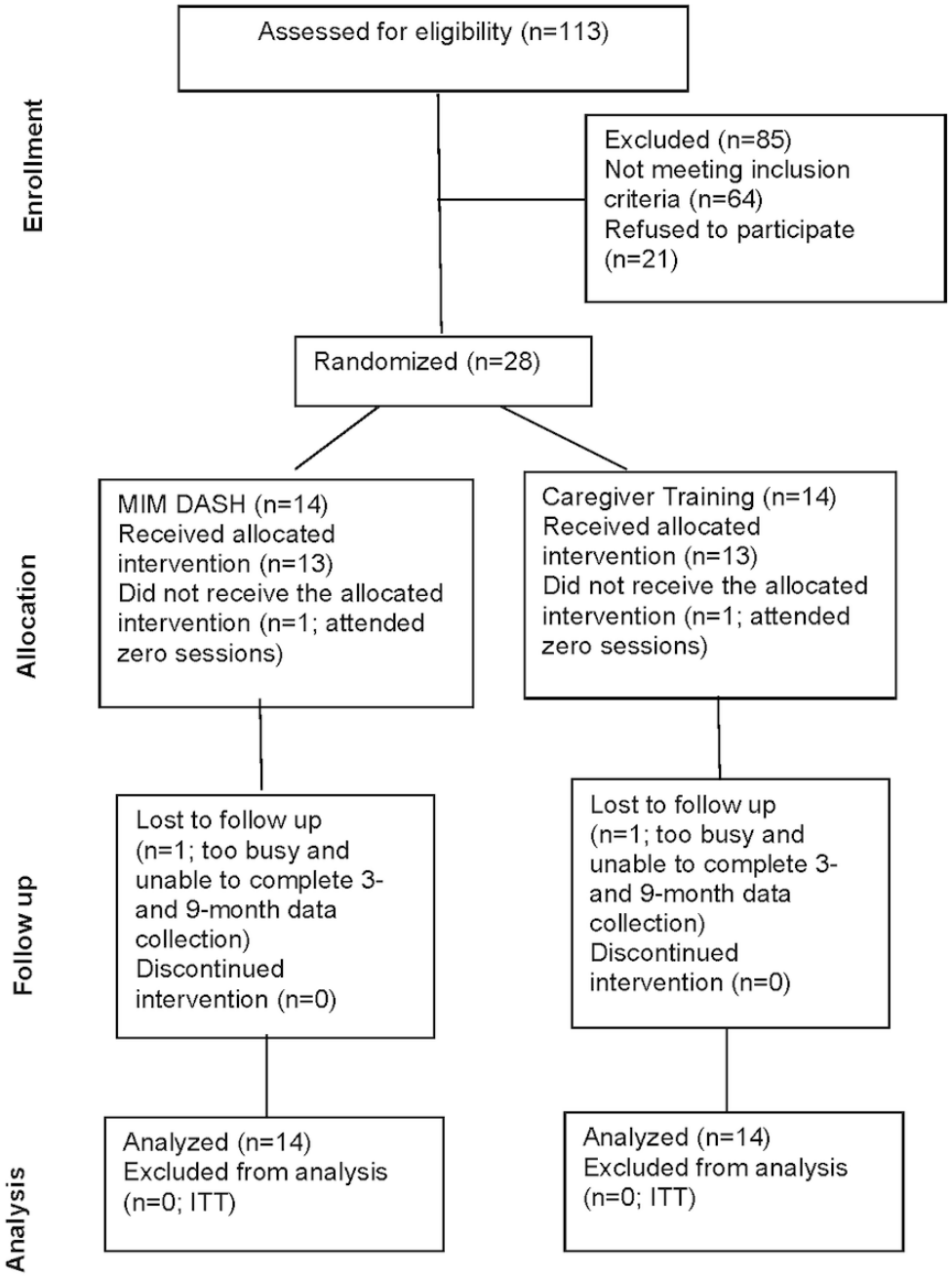
Results

The study was approved by the IRB in April 2022 and funded in May 2022. The first data were collected in January 2023, and the last data were collected in September 2024. Participants were recruited beginning in February 2023. Intervention delivery commenced in April 2023 for the first cohort and November 2023 for the second cohort. Completion of data analysis for all aims is anticipated in spring 2025. A CONSORT (Consolidated Standards of Reporting Trials) flow diagram is presented in Figure 2.

Of the 28 individuals enrolled, 82% (n=23) and 92% (n=26) completed the 3-month and 9-month data collection, respectively. Two participants were lost to follow-up. The mean age of the participants was 62.4 (SD 7.98) years. Eighteen participants were included in the first cohort, and 10 were included in the second cohort.

The participants had a mean systolic BP of 128 (SD 19) mm Hg and diastolic BP of 79 (SD 10) mm Hg. The Newest Vital Sign (health literacy) screen had a mean score of 4.08 (SD 4.5), with a reference range of 0-6 where lower scores indicating lower health literacy. and The Perceived Stress Scale had a score of 12.75 (SD 6.7), with a reference range of 0-30 where higher scores indicating greater stress. Most participants reported that MIM DASH was acceptable (at a mean score of 59.08, SD 7.38, compared to 60.83, SD 5.56 for caregiver training). Regarding feasibility, as reflected in attendance, MIM DASH participants had a mean attendance of 6.3 (SD 2.3) sessions, and the caregiver training group had 4.9 (SD 2.9) sessions.

Figure 2. CONSORT flow diagram illustrating participant progression through the eligibility, allocation, follow-up, and final analysis stages of the clinical trial. CONSORT: Consolidated Standards of Reporting Trials; DASH: Dietary Approaches to Stop Hypertension; ITT: intention-to-treat analysis; MIM: Mindfulness in Motion.



Discussion

Principal Findings

This paper presents a protocol to deliver a culturally responsive mind-body intervention (MIM DASH) specifically designed for African American women who have hypertension and are family caregivers of individuals living with ADRD. We hypothesize that the MIM DASH intervention will be feasible and acceptable, reduce stress, and improve QOL for African American female caregivers. Additionally, we explore behavioral change mechanisms, stress reactivity, and stress resilience that may explain how self-care is adopted or not, which can inform future studies. We hypothesize that lower stress reactivity and higher stress resilience will result in higher adoption of self-care behaviors. Although numerous studies support self-care behaviors (eg, mindfulness practice, healthy eating, and physical activity) to prevent cardiovascular disease—a complication of uncontrolled hypertension [59]—gaps remain in targeting interventions to address the complex interplay of caregiving stress and adoption of healthy self-care for African American female family caregivers of individuals living with ADRD. The findings from this study may contribute to developing and disseminating culturally responsive interventions to improve self-care behaviors and augment the treatment of hypertension and other cardiovascular disease risk factors.

Our principal finding thus far—that MIM DASH is feasible and acceptable—is similar to other studies that have used

mindfulness as an intervention for stress and to promote healthy dietary habits [60-62]. Unlike previous interventions that lack cultural responsiveness or sufficient representation of African American participants, MIM DASH focuses on African American caregivers. This culturally responsive intervention integrates evidence-based approaches such as DASH and mindfulness, offering 8 weekly sessions focusing on healthy eating and stress reduction. The intervention also builds upon prior research but addresses critical gaps in cultural relevance and participant diversity. For example, noncaregiver studies on cardiovascular disease risk reduction, such as those promoting physical activity and healthy eating, often exclude culturally responsive strategies or include remarkably few African American participants, reducing their applicability to African American caregivers [59,60,63]. MIM DASH addresses these limitations by offering a potentially scalable, tailored approach that acknowledges this population's cultural and systemic barriers.

Limitations of This Study

This study will examine the feasibility and acceptability of the MIM DASH intervention in African American female caregivers of individuals living with ADRD. However, this protocol may have some limitations. The small sample size is a notable limitation, which may restrict the generalizability of the findings. Re-evaluation of inclusion criteria, including only those with a diagnosis of hypertension and those on an antihypertensive basis, may be too restrictive, making this study less generalizable. The multiple measures for data collection and the use of the Pittsburgh Stress Battery as measures of stress and resilience may increase the risk of burden and missing data. Although the Pittsburgh Stress Battery provides a standardized means of cardiovascular reactions to acute stress, it is limited in assessing chronic stressors. The limitations of using the Pittsburgh Stress Battery inventory include time to administer the test, challenges of internet connectivity to access the mirror test, and the cost of materials for administering the test. Other measures, such as heart rate variability, would burden participants and data collectors less [48]. Additionally, other theoretical mechanisms of behavior change, such as self-regulation (temporal discounting of immediate small rewards over larger future rewards) and interpersonal and social processes (social interactions), could be used as the facilitators of behavior change. Given that the MIM DASH intervention was delivered in a group setting and includes elements of self-regulation through mindfulness practice, future studies may consider exploring other, less costly mechanisms of behavior change.

Future studies with more extensive and diverse samples will be necessary to validate and scale the intervention. Furthermore, while this study aims to evaluate feasibility and acceptability, long-term outcomes such as sustained behavior change and clinical improvements in hypertension management remain unexplored.

Future Directions

The findings of this study will be disseminated to this study's participants in the form of a brief report or newsletter that will be submitted for approval to the Ohio State University IRB. Additionally, presentations will be given to the local African American community, churches, and Alzheimer's disease support groups. The findings will be disseminated to the scientific community using multiple strategies, such as presentations at the Gerontological Society of America, the Alzheimer's Association International Conference, and nursing and interprofessional peer-reviewed journals. By disseminating our study findings via traditional (researchers) and nontraditional (community), we will contribute to the science of behavior change and ADRD research for African American caregivers with hypertension.

To prepare for scalability, we will evaluate the delivery of the intervention from the facilitators' perspective to determine what worked well and what needs to be refined. We are refining the training materials and facilitator fidelity monitoring for a larger trial. Data from the pilot feasibility study will help to inform the sample size for efficacy testing. To scale up, we will include additional measures of self-care management and behavioral change, such as actigraphy. We will use a framework such as Reach, Effectiveness, Adoption, Implementation, and Maintenance (RE-AIM), which provides a guide for evaluating the reach, effectiveness, adoption, implementation, and maintenance within the objectives of a larger randomized controlled trial [62]. If efficacy is successful, then using such a framework as RE-AIM would position the work for real-world implementation. Funding for the efficacy trial will be sought through grants from the National Institute on Aging or nonprofit organizations such as the American Heart Association, Alzheimer's Association, or Bright Focus.

Conclusion

The burden on African American dementia caregivers is expected to rise alongside the aging US population. Addressing the health of these caregivers is paramount to sustaining effective care for individuals with ADRD. The MIM DASH intervention represents a step toward providing culturally responsive hypertension self-care strategies for African American caregivers. This protocol sets the stage for improved caregiver health and contributes to the growing body of research on tailored interventions that address health disparities in minority populations.

Acknowledgments

KDW is supported by the Robert Wood Johnson Foundation Harold Amos Medical Faculty Development Program. This study is also supported, in part, by the National Center for Advancing Translational Sciences of the National Institutes of Health (NIH) under grant UL1TR002733, R01HL170038, and the NIH–National Institute on Aging 1R21AG077069. The content is solely the authors' responsibility and does not necessarily represent the official views of the NIH or any other funding entity.

Data Availability

The datasets generated and analyzed during this study are not publicly available but are available from the corresponding author upon reasonable request. Data sharing will comply with ethical guidelines and any applicable regulatory requirements.

Authors' Contributions

KDW, IKRA, MDK, and KMR designed the study. NPH contributed to the statistical planning and analysis. KDW, IKRA, NPH, SPB, NP, BK, and MDK contributed to the writing of the paper. All authors (KDW, IKRA, NPH, KMR, KOM, DN, NP, BK, SPB, CN, DA, and MDK) reviewed and edited this paper before submission. All authors have read and agreed to the published version of this paper.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer review reports by the MESH - Biobehavioral Mechanisms of Emotion, Stress and Health Study Section (National Institutes of Health, USA).
[PDF File (Adobe PDF File), 152 KB - resprot_v14i1e66975_app1.pdf]

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Abbreviations

ADRD: Alzheimer disease and related dementias
BP: blood pressure
CONSORT: Consolidated Standards of Reporting Trials
DASH: Dietary Approaches to Stop Hypertension
GAD-7: Generalized Anxiety Disorder Assessment
IRB: institutional review board
ITT: intention-to-treat analysis
MIM: Mindfulness in Motion
MOCS: Measure of Current Status
NIA: National Institutes on Aging
PHQ-9: Patient Health Questionnaire-9
QOL: quality of life
RE-AIM: Reach, Effectiveness, Adoption, Implementation, and Maintenance
REDCap: Research Electronic Data Capture
ROC: receiver operating characteristic

Edited by A Schwartz; submitted 27.09.24; this is a non–peer-reviewed article;accepted 14.02.25; published 27.03.25.

Please cite as:
Wright KD, Richards Adams IK, Helsabeck NP, Rose KM, Moss KO, Nemati D, Palmer N, Kim B, Pokhrel Bhattarai S, Nguyen C, Addison D, Klatt MD
Stress and Hypertension Among African American Female Family Caregivers of Persons Living With Alzheimer Disease and Related Dementias: Protocol for a Pilot Internet-Based Randomized Controlled Trial
JMIR Res Protoc 2025;14:e66975
URL: https://www.researchprotocols.org/2025/1/e66975
doi:10.2196/66975
PMID:

Protocol

Escape Game to Promote Students' Mental Health Outcomes in the Aftermaths of COVID-19 Pandemic: Protocol for a Mixed Methods Study Evaluating a Cocreated Intervention

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Abstract

Background: The COVID-19 pandemic and the protracted lockdowns have heavily impacted university students' mental health. Digital Escape Games represent a good means to reach students and propose them solutions for their psychological well-being.

Objective: This study aimed to evaluate a cocreated digital Escape Game on students' mental health in the aftermath of the COVID-19 pandemic, called EscapeCovid Game. The evaluation of the effectiveness of this stand-alone intervention concerns mental health outcomes (mental health literacy, appraisal and change of beliefs about mental health, management of emotions, and development of coping strategies) and the appreciation and relevance of the game.

Methods: A randomized controlled trial with pre- and posttest data collection (online questionnaires with validated scales) is conducted among 500 students in Bordeaux, France, to evaluate the EscapeCovid Game cocreated with students, researchers, health professionals, and web developers. A subsample of students is randomly selected for responding to a semistructured interview following a mixed methods design. Recruitment is done through mail invitations from student associations and presentations in university classes. Half of the sample of the trial plays the Escape Game, while the other half receives an email with mental health–related information. Within the game, students discuss their personal experiences. The text is further used for the qualitative analyses. The whole study is carried out online.

Results: The EscapeCovid Game has been developed, tested, and finalized by the end of March 2023. As of November 4, 2024, a total of 191 students have answered the baseline questionnaire (90 intervention vs 101 control). A total of 23 students have played the game and 53 are in the control arm. Among participants, by the end of September 20, 2023, twenty were interviewed (10 intervention and 10 control) reaching sample saturation. According to preliminary results, the EscapeCovid Game has had a positive impact on all defined outcomes, while the email has been effective in increasing knowledge on resources available and on coping strategies and meditation techniques. We expect the trial to be completed by the end of June 2025.

Conclusions: The mixed methods findings of this study are due to demonstrate the effectiveness of the EscapeCovid Game in improving students' mental health outcomes. Preliminary results from the qualitative substudy are promising: in the aftermath of the COVID-19 crisis, this intervention is intended to promote players' mental health through gamification, knowledge transfer, and a learning-by-doing approach.

Trial Registration: ClinicalTrials.gov NCT06720792; https://clinicaltrials.gov/study/NCT06720792

International Registered Report Identifier (IRRID): DERR1-10.2196/64068

(JMIR Res Protoc 2025;14:e64068) doi:10.2196/64068

KEYWORDS

Escape game; pilot randomized controlled trial; Covid-19; cocreation; students; mobile phone

Introduction

Background

Mental health problems among young people have skyrocketed with the COVID-19 crisis [1]. Repeated lockdowns and curfews between 2020 and 2021 were the causes of a general mental distress well-documented in the literature [2]. These measures had detrimental and long-lasting psychosocial consequences like acute stress and trauma-related disorders, particularly in specific at-risk populations such as students [3].

University students were in fact concerned as a vulnerable population. Independently from the presence of a pandemic, suicide is the second leading cause of death among them and, by the age of 25 years, 75% of those who will have a mental health disorder have had their first onset [4,5]. During the COVID-19 crisis, students were exposed to supplementary heavy stressors: isolation, classes exclusively online, and uncertainty about their academic and professional future. Several studies have shown how the COVID-19 pandemic and its lockdowns had negatively affected students' mental health across the world [6,7]. Therefore, it is fundamental to implement mental health promotion and prevention interventions aimed to support students during this crisis. Evaluation of these interventions is a pivotal process in public health research to determine their effectiveness and improve their quality in relation to the targeted population [8].

Among innovative interventions, Escape Games are "live-action team-based games where players discover clues, and solve puzzles [...] in order to accomplish a specific goal, usually escaping from the room, in a limited amount of time" [9]. Escape Games are the digital internet-based online version of Escape rooms. Previous research has proved that Escape Games can increase knowledge on health-related topics using the learning-by-doing technique [10]. Furthermore, gamification is based on a learning by making mistakes approach. Related flow theory states that simple simulation can be perceived as more anxiety-provoking than the purely playful approach which integrates error as a dynamic element.

Compared with other interventions, they are supposed to be more attractive and acceptable for a young audience, especially because of their gamification approach. Gamification relies on immersion through which players feel embedded in the game as several psychosocial determinants (eg, social support, environment) are leveraged. In particular, health-related Escape Games use puzzle solving as a strategy to access health promotion and prevention messages. The step-by-step sequencing and the resolution of the enigmas stimulate the learning loop and over-solicit the cognitive capacity of participants (ie, better awareness of the concerned topic, and better capacity to deconstruct one's beliefs).

Escape Games can contribute not only to increasing knowledge, but also to behavioral change by providing instruments to act in real-life. For instance, by relying on teamwork, participants can develop the notion of mutual support which could be transposed to their communities. Thus, individual and collective behaviors are at stake. The positive outcomes of Escape Games are boosted by their digitalization: through the internet, Escape Games can reach a larger audience with no time or space limit. This should be even more promising in a period where face-to-face contact is very limited. Success of these interventions can also be fostered if they are cocreated with the target population through a design thinking approach (ie, understanding of users' experience and needs, brainstorming sessions with several stakeholders, and testing of the tool). Cocreation is a collaborative approach offering various benefits such as enriched insight into problems and increased feasibility and acceptability [11]. We applied this approach to produce the EscapeCovid Game, a stand-alone intervention to promote mental health and prevent psychological diseases among university students in the era of COVID-19.

The EscapeCovid Game

The EscapeCovid Game is focused on four main outcomes: (1) mental health literacy (knowledge of the concept of mental health, from illnesses to psychological well-being), (2) appraisal and change of beliefs about mental health (destigmatization), (3) management of emotions (their recognition and regulation), and (4) development of coping strategies (building resilience). It addresses specifically anxiety and depression whose symptoms were exacerbated by the COVID-19 crisis including the measures undertaken to limit the spread of the virus (eg, repeated lockdowns and curfews, University closure).

The underpinning theories of the game are the COM-B model of behavior (capability, opportunity, and motivation to change behavior) [12], the Plutchik's wheel of emotions (visualization of emotions to change behavior) [13], and the Transtheoretical model of behavior change (stages of change, processes of change, levels of change, self-efficacy, and decisional balance [14]).

The EscapeCovid Game takes place in Thomas' apartment which he shares with another student, Hana. Thomas is a university student and we follow him during a typical day in lockdown. To move from one room to another, players must solve all the puzzles by clicking on the objects spread out in Thomas' room. At the end of each room scenario, a set of cards is shown, with each card containing a mental health-related message. The cards synthesize the messages transmitted through the puzzles in the room.

The game can be played in groups of 4 players who help each other and discuss using their computer cameras and headphones. All along the game, they are helped by a game guide who explains the rules and answers any questions. The same guide concludes the game session with a final debrief where all participants share their experiences.

The EscapeCovid Game has been cocreated jointly by a team of researchers at the University of Bordeaux and a start-up specialized in the production of both physical and digital Escape Rooms, Tricky, in France. We used the PRODUCES (Problem, Objective, Design, End Users, Cocreators, Evaluation, and Scalability) framework [15] composed of 3 steps. First, we tested the hypothesis that the game was effective in promoting the four mental health-related outcomes. Second, we

accumulated evidence on the good functioning of the game. Third, we leveraged the right behavior change mechanisms.

Within this framework, the game was cocreated in particular by 1 project manager from a public health research center, 1 student intern completing a degree in cognitive engineering, 1 game designer, 1 developer specialized in computer science, 1 medical doctor, and 1 psychology researcher. Supplementary data to improve the game was provided by 45 questionnaires on the appreciation and relevance of the game by student players, and qualitative semistructured interviews with 10 students of the same sample. The cocreation of the game is detailed in an article by Labrosse et al [16].

Objective and Hypotheses

The objective of this study is to evaluate among a population of university students the effectiveness of the EscapeCOVID Game on 4 mental health outcomes: mental health literacy, appraisal and change of beliefs about mental health, management of emotions, and development of coping strategies. The appreciation and relevance of the game are also considered in the overall evaluation of the game. This stand-alone intervention is implemented in the era of the COVID-19 pandemic.

Consequential research hypotheses of the study are (1) compared with a group receiving another classical intervention, after playing the digital Escape Game and having received a debriefing, students remarkably improve their mental health literacy, appraisal, and change of beliefs about mental health, management of emotions, and development of coping strategies; and (2) cocreation enhances appreciation and relevance of the digital Escape Game among university students.

The objective of this study is original since, to the best of our knowledge, no Escape Game on students' mental health outcomes has been developed before following a cocreation approach and evaluated through mixed-methods to prove its effectiveness.

Methods

Evaluation of the EscapeCovid Game

Mixed Methods Research Design

The EscapeCovid Game is evaluated through a mixed-methods approach using exclusively online data from a Randomized Controlled Trial (RCT) including 2 web-based questionnaires, and video interviewing. Within the mixed methods framework, we apply the embedded design [17]. According to this design, the quantitative and the qualitative data are collected simultaneously, but the qualitative data is embedded within the quantitative data. This means that the data from the questionnaires is prominent, but we still need to understand how the qualitative data further explains the effectiveness of the intervention.

As for the cocreation of the Escape Game, all tasks of the evaluation are conducted jointly by the university research team and the private start-up, thus proving the sharing of skills and the management of potential risks and their solutions in a combined effort. In particular, the research team is in charge of the collection and analyses of the data, while the start-up handles logistics including the organization of the game sessions. The postulate of the start-up is that a product can be really evaluated as significantly efficient in the serious game industry mostly or exclusively through the collaboration with a public research laboratory.

The Randomized Controlled Trial

We implement a rigorous RCT design using pre- and postintervention data coming from online self-administered questionnaires. The sample must be of at least 500 students at the University of Bordeaux. We estimated a sample size of 500 participants for the 2 arms: statistical power=.80, Cronbach α=.05, Cohen d=0.5, and 40% attrition with a 2:1 allocation ratio for the intervention group.

At study entry, the 500 students complete the online baseline questionnaire. Among them, 250 students play the EscapeCovid Game while 250 students receive an email with tips and resources for managing their stress during the COVID-19 pandemic. Participants are randomized so that the 2 groups are similar in terms of sex, age, and field of study (stratified balanced randomization). Participants are informed from the beginning of the study that they can be allocated to either the intervention of interest or the comparator. We tell students in the control arm that they are in a waiting list and that they can play the game once the experiment is concluded.

Inclusion is stopped when at least 500 participants have completed at least 3 quarters of each questionnaire, and 250 have played the game until the end. The statistician and the project manager of the EscapeCovid study are in charge of generating the random allocation sequence, enrolling participants, and assign them to one of the 2 arms.

Briefly, the 250 students of the intervention arm (1) complete the online baseline questionnaire, (2) play the EscapeCovid Game at their home within the week after the online baseline questionnaire—a link to the game is given at the end of the questionnaire, and (3) complete the same online questionnaire of the baseline plus some items on the appreciation of the game (satisfaction survey) 2 days after having played the game. After some tests with Tricky staff, the game duration is estimated at about 2 hours, from the online registration with the creation of an account, until the end of the debrief. Instructions to connect and play online are provided in an email sent by the start-up to the student of the intervention arm 2 days before the game session.

The 250 students of the control arm will (1) complete the baseline online questionnaire, (2) receive the same day an email with tips and resources to manage their stress during the COVID-19 pandemic, and (3) complete the same internet-based questionnaire of the baseline 2 days after having received the email with tips and resources.

Students can complete all steps of the evaluation from anywhere using a smartphone or a computer. However, they can play the game exclusively from home, considering the need for a stable internet connection and a performance computer.

Internet-Based Interviews

There are two sources of qualitative data: (1) semistructured interviews after the intervention with students from both arms and (2) open discussion with the game guide at the end of the game session. Concerning the first source of qualitative data, 20 students were randomly selected among the 2 groups (10 for the intervention arm, and 10 for the control arm) to respond to a semistructured interview. For the discussion embedded in the game, the text produced during the debrief is recorded and analyzed so that the developers of the start-up can work on an algorithm for building a chatbot messenger capable of providing tailored advice to gamers, replacing the game guide. Machine learning will be used for this purpose. In terms of simplicity and feasibility, the sample is recruited on the sole criterion of sex, 50% of girls, through sample saturation. The interviews have been conducted remotely by a public health researcher through an internet-based interview tool. Students are recommended to make the interview at home.

Recruitment of Study Population

Inclusion criteria are (1) being a student at the University of Bordeaux, (2) being aged ≥18 years, (3) understanding, speaking, and writing French, and (4) having given the electronic consent to be enrolled in the study. We consider that students have a sufficient level of computer literacy for playing the game as only few basic skills are required: knowing how to navigate the web, keyboarding, and typing. These skills are essential for any student from any field of study and represent a prerequisite for the undergraduate and graduate programs at the University of Bordeaux.

Students are invited through the social media of the study partners (University of Bordeaux and Tricky), posts in the Facebook groups of more than 100 student associations, and mailing lists from the University of Bordeaux. The associations are manually selected from a list provided by the University of Bordeaux to cover the different fields of study. Overall, we plan to reach about 10,000 students which is a substantial number considering potential very low enrollment and retention rates. The invitations by email are sent to a maximum of 500 recipients at a time, so that we can proceed step by step with the inclusion of participants and the organization and schedule of the game sessions. The invitations will be sent until we reach a sample of a minimum number of 500 students.

The recruitment is exclusively web-based. Clicking on the link displayed on social media posts or on the text of the email, students will access an online form to enter the study.

The inclusion of participants to the RCT will be conducted based on a continuous monitoring through statistical analysis. Data on sex are available only for males and females, since information on gender is not reported in the University records. The year of study goes from 1 (first year of university) to >8 (corresponding to a doctoral degree or a diploma in medicine). The fields of study offered by the University of Bordeaux are more than 50,000 and are categorized in Health Studies, Law and Economics, Technical Sciences, and Human and Social Sciences.

Finally, a maximum of 5 reminders will be sent through email to all 500 participants for the completion of the second questionnaire. For the intervention group, an additional maximum of 5 reminders will be sent to schedule a game session and eventually play the game. An additional maximum of 5 reminders will be sent to the students randomly selected to be interviewed. If after the 5 reminders per phase of the study, the student does not reply, we will proceed with the invitation of new students from the contacts we have from the University and attached associations.

The participation to the study is completely voluntary and all students are rewarded with a €20 (US $21.59) gift card.

Data Collection Tools

The pre and postintervention questionnaires are administered through the Sphinx software (Georg Brandl) distributing surveys on all media (web, smartphone, QR code, and SMS). The data are automatically imported in a Microsoft Excel file.

The first questionnaire is composed of 112 items. It includes validated scales measuring mental health literacy (French Mental Health Literacy Scale [MHLS-FR]) [18], beliefs about mental health (Health Belief Model [HBM]) [19], emotions (Plutchik's wheel of emotions) [20], Coping Strategies (Ways of coping questionnaire) [21], Depression (Patient Health Questionnaire-9 [PHQ-9]) [22], Anxiety (Generalized Anxiety Disorder-7 Scale [GAD-7]) [23], Stress (Perceived Stress Scale [PSS4]) [24], and Help-seeking actions (Kessler Psychological Distress Scale in help-seeking youth [K6]) [25]. Sociodemographic information (email address, gender, date of birth, field of study, year of study, and self-perceived health) are also collected to assess the representativeness of the sample (stratifications by sex, age, field of study etc). A question specifically asks the gender giving students the possibility to indicate whether they belong to the LGBT (lesbian, gay, bisexual, and transgender) category (considering the confidentiality of this data). The question of gender as a determinant of mental health will be important to analyze the results considering this confounding variable if the number of individuals is sufficient. The questionnaire is developed by several researchers through different stages of drafts and reviews, following a structured survey construction method in 5 steps [26]. Operational staff members from the team of the coordinator and a group of students pretest the questionnaire for readability, comprehensibility, and face validity. The response modalities are varied: multiple choice, binary responses, Likert scales, and visual analog scales. Mental health indicators and appreciation and relevance results are the main outcomes of the study. All items provided the nonresponse option "not applicable," "I don't know," and "I do not want to answer." Respondents are required to select an option from a predefined list. The questionnaire is not validated if at least one question is not answered. Respondents are not able to review and change their answers, but they can ask the principal investigator for a document with exclusively their answers. Corrections cannot be made manually in the database in order to avoid any further error.

The second questionnaire is the same, but it does not include the sociodemographic items. It contains new items on the appreciation and relevance of either the game or the email

(satisfaction survey). These items are created ad hoc, but are also inspired by existing instruments evaluating digital health interventions (eg, items by Fadda et al [27]). The questionnaires, composed of both validated scales, sociodemographic items, and satisfaction survey questions, have been developed by 1 researcher and 1 project manager in public health. A pool of researchers in psychology and in statistics have reviewed the questionnaire to assess its readability, understanding, and relevance. The questionnaires have been tested on the internet by 10 students of the School of Public Health of the University of Bordeaux. Testers reported some technical errors, that has bugs and repetitions of items, and suggested different wording for making the questionnaires more adapted to a young target population between 18 and 25 years of age. The questionnaires were constructed following the CHERRIES (Checklist for Reporting Results of Internet E-Surveys) [28]. For both questionnaires, outcomes are self-assessed. The questionnaires are available in Multimedia Appendix 1.

Qualitative data from the semistructured interviews are collected through an ad hoc grid including questions on the impact of the game or email on mental health–related knowledge, on the access to mental health care services and the attitudes toward mental illnesses or stigmatization. Participants are particularly asked to evaluate whether the game is adapted to their needs and to discuss the cocreation approach as a means to produce tailored interventions. The main objective of these interviews is to assess the appreciation and the relevance of the game. The interview grids are available in Multimedia Appendix 2.

Questions addressed to the control group allow to capture the utility of the contents of the email (eg, list of mental health care services and a short description of mental health problems) and to compare the contribution of each tool to knowledge about mental health. Qualitative data form the debrief correspond to the free discussion between the players and the game guide. The latter follows a script and makes questions on the specific topics covered by the game: overall recognition and management of the emotions; symptoms of depression, stress and anxiety; relevance of mental health in daily life; and sources available in the case of a mental health problem.

The semistructured interviews were conducted by a public health researcher trained in qualitative data analyses. The project manager analyzed the same dataset using the triangulation approach.

The quality of both quantitative and qualitative data is ensured by keeping documentation accurate, that are clean databases and well-stored texts. Ensuring ethical standards is a further guarantee of the quality of this study.

Data Analyses

Overall Mixed Methods Analyses

First, we will conduct statistical analyses on quantitative data (descriptive statistics, modeling, and exploratory data analysis) processed from the RCT; second, we have analyzed the discourse of qualitative data (thematic analysis based on a predefined interview guide); and third, we will couple the analysis of both types of data. In particular, we will integrate quantitative and qualitative data for the purposes of convergence, contextualization, and expansion to gain a detailed understanding of the evaluation and impact of the game.

Quantitative Data Analyses

For the data from the RCT, we will compare the answers between exposed and nonexposed students (intergroup) and measure the change in their answers within the intervention group before and after playing the game and debriefing (intragroup). Our primary analysis will be based on intention-to-treat at the individual level using linear regression comparing the outcomes of the intervention and the control arm. We will measure our primary outcomes in terms of absolute scores and as a percentage of the total possible score. We will control baseline covariates: (1) gender, (2) age, (3) field of study, (4) year of study, and (5) self-perceived health. We will analyze the data from all participants only if at least 3 quarters of the questions are completed. We consider that some users will not go through all questionnaire pages. Missing values will be imputed by replacing them with the mean or median values of the dataset at large, or some similar summary statistics.

Qualitative Data Analyses

Concerning qualitative data from the semistructured interviews (intervention and control groups), they have been analyzed through content analysis: we have identified patterns across collected texts which are coded according to key elements. These can include, for instance, reported advantages and drawbacks of the game, or players' opinions on the usefulness of the game in general. The semistructured interviews are either video or audio recorded depending on the availability of the participants, during the lunch break or in the late evening after the classes. In-depth analyses were conducted using a reflexive approach so as to appraise and evaluate how subjectivity and context influence the research processes, especially during the interpretation of the data on intimate topics like mental health. Before the association with the quantitative data, the texts will be cross-analyzed to identify similarities and differences between the experience with either the escape game or the email.

Data from the debrief at the end of the game were recorded automatically within the game. The texts were collated in a single document which was used to generate repeated and automated messages. Through artificial intelligence and, more specifically, the machine-assisted topic analysis (MATA), the human conversation will be processed to simulate answers to players' requests. The outcome will correspond to a chatbot, which will a computer program that will be able to animate a discussion and provide tips concerning mental health–related issues.

Ethical Considerations

The study has received the French identifying number (ID-RCB) 2024-A00436-41 from the National Agency for the Safety of Medicines and Health Products. This number is compulsory for registering projects on human subjects in France.

The Ethics and Health Research Center of the University of Bordeaux approved the study (2024-A00436-41). The procedures are in accordance with the Helsinki Declaration of 1975, as revised in 2024.

It is compulsory that students carefully read the consent form and sign it electronically (by clicking on the "I agree button") in order to participate to all steps of the study and share their data collected through questionnaires, interviews, and during the game. The consent form includes all the details of the study: (1) principal investigator, (2) rationale, (3) objectives, (4) methods, (5) length, (6) conditions of the storage data and analyses, and (7) expected impact. Students access directly to the consent form when they click on the link in the social media posts and the study invitation email. Participants are given the chance to opt out.

All confidential information, including participants' contact details or other sensitive data like self-reported mental health status will only be accessible to authorized staff members from the study. Thus, information is quasi-anonymous for the proper running of the study. In fact, the email address is necessary to organize the game sessions, to send the links to the web-based questionnaires and to schedule the internet-based interview. The phone number is also required to resolicit the participants, only once, for the organization of the game session. We guarantee the noncommercial use of the email addresses and the phone numbers.

Overall, participants are informed that they are not blinded.

All data, including the sensitive ones, are imported automatically from the software Sphinx to Excel. The document is protected by a password known only to the principal investigator and the statistician of the research team. The data will be destroyed 2 years after the last article based on this study is published. The collection, storage, and analysis of the data comply with the European General Data Protection Regulation (GDPR).

As already mentioned, students will receive US $21.5 gift cards for their participation to the study. The authors have filled the CONSORT-EHEALTH (Consolidated Standards of Reporting Trials of Electronic and Mobile Health Applications and Online Telehealth) form V1.6.1 (Multimedia Appendix 3).

Results

Key Dates of the Study

The study received funding by the French National Research Agency in January 2022. The production of the EscapeCovid Game ended in March 2023. The cocreation process, the test, and the refinement of the intervention lasted 15 months. For the evaluation of the finalized game, the collection and analyses of qualitative data through semistructured interviews has been completed by September 2023. The end of the evaluation phase through the RCT is scheduled to be completed by the end of June 2025. The results of the mixed methods analyses are expected to be published by the end of December 2025. The timeline of the study is illustrated in Figure 1.

Figure 1. Timeline of the phases of the study.

Study Population

The recruitment started in December 2023.

As of November 4, 2024, a total of 191 students have answered the baseline questionnaire and have been randomly assigned to one of the 2 arms, 90 intervention versus 101 control. A total of 23 students have played the EscapeCovid Game (intervention arm) and 53 are in the control arm. Specifically, 54% (103/191) of the participants at the baseline are students in health care disciplines; 11.5% (22/191) in sciences and technologies; and the remaining participants study other subjects 34.5% (66/191) including psychology, law, and so on.

Concerning qualitative data, 20 students (10 for each arm) have been interviewed on the appreciation, relevance, and acceptability of either the game or the email. Students of the game arm were between 18 and 28 years of age. There were 9 females and 1 male. Their year of study ranged from the first year of their bachelor's degree to the first year of their doctoral

studies. Fields of study included medicine, chemistry, physics, biology, sociology, speech therapy, and political science. Students of the control arm were between 18 years and 28 years old. Their year of study ranged from the second year of their Bachelor's to the third year of their doctoral studies. Fields of study included medicine, physics, nursing and marketing.

Preliminary Quantitative and Qualitative Results

As of November 4, 2024, the sample size of the trial is too small for providing robust data and for reaching significance level.

As far as qualitative data are concerned, we completed all 20 interviews. According to the students from the intervention harm, the game was appealing and fun. The use of gamification to communicate mental health-related messages was appreciated.

> *I like the initiative of doing something more fun, more educational than just distributing information, which is also a way in itself, we agree, but I like the way of trying to learn.* [Student 7–Male]

The game was described as "innovative," "unique," "instructive," and "beneficial" considering its alternative approach to conventional public health interventions, for example, educational materials, and social marketing campaigns.

The notion of stigmatization emerged. Attached outcome was the appraisal and change of beliefs about mental health.

> *I found it very interesting that we raise awareness about mental health because I have the impression that it is something that we talk about more than before but there is still a taboo behind it.* [Student 2–Female]

The game also contributed to increase participants' mental health literacy.

> *It gave me knowledge I didnot have about mental health.* [Student 1–Male]

The impact of the intervention on support recognition and management of emotions was also positive.

> *The way in which the symptoms or rather really what the person thinks to themselves are well represented and so it really allows us to understand what is going on in the person's head and also to know the symptoms and emotions. So it's very interesting, rather than just listening to someone talk about it and having a slide, it's much better.* [Student 9-Female]

The other study outcome (teach positive coping strategies) was also reported:

> *Well, you see that I have to do things that finally make us happy and otherwise, not to work too late, to take a break to eat, to see my friends and that's it and from time to time go out when we need to get some fresh air.* [Student 5-Male]

However, the students also declared that the content of the game should be enriched with the presentation of more coping strategies in order to support the player's psychological well-being. Thus, the impact of the intervention should be directly on the mental health of the players and not only on their knowledge and beliefs.

> *Not particularly, I don't think so, it was more focused on knowing emotions rather than how to manage them.* [Student 1-Male]

In comparison to the game, the informative email was not an immersive experience and was not expected to influence students' cognition, affect, potential, and health behavior. However, it provided useful tips to students from the control arm, including the following: a list of existing sources in case of mental health distress (eg, helplines and free-of-charge consultations with a psychology based at the University of Bordeaux); breathing techniques and meditation; and mental health problems explained with accessible but accurate terminology.

> *It gave me knowledge I didn't have, about the numbers to contact in case of need [...] we can't know them all by heart and I think that having them all written down in an email or in a document, well I think that it can help us because not everyone knows where to refer and where to go in case of need.* [Student 1-Male]

The usefulness of the email consisted in the fact that it could be used as a memorandum and repertoire of the basics of mental health literacy: knowing that mental health includes both positive mental health and the absence of a mental health problem; knowing the signs of the most common mental health problems (depression, anxiety, and stress); recognizing and managing emotions; learning coping strategies; and having a list of the most known services in case of a mental health distress.

As of November 4, 2024, data from the game debriefs is not transcribed and cannot be analyzed.

Discussion

Principal Findings

This paper outlines the protocol for the evaluation of a cocreated Escape Game on students' mental health outcomes contributing to prevent and manage mental health diseases and promoting psychological well-being: mental health literacy, appraisal and change of beliefs about mental health, management of emotions, and development of coping strategies. The evaluation is conducted through mixed methods, combining the quantitative results of a RCT with the qualitative results of semistructured interviews.

Concerning quantitative, as of November 4, 2024, the recruited sample is too small to make inferences on the impact of the game. Actually, recruiting students is the hardest challenge of the trial. All along the study, we have observed that the most successful recruitment strategies are: offering gift cards to students completing the whole study (baseline questionnaire, intervention or control arm, and repeated questionnaire); counting on the support of student associations promoting the study among members; and involving professors who present the study during their classes. We will reinforce these strategies to attract and retain students in the trial.

As for the qualitative data, the recruitment of students was far easier and we rapidly interviewed 20 participants by September 2023. The comparison of the responses across the 2 groups, game versus email, showed that gamification improved the retention of messages, especially in terms of recognition and management of emotions. On the other hand, email was considered useful as a memorandum of mental health–related information. In particular, students appreciated the list of available services that they could keep and save for contacting professionals in case of need.

Based on preliminary results, these 2 distinct tools, the EscapeCovid Game, and the informative email, could prove to be mutually complementary in promoting student mental health. By consolidating the specific advantages of each approach while mitigating their respective limitations, we can aspire to a more holistic and informed approach to strengthening psychological well-being within the student community.

Comparison to Previous Work

Recently, interventional research took an interest in digital games to promote positive well-being and prevent mental health problems. This might be due to the emerging mental health challenges because of the COVID-19 pandemic [29]. A scoping review of 16 articles has identified positive effects of gamified interventions, with beneficial consequences for psychological well-being and depressive symptoms [30]. Three articles focused specifically on university students, but described interventions were gamified mobile or web applications, and did not include Escape Games.

Overall, Escape Games addressed to university students are mostly used as educational tools aimed at guiding learners toward achieving specific learning outcomes through a game-based design [31]. Concerning mental health, the literature reports 1 game addressed to students to improve their knowledge on psychological well-being and mental illnesses, but it is an Escape Room exclusively on site [32].

It is essential to support this population and reinforce their psychological status and resilience since they will be the future workforce. They will especially be in charge of rebuilding the economy of the country after this huge crisis.

Strengths and Limitations

The robust evaluation process of this study will provide evidence of the effectiveness of one of the few digital gamified interventions addressed to students' mental health. This will be among the first promising Escape Games produced jointly by a public university research team and a private start-up. The collaboration between these 2 institutions is an added value guaranteeing that, on the one hand, the intervention is well-designed and functioning, and that, on the other hand, researchers have accurately assessed its performance.

The main strength of the evaluation process in that relies on mixed methods. This approach can balance out the limitations of each method (questionnaires from an RCT and qualitative data from semistructured interviews and game briefing); it can lead to stronger evidence and reliability; and it can provide more details than each individual method. Concerning quantitative data, mixed methods limit straightforward and stereotyped interpretations, and reduce ambiguity and misunderstanding.

On the other hand, the limitations of qualitative data are mitigated by a rigorous quantitative approach: coding of the text in structured interview grids, word-by-word data management, and detailed records of data collection and analysis like in an audit trial [33].

Thus, mixed methods can increase the trustworthiness, transferability, dependability, and confirmability of the thick description of combined quantitative and qualitative data.

This study is primarily limited by the low participation of students and inclusion at the baseline. This might be due to the fact that the game lasts more than 1 hour and requires a good computer operating system, as it is already stated in the interviews. Students' agenda are really busy and their workload is heavy. As suggested, new structured communication strategies would improve the participant recruitment. Furthermore, the inclusion in the study is completely voluntary and, considering that we do not use quota sampling because of feasibility, results may not be generalizable to students in Bordeaux and to French students in particular.

Another barrier is the correct implementation of a complex evaluation through an RCT and mixed methods design with the collection of several data. Researchers involved in the study have renowned experience on this type of methodology and are keen to ensure the smoothness of the evaluation process. As far as technical barriers are concerned, the development of the digital Escape Game has to overcome potential IT challenges. The final product will need to be both high-tech and appealing, mixing solid technology with a modern design and avoiding bugs. IT developers of the start-up of the study have already proven their competencies and skills for that.

Future Directions

If the results of the study show the impact of the intervention on mental health outcomes (mental health literacy, appraisal and change of beliefs about mental health, management of emotions, and development of coping strategies) among students, the game will be commercialized and sold to universities for its deployment on the campuses across France. The evaluation process is meant to guarantee that the game can be diffused with an economically sustainable model defined by the start-up. In particular, this study will help the start-up to define a "gold standard" for selling other similar interventions.

The promising results of the study open the way to crucial questions: how can we secure funding and optimize the economic efficiency of the EscapeCovid Game in order to guarantee its sustainability and make it a mental health promotion tool, accessible to a wide range of students from diverse backgrounds? For instance, using artificial intelligence, it will be possible to make the intervention autonomous with automatized debriefing. This will make the game more sustainable cutting the costs of the salary of the game guide.

Furthermore, who will be the legal owner of the EscapeCovid Game? Intellectual property must be deeply discussed to ensure the shared collaboration of the partners to create the game before

its real commercialization. In order to overcome any potential disagreement, the roles of all parties must be clearly stated in a business partnership agreement.

Thus, the protocol of this study describes how to evaluate with a robust methodology a game on students' mental health as an example for producing further effective interventions on the same topic. Based on evidence, these interventions can be commercialized through an economically sustainable model.

Finally, this protocol presents a study whose objectives are both research (studying several indicators of young people's mental health during the COVID-19 pandemic)- and business-oriented (producing an evidence-based tool for further deployment).

Acknowledgments

The authors acknowledge and thank all students who participated to the study. The authors are also indebted to the student association for helping recruit participants. We especially thank Clément Tisseron and Flavie Coudouin for their valuable contribution to the launch of the study and its first results. Florence Francis Oliviero also assisted the authors with the definition of the best methodology for the study. We thank Antoine Lanusse for the development of the R programming (R Development Core Team) for the statistical analyses to be conducted for the RCT quantitative data. Finally, we particularly acknowledge Lucie Pariente for the coordination of the RCT.

The study was funded by the French National Research Agency (ANR; grant ANR-21-CE36-0011-02). IM was supported by the Digital Public Health Graduate Program within the framework of the PIA3 (Investment for the Future; project reference 17-EURE-0019). Further support was given by the Agence Universitaire de la Francophonie (CO//ectif; DREO-7450).

Data Availability

The text of fully transcribed interviews is available from the corresponding author upon request. Quantitative data from the first participants to the randomized controlled trial are preliminary and cannot be shared until the study is concluded.

Authors' Contributions

DL and IM conducted conceptualization and writing-reviewing. DL handled investigation. CV managed data curation and writing-original draft preparation. MH performed qualitative data curation and writing—final manuscript preparation. IM handled methodology, investigation, writing—reviewing and editing, and supervision.

Conflicts of Interest

DL is the chief executive officer of the start-up Tricky developing the game described in this paper. Results of the study are totally transparent.

Multimedia Appendix 1
Original Questionnaires for the quantitative evaluation of the EscapeCovid game.
[PDF File (Adobe PDF File), 561 KB - resprot_v14i1e64068_app1.pdf]

Multimedia Appendix 2
Original interview guides for the qualitative evaluation of the EscapeCovid game.
[PDF File (Adobe PDF File), 176 KB - resprot_v14i1e64068_app2.pdf]

Multimedia Appendix 3
CONSORT-EHEALTH (Consolidated Standards of Reporting Trials of Electronic and Mobile Health Applications and Online Telehealth) checklist.
[PDF File (Adobe PDF File), 2751 KB - resprot_v14i1e64068_app3.pdf]

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Abbreviations

CHERRIES: Checklist for Reporting Results of Internet E-Surveys
COM-B: capability, opportunity, and motivation to change behavior
CONSORT-EHEALTH: Consolidated Standards of Reporting Trials of Electronic and Mobile Health Applications and Online Telehealth
GAD-7: Generalized Anxiety Disorder-7 Scale
GDPR: General Data Protection Regulation
HBM: Health Belief Model
K6: Kessler Psychological Distress Scale
LGBT: lesbian, gay, bisexual, and transgender
MATA: machine-assisted topic analysis
MHLS-FR: French Mental Health Literacy Scale
PHQ-9: Patient Health Questionnaire-9
PRODUCES: Problem, Objective, Design, End Users, Cocreators, Evaluation, and Scalability
PSS4: Perceived Stress Scale
RCT: randomized controlled trial

Edited by A Schwartz; submitted 08.07.24; this is a non–peer-reviewed article;accepted 30.12.24; published 02.04.25.

Please cite as:
Labrosse D, Vié C, Harb M, Montagni I
Escape Game to Promote Students' Mental Health Outcomes in the Aftermaths of COVID-19 Pandemic: Protocol for a Mixed Methods Study Evaluating a Cocreated Intervention
JMIR Res Protoc 2025;14:e64068
URL: https://www.researchprotocols.org/2025/1/e64068
doi:10.2196/64068
PMID:

Protocol

Comparison of Smart Display Versus Laptop Platforms for an eHealth Intervention to Improve Functional Health for Older Adults With Multiple Chronic Conditions: Protocol for a Randomized Clinical Trial

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Abstract

Background: Maintaining functional health, or the ability to live independently, is a primary goal of individuals as they age, but most older adults develop chronic conditions that threaten this goal. Physical activity is a key aspect of self-care that can improve functional health, and digital interventions offering guidance on appropriate exercise can help. However, older adults with multiple morbidities may be unable to use a laptop or smartphone-based eHealth because poor vision, dexterity, mobility, or other physical challenges make typing or touch navigation difficult. A smart display platform—comprising a smart speaker plus a small visual screen—has the potential to remove these barriers because it is voice-activated.

Objective: The study aims to compare usage patterns of an eHealth intervention for older adults when delivered via a voice-based smart display versus a typing-based laptop, and assess whether the smart display outperforms the laptop in improving functional health and its specific physical and mental aspects.

Methods: A minimum of 356 adults aged 60 years and older with at least 5 chronic health conditions are to be recruited from primary care clinics and community organizations. Participants will be randomized 1:1 to 12 months of access to an evidence-based intervention, ElderTree, delivered on either a smart display or a touchscreen laptop, with a postintervention follow-up at 18 months. The primary outcome is differences between groups on a comprehensive measure of physical and mental functional health. Secondary outcomes are between-group differences in the subscales of functional health (eg, physical function and depression), as well as measures of health distress, loneliness, unscheduled health care, and falls. We will also examine mediators and moderators of the effects of ElderTree on both platforms. Participants will complete surveys at baseline, 6, 12, and 18 months, and ElderTree use data will be collected continuously during the intervention period in system logs. We will use linear mixed-effect models to evaluate outcomes over time, with treatment condition and time point as between-subjects factors. Separate analyses will be conducted for each outcome.

Results: Recruitment began in July 2023 and was completed in May 2024, with 387 participants enrolled. The 12-month intervention period will end in May 2025; data collection will end in November 2025. Findings will be disseminated via peer-reviewed publications.

Conclusions: Voice-activated digital health interventions have theoretical but untested advantages over typing-based technologies for older adults with physical limitations. As the population ages, and as multiple morbidities threaten the functional health of the majority of older adults, innovations in self-management are a matter of public health as well as individual quality of life.

Trial Registration: ClinicalTrials.gov NCT05240534; https://clinicaltrials.gov/study/NCT05240534
International Registered Report Identifier (IRRID): DERR1-10.2196/64449

(JMIR Res Protoc 2025;14:e64449) doi:10.2196/64449

KEYWORDS

eHealth; aged; geriatrics; functional health; multiple chronic conditions; smart display; smart speaker; primary care; quality of life

Introduction

Background

A key measure of the physical and mental quality of life, functional health is the ability to perform basic personal care activities as well as more complex skills such as finances, transportation, and housekeeping: in essence, the ability to maintain one's own agency [1]. Maintaining such agency, including living at home rather than in a care facility, is a primary goal of older adults [2]. Yet with age, most older adults develop chronic health conditions that erode their functional health and threaten their independence [3].

In the United States, chronic conditions such as diabetes, hypertension, and arthritis affect almost 95% of adults aged 60 years and older [4]. Among Medicare beneficiaries, about two-thirds have 3 or more chronic conditions and nearly one-fourth have 5 or more [5,6]. Treatment of co-occurring morbidities is complicated and costly given their complexity, prevalence, and ongoing nature [5,7]. For these same reasons, self-management is a vital aspect of patient care. Self-management includes skills and knowledge related to one's health conditions, attention to emotional and cognitive states, and efforts related to lifestyle factors such as nutrition and exercise [8].

In its most recent Healthy People initiative, issued every 10 years since 1980 [9], the US Department of Health and Human Services (DHHS) declared a goal of improving the health and well-being among older adults. The first objective in meeting the goal is: "Increase the proportion of older adults with physical or cognitive health problems who get physical activity" [10]. According to health guidelines established by the Centers for Disease Control and Prevention [11], a consistent regimen of strengthening, balance, and aerobic activity can help older adults "feel, function, and sleep better; stay independent and fit so [they] can complete daily tasks; improve [their] mental health; and decrease pain and improve function". Moreover, these beneficial impacts may be experienced immediately [12].

To accomplish this objective, labeled OA-01 (Older Adults-01), *Healthy People2030* recommendations include the use of digital health interventions that provide instruction and guidance in the form of "web-based interactive content" and "apps with goal-setting, activity tracking, and reminder functions" [13]. The initiative's Community Preventive Services Task Force found that appropriately tailored home-based digital interventions with exercise content improved older adults' balance, strength, and muscular endurance. In addition, people who used such interventions reported spending more time doing physical activity than they would have otherwise [14].

Digital health interventions have typically been delivered via computer websites (which require typing) or smartphone apps (which require touch navigation). Various academic and popular press accounts have suggested that smart speakers and smart displays, which also access the internet but are primarily navigated by voice rather than touch or typing, might be more accessible and appealing for older adults and others struggling with physical limitations [15-19]. Specifically, they have proposed that voice interactivity could alleviate challenges of hand tremors and vision loss and might seem more intuitive and companionable than a traditional app or website [20-22].

On the other hand, researchers have also suggested potential difficulties: age-related reductions in the volume, clarity, and pace of older adults' speech may lead the device to misinterpret their questions and commands, and hearing loss may make it challenging for some older adults to understand the device's responses [23-26]. More broadly, there is some indication that older adults may be less inclined to use technology-based interventions than to engage with traditional, in-person treatment. A 2023 meta-analysis of randomized trials of interventions for older adults' functional mobility found slightly higher dropout rates for older adults assigned to technological interventions (eg, virtual reality exergaming, wearable devices, and telerehabilitation) than those assigned to conventional in-person rehabilitation or no treatment [27].

To summarize, it remains unclear whether voice interactivity versus touch or typing delivery of intervention will be more effective for older adults and help advance the objectives for older adults' health and physical activity outlined in *Healthy People 2030*. This paper reports on the protocol of a large clinical trial comparing the effectiveness of an eHealth intervention delivered on a smart display versus a laptop.

The intervention, ElderTree, is a web-based system that aims to improve the health and quality of life of older adults by offering interactive, informational, and motivational content and services such as health tracking, reminders, and social support. Developed by our Agency for Healthcare Research and Quality Center of Excellence in Active Aging, it was first tested in a randomized controlled trial (RCT) involving a community sample of 390 participants age 65+ years who received a laptop either with or without ElderTree access for 12 months [28]. In that study, participants in the ElderTree group who reported 3 or more primary care visits in the 6 months before baseline showed significantly better results on measures of mental quality of life, social support, and depression compared to control participants. Because primary care use is relatively high among patients who are managing multiple chronic conditions, these results suggest that patients with comorbidities may be most

likely to benefit from a system such as ElderTree. A subsequent RCT testing a version of ElderTree among a clinic-based sample of older patients with at least 3 chronic conditions found socio-emotional health improvements, especially among women [29,30]. In the most recent RCT (ClinicalTrials.gov NCT04798196), ElderTree was adapted for older adults experiencing chronic pain and at least three comorbid conditions, with the primary aim of reducing pain interference. As in the current trial, participants were randomized to receive the intervention via a laptop or a smart display [31]. The outcome paper is currently in preparation.

The current study differs from the chronic pain study, by focusing on functional health among older adults with 5 or more chronic conditions. We recruited adults with an array of conditions known as metabolic syndrome (ie, vascular risk factors including hypertension, hyperglycemia, abdominal obesity, and dyslipidemia), for whom physical activity is of particular therapeutic import [32,33]. We increased the number of chronic conditions required to participate from 3 to 5. Almost a quarter (23%) of Medicare beneficiaries have 5 or more chronic conditions [34] and health risks and costs increase with the number of comorbid conditions [35,36]. As such, it is important to understand whether this sizable, high-risk, high-expenditure group is more likely to use and benefit from a voice-activated intervention for functional health, rather than a laptop version.

Study Objectives

Although voice-activated systems seem to offer an easy, engaging way to use an intervention, it is an open question whether older adults coping with multiple chronic conditions would show more sustained use of a voice-activated platform and whether this would lead to improved health outcomes. To test this hypothesis, we propose a trial comparing the text and typing-based version of ElderTree delivered on a laptop to a voice-based version delivered on a smart display. The goal is to compare usage patterns of the two platforms and assess whether the smart display version outperforms the laptop in improving our primary outcome of functional health and associated secondary outcomes.

Methods

Trial Design

This is a nonblinded, 2-arm, parallel-design randomized trial, with participants allocated 1:1 to receive ElderTree on either a voice-based smart display or a text and touch-based laptop. The intervention period is 12 months, with surveys at baseline, 6, and 12 months, and a follow-up survey at 18 months.

Sample Size and Study Setting

We planned for a minimum of 356 older adult participants to be recruited from both clinic and community settings throughout the state of Wisconsin.

Study Arms

ElderTree Via Laptop

Participants in the ElderTree via Laptop (ET-LT) arm receive a touchscreen laptop computer, access to ElderTree, and Internet service for 12 months, and continue with their usual care. They will also receive US $10 for each completed survey, for a possible maximum of US $40.

ElderTree Via Smart Display

Participants in the ElderTree via Smart Display (ET-SD) arm continue with their usual care and receive a smart display, Internet service, and access to ElderTree for 12 months. The smart display consists of a voice-activated smart speaker and a small visual display that is optionally touch-activated. They will receive US $10 for each completed survey, for a possible maximum of US $40.

Eligibility Criteria

Eligible participants must (1) be age 60 or older, (2) have at least 5 chronic conditions identified by the Centers for Medicare & Medicaid Services as prevalent among older adults [5,37], (3) among which 3 of which must be hypertension, hyperlipidemia, obesity, prediabetes, diabetes, or depression, (4) be willing to share medical record data about health care use (30-day hospital readmissions, emergency room urgent care, primary care, and specialty care visits), (5) allow researchers to share information with the patient's primary care provider, (6) have no current psychotic disorder or form of dementia, (7) no acute medical problem requiring immediate hospitalization, (8) no need of an interpreter, and (9) no physical impairments preventing use of a computer or tablet.

Recruitment

The Clinical and Health Informatics Institute at the University of Wisconsin–Madison (UW–Madison) searched clinic records from the Department of Family Medicine and General Internal Medicine system (UW Health) to identify patients meeting eligibility criteria and has sent eligible patient data (name, address, birth date, age, UW Health clinic location, primary care doctor) to the UW (University of Wisconsin) Office of Clinical Trials (OCT) via REDCap (Research Electronic Data Capture, Vanderbilt University). OCT then sent potential participants an opt-in letter describing the study, a consent form, and a stamped return letter inviting contact from the study team.

We supplemented recruitment from UW Health with additional clinic and community efforts aimed at achieving a diverse patient population. To increase our outreach to both participants of color and underserved patients, we worked with staff at Access Community Health Centers in Madison, who disseminated a recruitment flyer, consent form, and return card or opt-in to potentially eligible patients. In addition, advertisements on local television stations have been deployed in Madison, Milwaukee, Beloit, and other communities within driving distance, with specific outreach to older adults and African Americans. Last, through collaborations with leaders in the Black community, we reached out to churches, community centers, senior living communities, and other organizations, distributed a recruitment flyer and consent form with a return

card or opt-in, placed advertisements in local publications, and conducted community sessions to introduce the study and invite participation.

Finally, we sent a one-time mass email to all current UW–Madison faculty and staff with information regarding the study, asking those interested to reply via email or call for more information. We also encouraged recipients to share the email with others they believed might be interested (eg, a parent or neighbor with multiple chronic conditions).

Regardless of recruitment method, when a return card or opt-in was received or a potential participant called, study staff assessed eligibility over the phone; provided a study overview that included potential benefits and risks, study procedures, and compensation; thoroughly walked through informed consent; conducted a brief exercise screen to allow tailoring of exercise content [38]; and addressed questions. If the individual met eligibility criteria, the baseline survey was mailed; community participants also received the consent form, while clinic participants had already received it with their opt-in letter. Patients were given as much time as needed to decide whether to participate and had the option for a follow-up call after reviewing the materials. The baseline survey takes 20-30 minutes to complete. Measures are the same in both arms to avoid differential dropout. As the trial progresses, we document those who choose not to participate and why, following the CONSORT (Consolidated Standards of Reporting Trials). Patients can opt to stop their participation at any time by contacting the research team.

Randomization

The project manager used a computer-generated allocation sequence to randomize participants on a 1:1 ratio to ET-SD or ET-LT, stratified on gender (male or female), number of chronic conditions (5-7 or 8+), and recruitment site. There are 7 site variables: 3 UW Health clinics, the Access Community Health clinic site, and 3 communities (Madison, Milwaukee, and Beloit). Once an individual verbally consented, a home visit was scheduled to collect the baseline survey, randomize, determine the preferred location of the laptop or smart display, and set up the device. Staff then conducted training on the assigned intervention. If no visit was desired, equipment could be shipped after the completed baseline survey was mailed and received, and technology setup and training could be conducted by phone. The research team is available during usual operating hours for participants to contact them with questions or issues.

Once an assignment has been made, it is of course not possible to blind participants to their condition. Further, in order to set up participants on their assigned system, the researcher conducting the training also could not be blind to the condition after the assignment.

Timeline

Table 1 shows the timeline by year of the study, with year 1 beginning in August 2021 and year 5 ending in July 2026.

Table 1. Timeline of key project activities.

Activity	Timeline
Develop and test ElderTree intervention on the smart display	Year 1, months 2-11
Develop content plan for ElderTree on both platforms	Year 1, months 5-9
Prepare and finalize study and data collection materials	Year 1, months 7-9
Obtain institutional review board approvals	Year 1, month 8
Finalize data quality monitor plan	Year 1, month 9
Train research staff	Year 1, months 9-10
Recruit and randomize patients	Year 1, month 9 to year 3, month 10
Produce and manage ElderTree content for both systems	Year 1, month 9 to year 5, month 4
Collect data	Year 1, month 9 to year 5, month 4
Clean and prepare data	Year 2, month 4 to year 5, month 6
Analyze results	Year 5, months 7-10
Publish	Year 5, months 11-12

Intervention

System Overview

ElderTree is one of a suite of eHealth systems developed by our Center and collectively known as CHESS (Comprehensive Health Enhancement Support System). Like other CHESS systems, ElderTree is built on principles of continuing care and self-management, such as long duration [39], tracking [40], prompts [41], goal setting and action planning [42], problem-solving and self-tailoring [43], and social support [44]. In randomized trials, CHESS systems have significantly improved risky drinking [45]; asthma control [46]; quality of life and cost of care in human immunodeficiency virus patients [47]; quality of life and self-efficacy in breast cancer patients [48-50]; and caregiver burden, symptom distress, and median length of survival in patients with lung cancer [51]. All CHESS systems, including ElderTree, are consistent with self-determination Theory, which asserts that satisfying these 3 basic psychological needs contributes to adaptive functioning: competence (feeling effective or not overwhelmed), social

relatedness (feeling connected to others or not isolated), and intrinsic motivation (feeling autonomous about behavioral changes or not coerced) [52].

ElderTree is a multifaceted system focused on older adults' physical and mental health and quality of life. As reported in earlier ElderTree studies [28-30], the laptop system is a members-only website free of ads, with design features based on older users' feedback and best practices for older populations (eg, larger fonts or uncluttered screens) to optimize comprehension, navigation, and usability [53]. The ET-SD version follows these usability principles as well. Both systems substantially replicate ElderTree as described in an earlier study comparing ET-LT to an attention control [29,30], with modifications and enhancements to focus on the functional health of individuals with multiple morbidities and to align with the technical capabilities of the smart display platform.

System Content

ElderTree offers video content in the areas of functional movement, information and advice, mood and mental health, and entertainment, as well as social engagement and health tracking features. Video content is both originally produced and curated from high-quality external sources. Descriptions of each feature or function are listed in Table 2, and the home screen organization for both platforms is shown in Figure S1 in Multimedia Appendix 1: ElderTree screens and physical activity decision tree.

Table 2. Key features of the ElderTree eHealth intervention.

Feature or function	Description
"Let's Move" videos	Functional movement videos, in 3 assigned ability groupings based on participants' physical health screening and doctor approval.
"Tips & Info" videos	Short, practical information and advice on a wide range of topics related to physical and mental health (eg, "How Blood Pressure Works", "Finding Friends as an Older Adult", "Easy Ideas for Healthy Eating").
"Relax & Inspire" videos	Meditation, relaxation, and breath work videos for sleep, reducing stress, creativity, and more.
"Just for Fun" videos	Humor, music, and human interest are for pleasure (this content is located in "Relax & Inspire" on the smart display platform).
CalmConnect multisensory videos [54]	Program of short practice videos that combine rhythm, hand movement patterns, and facial expression cues, engaging the user physically, cognitively, and emotionally with the goal of strengthening social connectivity and mental health.
Wednesday Meetup	One-hour weekly facilitated group video meeting with a topic presentation (eg, balance, falls, and vision health) and small breakout rooms for socializing.
Weekly Survey	Tracking of 10 self-reported general health indicators (eg, sleep, mood, exercise), with results presented in graph form over time.
Thought of the Day	A new motivational or inspirational quote delivered daily at with the user's first visit to the intervention.
Prompts	Reminders to take the weekly health tracking survey; notifications of new content.
Featured content	On the home screen, new and existing content is highlighted to encourage exploring services and resources, and is continually rotated to keep ElderTree fresh.
Favorites	Bookmarking and retrieval feature.
System tutorials	Instructional videos for accessing ElderTree features and content.

The critical physical exercise content is located in ElderTree's "Let's Move" area, offering videos targeting balance, strength, endurance, and flexibility. After randomization, participants in both conditions were placed in one of three activity-level groups on the basis of their responses to the Exercise and Screening for You (EASY) Tool [38] and approval from their primary care physician (PCP), to ensure safety and accessibility. Figure S2 in Multimedia Appendix 1 shows the decision tree for assigning each participant to their group within the study arm. The three groups are as follows:

1. Group 0: restricted based on the EASY Tool and do not have approval from their PCP to use standing activity content on ElderTree. The fitness activities available to them are limited to gentle seated movements for coordination, dexterity, and mental stimulation (eg, "Wake Up Your Brain"). Also, in Let's Move, Group 0 has access to an 8-module course on managing chronic pain, developed by our research team.

2. Group 1: restricted based on the EASY Tool, but their PCP has given approval to engage in supported standing activities. For this group, we developed a collection of instructional and practice videos with a geriatrician expert in functional movement for older adults who have health conditions. The videos are available in all areas of fitness: balance, flexibility, strength, and endurance. Group 1 participants must view a safety video for each of the 4 fitness categories before access to the movement videos is unlocked. Group 1 also has access to all Group 0 content.

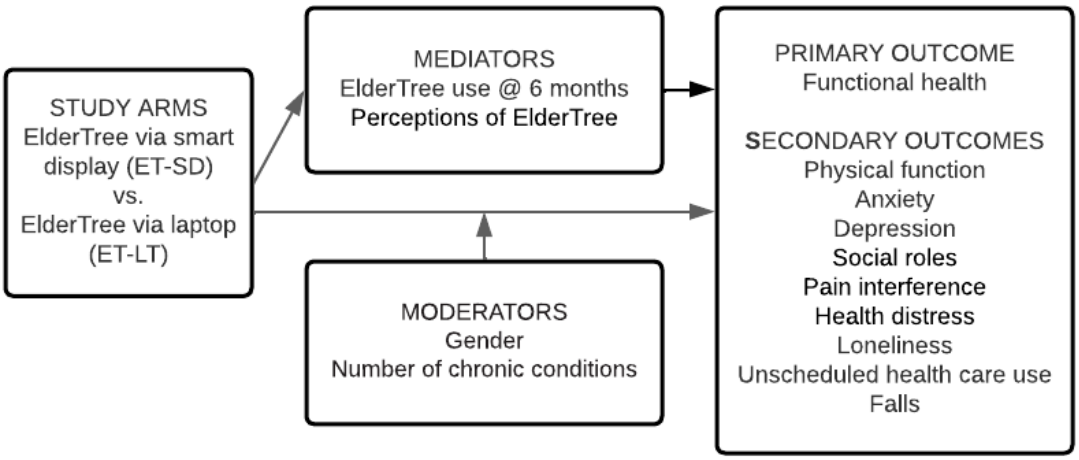
3. Group 2: no restrictions, based on the EASY Tool, and may use all the movement videos on ElderTree after viewing the safety videos in each of the 4 fitness categories. The Group 2 content includes all activities available to Groups 0 and 1, as well as videos provided by outside experts in fitness and functional movement for older adults. These externally sourced videos have been vetted by the study's geriatrician for safety, suitability, and quality. Playback times and challenge levels are

indicated in every video title to enable users to self-tailor their selections on any given day.

Outcomes

The primary outcome is differences between groups over time in functional health, a multifaceted variable that includes physical function, pain interference and intensity, fatigue, sleep disturbance, anxiety, depression, and satisfaction with one's social roles and activities. To tease apart these elements, the secondary outcomes include the functional health subscales of physical function, pain interference, anxiety, depression, and social role satisfaction. Additional secondary outcomes are health distress, loneliness, unscheduled health care use, and falls. Figure 1 diagrams the study logic.

Figure 1. Study logic.



Measures

Primary Outcome

The 29-item PROMIS (Patient-Reported Outcomes Measurement Information System)-29 v2.1 is used to measure functional health [55]. Items tapping physical function, pain interference with aspects of daily life, anxiety, depression, ability to participate in social roles and activities, fatigue, and sleep disturbance are scored on 5-point Likert scales, while a single 11-point item (range=0–10) rates pain intensity. The possible ranges, scored by providers of the measure [56], are 21.2–67.6 for a social-emotional cluster and 16.2–67.7 for a physical cluster of functional health, with higher scores indicating better functioning.

Secondary Outcomes

We are using PROMIS-43 v2.1 subscales to separately assess physical function, pain interference, anxiety, depression, and satisfaction with social roles and activities [57]. For each subscale, participants respond on a 5-point (1-5) Likert scale to 6 items modified from occurring "currently" to "in the past 7 days," for consistency with other survey items. For the physical function items (eg, "Are you able to go for a walk of at least 15 minutes?"), higher scores indicate poorer function (total possible range=22.9-56.9). For pain interference (eg, "How much did pain interfere with the things you usually do for fun?"), higher scores indicate greater interference (total possible range=41.6-75.6). Anxiety items include "I felt nervous" and "My worries overwhelmed me"; higher scores indicate greater anxiety (total possible range=40.3-81.6). Depression items include, "I felt like a failure" and "I felt unhappy"; higher scores indicate more depression (total possible range=41-79.4). For social roles items (eg, "I have to limit my regular activities with friends"), higher scores indicate more difficulty or limitation (total possible range=29-64.1).

Health distress is measured with the 4-item Lorig Health Distress Scale [58,59]. Sample items are how often in the past month a participant has been "discouraged by your health problems" and "fearful about your future health." Higher scores on the 6-point (0–5) Likert scale indicate greater distress. The total possible score is the mean of the 4 items (range=0 5).

Loneliness is assessed with the 5 Loneliness scale items in the NIH Toolbox Social Relationship scales item bank v2.0 [60]. Sample items include how often in the past month a participant has felt "alone and apart from others" and "left out". Scores are calculated by the scale developer; the possible range=37–85, with higher scores indicating greater loneliness.

For unscheduled health care visits, participants will report at each survey time point their number of urgent care clinic visits, emergency room visits, and overnight hospital stays in the past month.

The number of falls in the past 6 months, as well as the number requiring medical attention, will also be surveyed at each time point. A fall is defined in the survey as "when your body goes to the ground without being pushed."

Measures for all planned outcomes and their psychometrics are presented in Table 3.

Table 3. Outcome measures, the number of survey items, and psychometrics.

Variable	Measure	Items, n	Psychometrics
Primary outcome			
Functional health	PROMIS[a]-29 v2.1	29	α≥.94 [55]
Secondary outcomes			
Physical function	PROMIS-43 physical function subscale	6	α>.9 [57]
Pain interference	PROMIS-43 pain interference subscale	6	α>.9 [57]
Anxiety	PROMIS-43 anxiety subscale	6	α>.9 [57]
Depression	PROMIS-43 depression subscale	6	α>.9 [57]
Social roles	PROMIS-43 social roles subscale	6	α>.9 [57]
Health distress	Lorig Health Distress Scale	4	α>.87 [58]
Loneliness	NIH Toolbox	5	α≥.93 [60]
Number of unscheduled health care visits	N/A[b]	3	N/A
Falls	N/A	2	N/A

[a]PROMIS: Patient-Reported Outcomes Measurement Information System.

[b]N/A: not applicable.

Mediation, Moderation, and Covariates

We will test whether functional health at 12 months is mediated by participants' amount of ElderTree use and perceptions of ElderTree at 6 months. ElderTree use will be assessed via continuously collected system data. For perceptions of ElderTree, participants rate 18 items (eg, "It is easy to use," "It helped me learn more about my health issues") on a 4-point (1-4) Likert scale and answer 6 open-ended questions (eg, "What stopped you or hindered you from using ElderTree or the computer or smart system in general?"). We will also examine possible moderation due to gender and the number of chronic conditions at baseline. Finally, as potential covariates we will test baseline race and ethnicity, education level, and barriers to technology due to physical limitations (eg, vision or hearing challenges); those that significantly predict our primary outcome will be included in the final analysis.

Power Analysis and Sample Size

The primary hypothesis is that the intervention modality (voice activation vs typing and touching) will affect functional health. Based on PROMIS validation studies (eg, chronic pain, arthritis, and cancer), a difference of 3 points or more between study arms is considered to indicate a clinically meaningful difference [61]. The PROMIS website also gives the mean and SD of the T-score metric (mean 50, SD 10). Power calculations for this primary hypothesis were performed using the SAS procedure PROC GLMPOWER (SAS Version 9.4) [62]. Results indicated that 282 participants after attrition would be needed for 80% power (P<.05) to observe a difference score of 3 points between the two study arms at 12 months. In our original ElderTree study, 79% of the sample completed the 12-month survey [28], and in the subsequent study, 92% of participants did so [30]. We based our sample size on the more conservative numbers from the original study and planned to recruit a total of 356 participants, or 178 per arm, to achieve 282 after attrition.

With regard to power for moderation analyses, we ran a sensitivity analysis to compute the smallest effect size our study would be powered to find using 280 given 4 groups (eg, 2 study arms × 2 genders). With N=280, G*Power calculations [63] show our study would have a 95% chance (with P<.05) of observing a moderation effect as small as a Cohen d of 0.22.

Data Collection

Patient Surveys

Patients will complete surveys at baseline, 6, 12, and 18 months. Baseline surveys were collected at training and setup, and subsequent surveys will be mailed to patients with a return stamped envelope. Participants are encouraged to contact the study staff if questions arise. All 4 surveys will assess primary and secondary outcomes using the measures detailed above. At 6, 12, and 18 months, participants will also respond to the checklist of chronic conditions used for eligibility screening as well as answer items assessing their perceptions of the intervention. Demographics were gathered only at baseline.

ElderTree System Data

ElderTree usage data are automatically and continuously collected in time-stamped log files, including logins, services used, pages accessed, and weekly surveys completed.

In addition, data are collected from the weekly survey of self-rankings for medication adherence, falls, thinking and memory, mood, healthy meals, snacks and drinks, physical activity, quality time with others, sleep, pain, and balance.

Retention

We are promoting study retention by providing telephone and email support for patients' use of the technologies and by following up with patients to encourage them to return surveys. If a survey is not returned within 2 weeks, a research team member will call to check that the survey was received and

encourage the patient to complete and return it in the provided envelope. The date and time of the phone call will be recorded in REDCap, along with whether the researcher talked to the participant directly (vs left a message) and any information gathered during the conversation. If we cannot reach the participant, another copy of the survey will be sent with a personal note asking them to complete it or call us on our toll-free number if they have questions or are no longer interested.

Data Quality and Management

Surveys comprise standardized measures that have been validated for older adults. In addition, the following strategies, developed during our previous large RCTs with this population, are implemented to reduce errors and missing data: (1) surveys are sent via hard copy, with paid return envelopes; (2) visual formatting is simple and clear, in large print on uncluttered pages; (3) tables of items and response options are designed with line-by-line alternate shading for easy tracking; and (4) instructions are explicit as to how participants should respond if they feel a question does not apply or they do not know the answer. Participants are encouraged to call in with questions. Once a survey is returned, trained research staff will evaluate it within a week of receipt; if data issues are found (eg, missing responses, multiple responses to a single item), staff will contact the participant to resolve the error.

To mitigate the risk of breaches in patient confidentiality, all participants are assigned a unique code number. Participant contact information and survey data are housed electronically in REDCap. Survey data are double-entered by two different individuals to ensure accuracy. Paper files are stored in a locked room in locked cabinets and can be accessed only by authorized personnel. The database administrator provides access to study data at appropriate levels for various members of the research team.

Statistical Methods

Predictor and Outcome Assumptions

Participants were assigned at random, with constraints that study arms would have roughly equal proportions for key covariates (eg, race, education, baseline number of chronic conditions). The effect of key covariates on outcomes will be assessed for each model. We will assess whether there are main effects of recruitment sites or interactions with the study arm (ie, whether data can be pooled across sites). Variables will be examined using standard summary statistics, visualizations, and tests for normality and homoscedasticity. Data will be transformed as needed.

Missing Data

With regard to survey data, in the previous ElderTree RCT of older adults coping with at least 3 high-risk chronic conditions, 320 of 344 participants (93%) completed the 6-month survey, 309 (89.8%) completed the 12-month survey, and 298 (86.6%) participants completed the 18-month survey [30]. In completed surveys, data were missing on about 2% of core items. Occasional out-of-residency time is also expected for participants (eg, travel and hospitalizations). We encourage patients to take the intervention with them when possible, but absences without ElderTree will be addressed as covariates in our outcome models.

We expect rates of missing data in this study to be similar to those reported above for the ElderTree RCT. We will report rates of missing data by study arm and time point. We will also use logistic regression to predict missing data as part of our evaluation of missing data patterns.

Effects of Study Arm on Outcomes

Primary and secondary outcomes will be analyzed using an intention-to-treat approach that includes all observed data from all participants who were randomized to a study arm. These analyses will follow a model-based approach that assumes missing data for outcomes at specific time points are missing at random (MAR) [64]. Specifically, a linear mixed model [65-68] will be used to examine the effects of the study arm (ET-SD vs ET-LT, a between-subjects factor) on the primary outcome, functional health, over time. Linear mixed models will also assess the effects of the study arm on each of the secondary outcomes over time (ie, an interaction of the between-subjects factor of the study arm and the within-subjects factor of time of measurement). Count variables that lack sufficient variability to be treated as count data (negative binomial distribution) will be treated as dichotomous variables and run using a binomial distribution in the linear mixed model.

Supplemental sensitivity analyses [69] will also be conducted to assess the robustness of conclusions to our assumption that missing data are MAR. Specifically, we will use comparable linear mixed-effects models to examine the effects of the study arm using only complete cases, as would be appropriate if data were missing completely at random. To address the possibility that the data are missing not at random, we will use both the Diggle-Kenward approach (which assumes that dropout is a function of time-specific outcomes) and the Wu-Carroll approach (which assumes that dropout is a function of one's developmental trajectory) [66-68,70].

Mediation of Effects of Study Arm on Primary Outcome

We predict effects of the study arm on functional health will be mediated by the amount of ElderTree use and perceptions of ElderTree at the 6-month midpoint. We will use structural equation modeling with separate models for the social-emotional and physical components of functional health.

Moderation of Study Arm on Primary Outcome

We predict that the effects of the study arm on functional health will be moderated by gender and the number of chronic conditions at baseline. We will use linear mixed models, testing each moderator separately, to examine the moderator-by-arm interaction while accounting for time.

Ethical Considerations

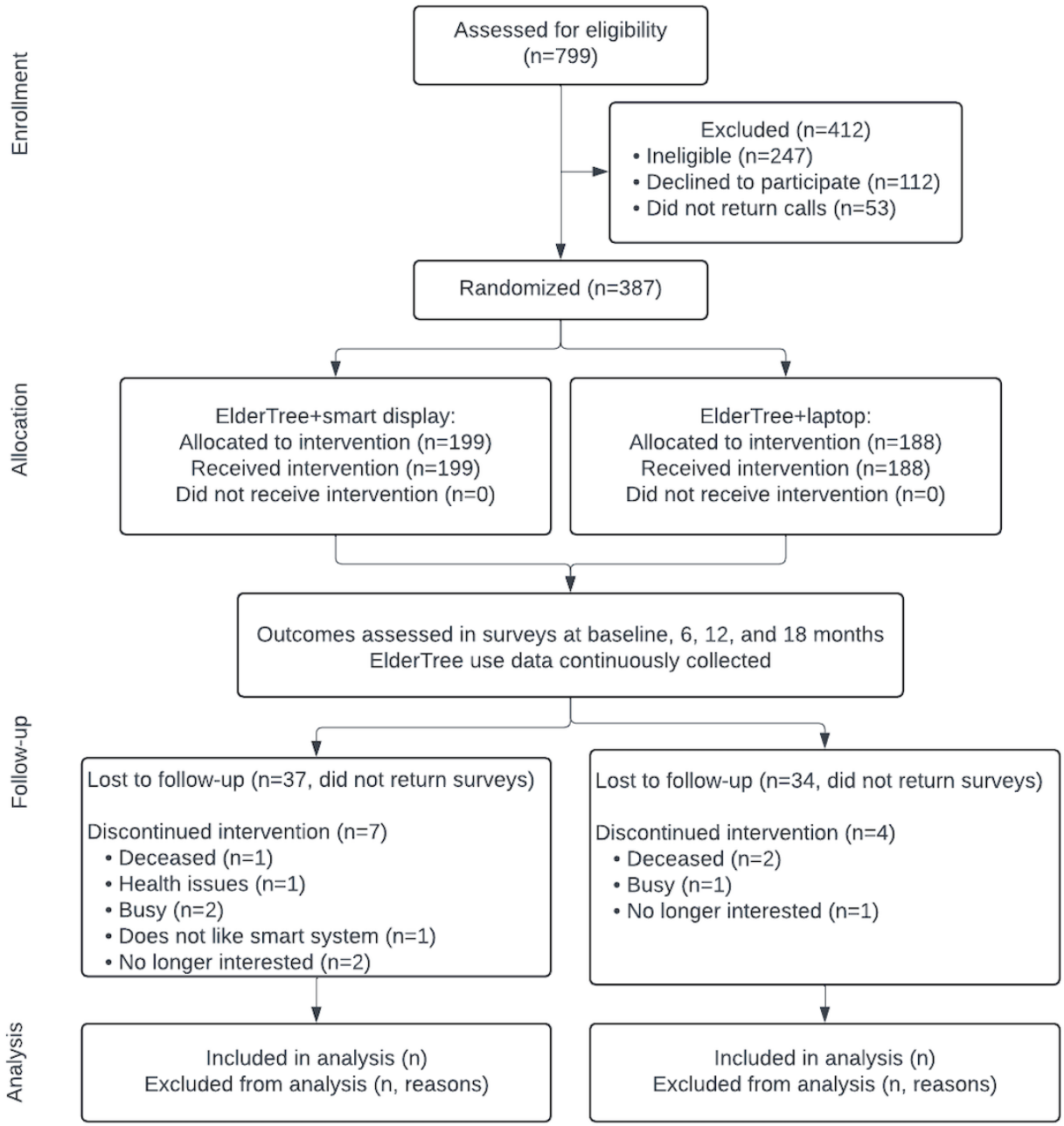
This study protocol received ethical approval from the University of Wisconsin Health Sciences and Minimal Risk Research institutional review board (reference number 2020-0984) and has been registered at ClinicalTrials.gov (NCT05240534). Consent forms were mailed to potential participants and research staff walked through informed consent

over the phone. Participation was voluntary and participants could opt out at any time. Only a small number of research staff has access to patient data and all outcomes and usage data are deidentified. Participants were paid US $10 for each outcome survey completed and received a free laptop or smart display and internet service for 12 months if needed.

Results

As of May 2024, a total of 387 new participants have been enrolled, concluding recruitment 2 months earlier than originally scheduled. The 12-month intervention period will end in May 2025, and data collection will end in November 2025. Findings will be disseminated via peer-reviewed publications. Figure 2 shows the status of participants throughout the trial. Interim numbers are shown in the Follow-up section, as the intervention and data collection are not yet complete. The final numbers for the Analysis section will be reported in the main outcome publication.

Figure 2. CONSORT (Consolidated Standards of Reporting Trials) flow diagram.



Discussion

Anticipated Findings

The central question of this study is whether a voice-activated smart system will be better than a laptop for delivering an intervention for functional health to older adults with ≥5 chronic conditions. The prediction is that those randomized to access the intervention via a voice-activated smart display will show more use of the intervention than those randomized to access it via a laptop and that greater use will lead to more positive

change over time in the primary and secondary health-related outcomes.

Few studies thus far have rigorously tested smart displays as a platform for health interventions for older adults. A 2024 scoping review found 22 studies (published between 2010 and 2022) examining community-dwelling older adults' use of personal voice assistants [26]. The overall conclusion was that many older adults found the devices convenient and easier to use than a computer for basic tasks like reminders or checking the weather, but they sometimes struggled to make themselves understood or to remember the necessary commands. As the authors noted, all of these studies were exploratory, and none examined effects on quality of life or health-related outcomes.

Since then, 2 studies have examined socio-emotional outcomes of older adults' uses of smart devices, but one lacked any comparison group (examining pre-post changes only) [71], and the other compared a smart speaker (audio only) versus a smart display (audio + screen) [72]. While both found that frequent use of smart systems was associated with positive socio-emotional changes (eg, reductions in loneliness), it is possible the same changes would have occurred with laptop use. A third, nonrandomized study examined whether a smartphone health intervention for older adults would be more effective if participants agreed to add a smart speaker with extra functions (eg, medication reminders, exercise programs, quizzes) [73]. There were no differences between the 2 self-selected groups in changes over time in depression or 5 of 6 health outcomes; only dietary diversity showed greater improvements in the group that agreed to have the smart speaker as well as the smartphone.

In sum, despite claims about the possibility that voice interactivity may increase the accessibility and effectiveness of health interventions for older adults, our project is one of the first randomized trials comparing a smart display versus a laptop for delivering an intervention for older adults, who face complex health challenges. As in any study, there are strengths and limitations.

The first strength lies in the methodological rigor involved in a randomized trial that followed 356 older adults over 12 months with a postintervention follow-up at 18 months. Another strength is that we can gather objective, ongoing data about participants' uses of the intervention, rather than relying on their recollections. Next is our recruitment of older adults with 5 or more comorbid conditions, given the need for effective interventions that will engage this sizable, high-risk population. In addition, the focus on functional health is a core determinant of older adults' ability to remain independent.

There are also a number of limitations. One is that this iteration of ElderTree, like those that came before it, was developed before the widespread availability of large language models and artificial intelligence (AI) interactivity. Although participants can interact with ElderTree on the smart speaker by voice, they must do so using specific commands, rather than the intuitive, conversational exchanges now made possible by AI. A second limitation is the absence of a randomized control group that does not receive access to ElderTree: we prioritized adequate power to detect a difference between the 2 intervention groups but will not be able to assess whether both improve outcomes relative to treatment as usual. Next is that we rely on participants' perceptions of their functional health, rather than using clinical data or direct assessment of their functional movement. We regard these limitations as invitations for further research, particularly research that would probe older adults' uses and responses to digital devices that are much more interactive and responsive to voice commands, given AI advances.

Conclusion

Whether the theoretical advantages of voice activation translate to improved effectiveness of eHealth interventions has yet to be determined. Although technologies are constantly developing, the issue of talking versus typing for health interventions for older adults is fundamental and supersedes specific devices. In this way, if ElderTree on the smart display does outperform the laptop in terms of use and health-related outcomes, this would have important implications for the design of future health interventions for this population.

Acknowledgments

This project was funded by a grant (4R33HL151870-02) from the National Heart, Lung, and Blood Institute, and supported by the Clinical and Translational Science Award (CTSA) program through the National Institutes of Health's National Center for Advancing Translational Sciences grant (UL1TR002373). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health. The authors wish to thank the research and technology staff at CHESS for their care and dedication regarding all aspects of this project: Kaitlyn Brown, Lynne Cotter, Dave Gustafson Jr, Hannah Lehr, Adam Maus, Sam Nowak, Sydney Saunders, Jen Stoughton, Kasey Thompson, Olivia Vjorn, Judy Woodburn, Katherine Wright, and Matthew Wright.

Data Availability

Following the completion of the final analysis, the datasets generated or analyzed during this study will be available from the corresponding author on reasonable request.

Conflicts of Interest

DHG Sr. has a small shareholder interest in CHESS Health, a corporation that develops health care technology for patients and family members struggling with addiction; this relationship is managed by DHF Sr and the University of Wisconsin–Madison's Conflict of Interest Committee. The authors have no other conflicts to report.

Multimedia Appendix 1
ElderTree screens and physical activity decision tree.
[DOCX File , 2762 KB - resprot_v14i1e64449_app1.docx]

Multimedia Appendix 2
SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) checklist.
[DOC File , 136 KB - resprot_v14i1e64449_app2.doc]

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Abbreviations

AI: artificial intelligence
CHESS: Comprehensive Health Enhancement Support System
CONSORT: Consolidated Standards of Reporting Trials
DHHS: Department of Health and Human Services
EASY: Exercise and Screening for You
ET-LT: ElderTree on a laptop platform
ET-SD: ElderTree on a smart display platform
MAR: missing at random
OA-01: Older Adults-01
OCT: Office of Clinical Trials
PCP: primary care physician
PROMIS: Patient-Reported Outcomes Measurement Information System
RCT: randomized controlled trial
REDCap: Research Electronic Data Capture
UW Health: University of Wisconsin–Madison Department of Family Medicine and General Internal Medicine system
UW: University of Wisconsin
UW–Madison: University of Wisconsin—Madison

Edited by A Schwartz; submitted 17.07.24; this is a non–peer-reviewed article;accepted 08.03.25; published 03.04.25.

Please cite as:
Gustafson Sr DH, Mares ML, Johnston DC, Curtin JJ, Pe-Romashko K, Landucci G
Comparison of Smart Display Versus Laptop Platforms for an eHealth Intervention to Improve Functional Health for Older Adults With Multiple Chronic Conditions: Protocol for a Randomized Clinical Trial
JMIR Res Protoc 2025;14:e64449
URL: https://www.researchprotocols.org/2025/1/e64449
doi:10.2196/64449
PMID:40080672

Protocol

Multilevel Intervention to Support Tailored and Responsive HIV Pre-Exposure Prophylaxis Care in Rural North Carolina: Protocol for a Randomized Controlled Trial

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Abstract

Background: While access to pre-exposure prophylaxis (PrEP) is an important tool for reducing HIV incidence in the United States, disparities in uptake by race, sex, socioeconomic status, and geography persist. In 2018, the US South accounted for more than half of all new HIV diagnoses but only one-third of PrEP users. PrEP use in North Carolina (NC) similarly lags, with uptake being the lowest among young, sexual and gender minority populations, who account for nearly two-thirds of the state's incident infections. The PrEP-to-need ratio, a metric of PrEP equity that measures PrEP uptake relative to new HIV diagnoses, highlights disparities in PrEP uptake among specific demographic groups such as women and Black, Hispanic, and Southern people, indicating that these groups are underserved relative to their epidemic need. Despite behavioral risk overlap of incident sexually transmitted infections (STIs) and HIV, in NC, PrEP is only offered at a few primarily urban health department–affiliated STI clinics. The lack of robust health care infrastructure in these areas presents challenges for HIV prevention services.

Objective: This protocol describes a randomized controlled trial of a multilevel PrEP intervention recruiting from rural and periurban STI clinics.

Methods: This trial aims to enroll up to 336 participants and randomly assign them 1:1 to either the intervention or control group. The intervention consists of access to a digital health app, linkage to a remote PrEP navigator, and the option of referral to telehealth-based PrEP services. Persons randomly assigned to the control condition will receive an enhanced standard of care, including access to a limited version of the digital health app. All participants will be followed up on quarterly for at least 3 months. The primary outcome is the initiation of PrEP within 3 months of an index STI clinic visit; secondary outcomes evaluate PrEP care engagement and adherence, incident HIV and bacterial STI infections, PrEP stigma, and cost-effectiveness. Binary outcome analyses will estimate the proportion of participants achieving an event (eg, PrEP uptake) in each arm and a probability difference and the corresponding 95% CI to compare the intervention versus control arm at each time point. Continuous end points will use nonparametric Wilcoxon rank sum tests comparing the intervention and control groups.

Results: Enrollment opened on August 31, 2023, at 15 health departments in NC and subsequently expanded to 21 facilities in 20 counties by July 2024. Completion of the enrollment and data collection phases is expected by May 2025. Results will be published thereafter.

Conclusions: This study directly addresses multiple barriers to PrEP use in rural and periurban areas of the Southeastern United States and can inform policy and programming that seek to expand PrEP access and promote use in underserved communities.

Trial Registration: ClinicalTrials.gov NCT05984030; https://clinicaltrials.gov/study/NCT05984030
International Registered Report Identifier (IRRID): DERR1-10.2196/68085

(JMIR Res Protoc 2025;14:e68085) doi:10.2196/68085

KEYWORDS

pre-exposure prophylaxis navigation; PrEP navigation; digital health app; mobile health; mHealth; telehealth; public health; sexually transmitted infection; HIV prevention; mobile phone

Introduction

Background

To meaningfully reduce HIV incidence, the United States needs integrated, scalable, and cost-effective prevention strategies. Despite the high efficacy of HIV pre-exposure prophylaxis (PrEP), only approximately one-third of PrEP-eligible people nationwide have received a prescription for PrEP; regional and racial disparities have been well characterized and mirror similar disparities in HIV care [1-5]. In 2021, the US South accounted for 52% of new HIV diagnoses but only 38% of PrEP users [6-8]. Coverage of those assigned male sex at birth with PrEP indications was reported by the Centers for Disease Control and Prevention (CDC) as 41% in 2022 but only 12.8% among Black and African American individuals [5]. In North Carolina (NC), the state-level PrEP coverage estimate is 30%, which belies the wide variability from urban to rural areas [9]. Indeed, in NC, where an estimated 1 in 112 residents will acquire HIV in their lifetime [10,11], PrEP use remains below the US average [6,11]. Similar to other states in the Southern region, PrEP uptake is lowest among young, sexual and gender minority men, who account for 76% of new HIV infections in NC [12]. Among the 15 NC counties with the highest rate of HIV diagnoses [13-23], 6 have nonmetropolitan designation, and 8 are small or medium metropolitan areas [12,24]. The lack of a robust health care infrastructure, including scarce HIV care providers, in these areas presents challenges for the sustainable expansion of HIV prevention services.

Similarly to most of the United States, NC's HIV statistics track alongside those of sexually transmitted infections (STIs) [13], with a disproportionately high burden among rural, young, sexual and gender minority men. Previous studies have demonstrated the potential role of STI clinics as effective PrEP linkage sites but have been limited to urban settings [14-23,25]. Despite behavioral risk overlap of incident bacterial STIs and HIV, PrEP is only offered at a few primarily urban health department–affiliated STI clinics in NC [26,27]. STI clinics are a logical entry point for PrEP services, but ineffective integration in rural STI clinics reflects heterogeneity in clinic structure and staffing—PrEP services require additional human resources and longitudinal engagement to be effective [28]. Leveraging STI clinics as an on-ramp to PrEP presents a compelling opportunity to capitalize on STI service encounters and address disparities in PrEP access for rural residents [15-17].

Multilevel impediments to PrEP scale-up in rural NC include provider shortages, intersectional stigmas, and lack of PrEP knowledge among providers and patients [29-33]. These challenges are compounded by poverty and incomplete insurance coverage of PrEP and PrEP services [34,35]. Building on collaborations with state and local partners, we will implement a multilevel intervention in partnership with rural county health departments and health care organizations that links PrEP and STI services to address PrEP use barriers while working within clinic operational limits and competing demands on physical and human resources. This intervention combines multiple evidence-based interventions, including PrEP navigation services [36-38], access to a digital health platform (HealthMpowerment) [39-42] that connects users to tailored social and informational support for PrEP initiation and persistence [43,44], and referral to telehealth PrEP services [45-48].

Research Aims

Our objective is to determine the effectiveness and cost-effectiveness of the proposed PrEP linkage strategy in 2 aims. Our primary effectiveness outcome is PrEP uptake within 3 months of an STI clinic visit, defined as confirmed receipt of PrEP prescription or evidence of detectable tenofovir diphosphate in the blood, evaluated through a randomized controlled trial (RCT). Secondary outcomes evaluate PrEP uptake within 6 months of an STI clinic visit, 3- and 6-month PrEP care engagement and adherence, incident HIV or STI infections, and PrEP stigma.

We will examine implementation outcomes as exploratory outcomes, capturing process indicators, including intervention costs, fidelity, and acceptability, to inform future refinement. We will use decision analytic modeling to determine the cost-effectiveness of the proposed intervention over a range of assumptions and inputs, as well as developing a budget impact analysis. Specifically, intervention effectiveness and prospectively collected cost data will be used to model cost per new PrEP initiation. Budget impact analyses will identify drivers of cost, informing strategy refinement for program staffing and scale-up.

This project is supported via a milestone-based funding mechanism, wherein if predefined effectiveness, implementation, and development milestones are met within the initial phase, we will pursue a second phase, in which we will use intervention mapping to refine the proposed strategy and expand implementation in a nonrandomized fashion with updated cost-effectiveness modeling. The second phase is not described further in this paper as the development and finalization of that protocol are dependent on this trial's outcomes.

This trial has been registered with ClinicalTrials.gov (NCT05984030), which includes reporting of all relevant items

from the World Health Organization Trial Registration Data Set.

Methods

Protocol Adaptations

We present our methods according to 2 participant recruitment stages: stage I, which focused exclusively on young, sexual and gender minority men seeking STI services from health department–affiliated STI clinics, and stage II, which reflects an amended protocol with modifications made in response to participant enrollment challenges and feedback from collaborating sites. Changes in stage II of protocol implementation include (1) expanding collaborating sites beyond the initially identified 15 health department–affiliated STI clinics, (2) offering a US $5 incentive for completing the brief screening questionnaire, (3) shortening the follow-up period to 3 months for participants enrolled in the final quarter of the study recruitment period, and (4) expanding eligibility criteria to include women assigned female at birth.

Expanding to women more closely aligns with 2021 CDC recommendations, including discussing PrEP with all persons with an STI in the previous 6 months, and reflects the evolving focus on PrEP for women put forth by the CDC, particularly racial minority women in the Southeastern United States. Among new HIV cases in women in the Southern region of the United States, Black women account for 67% of new HIV infections and 72% of new diagnoses among women reporting heterosexual sex [49]. Increasing PrEP use among cisgender women has the potential to significantly impact the spread of HIV in rural and periurban NC and contributes to a broader public health strategy aimed at reducing new HIV infections across various demographics. To explore the potential for our intervention to expand PrEP care to a broader population in NC, we conducted a change in scope that adapted our eligibility criteria to encompass women.

Study Design (Stage 1)

This RCT of a multilevel PrEP intervention strategy will open with recruitment of those assigned male sex at birth seeking sexual health services from rural and periurban NC STI clinics (Figure 1). Participants are randomly assigned 1:1 to the intervention or control condition. All participants regardless of study arm complete study measures and activities at enrollment and the 3- and 6-month follow-up time points, with a subset of participants enrolled in the first 6 months of recruitment also completing a 12-month follow-up assessment (Table 1). The timing of participant follow-up activities mimics the CDC-recommended frequency of testing, which includes screening for bacterial STIs every 3 months among men who have sex with men or among patients with ongoing risk behaviors [50,51]. Therefore, HIV and STI testing will be completed as part of patients' routine care at established STI clinics (not administered through this study). The HealthMpowerment app and study staff will help facilitate participants' return to the STI clinics for HIV and STI testing by providing in-app appointment reminders, SMS text messages, and phone calls as needed. Quarterly surveys will assess participants' adherence to CDC-recommended testing frequency.

Cost data and implementation outcomes are collected throughout study implementation examining organization-level determinants of success via surveys and in-depth interviews with participants, clinic staff, health care providers, and other key stakeholders for PrEP expansion.

Figure 1. Study schema—aims 1 and 2, years 1 to 3. PrEP: pre-exposure prophylaxis.

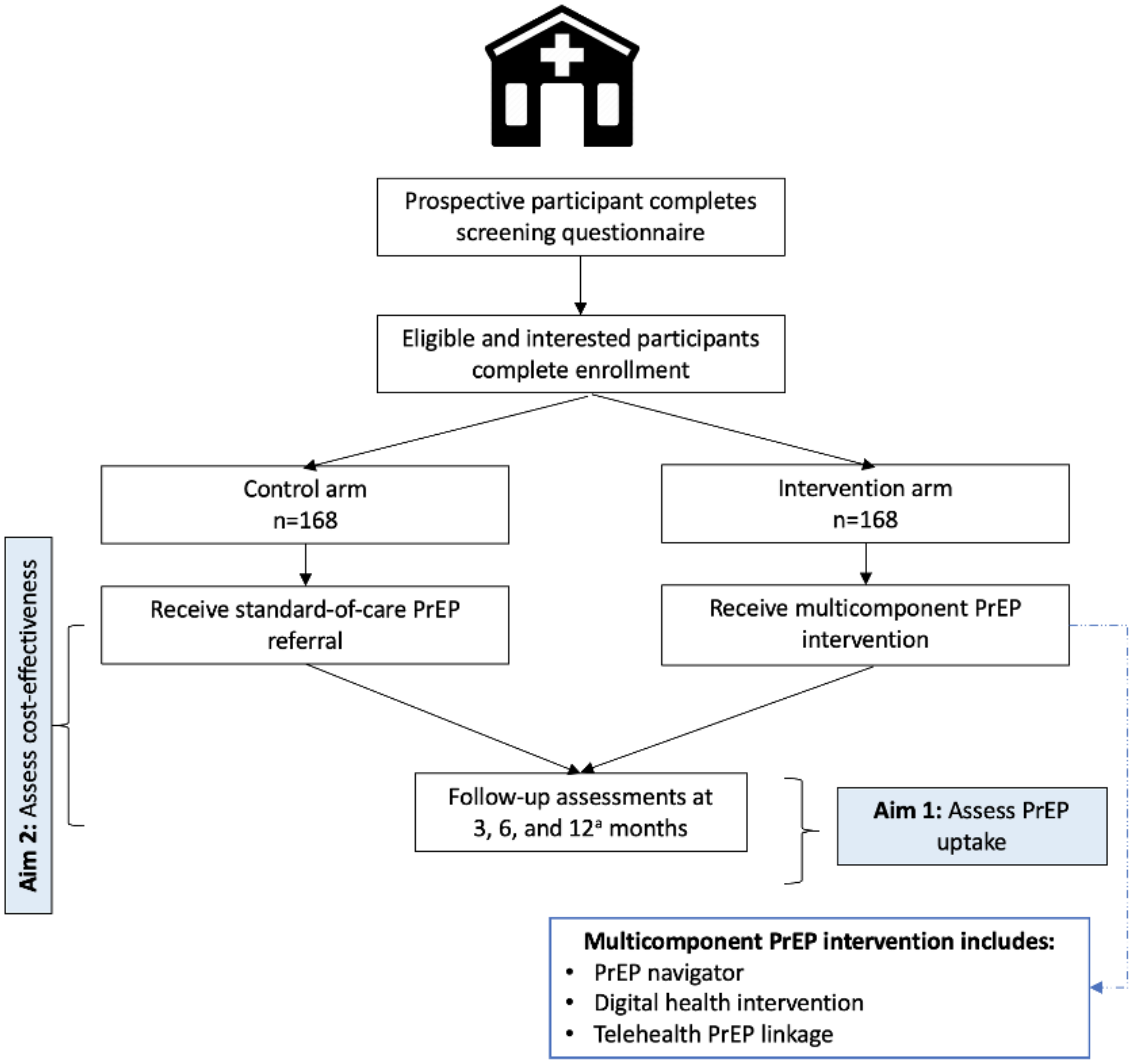


Table 1. Participant assessment timeline.

	Screening	Baseline	3-month follow-up	6-month follow-up	12-month follow-up
Screening questionnaire	✓				
Informed consent		✓			
HIPAA[a] record release authorization		✓			
App onboarding		✓			
Survey assessment (CASI[b])		✓	✓[c]	✓	✓[d]
DBS[e]			✓[c]	✓	
Qualitative exit interview (optional)			✓[f]	✓[f]	

[a]HIPAA: Health Insurance Portability and Accountability Act.

[b]CASI: computer-assisted self-interview.

[c]Participants enrolled in approximately the final quarter of study enrollment will only be followed up on for 3 months.

[d]Only applies to participants who enroll during the first 6 months of study recruitment.

[e]DBS: dried blood spot.

[f]A subset of up to 50 participants will complete an in-depth interview following their 3- or 6-month study visit.

Study Design (Stage 2)

The updated study design incorporates a shortened follow-up period to extend the enrollment window, allowing for a greater number of participants to contribute to the primary outcome of PrEP uptake assessed at 3 months. Randomization and intervention procedures remain unchanged, and study measure assessments are completed at baseline and 3 months (Table 1).

Eligibility

For stage I, RCT-eligible participants must (1) be assigned male sex at birth, (2) report sexual activity with a male individual in the previous 12 months, (3) report recent HIV testing (within the previous 90 days) and not be known to be HIV positive at screening or enrollment via self-report, (4) be aged 18 to 39 years, (5) have daily smartphone access, (6) be English speaking, and (7) deny recent PrEP use (defined as not having taken oral PrEP or received injectable PrEP within the previous 90 days).

For stage II, the eligibility criteria were updated to reflect the eligibility of persons regardless of sex assigned at birth. All other eligibility criteria from stage I remain unchanged.

We will also conduct qualitative interviews with up to 50 clinic staff members, providers, and other relevant stakeholders for PrEP provision or relevant to the proposed intervention. Interviewees will be purposively sampled to ensure a diversity of clinic roles and responsibilities relevant to STI and sexual health services and referrals, diversity in leadership level, and representation across all participating clinics.

STI Clinic Selection

We initially identified 15 health department–affiliated STI clinics in relatively high–HIV burden, rural, or periurban counties across NC. Counties were selected in coordination with partners in the NC Department of Health and Human Services using county-level 2019 to 2021 HIV and STI data (reported to the State Laboratory of Public Health). Specifically, we examined HIV and STI testing volume and test positivity rates by reported race or ethnicity among men aged <40 years, prioritizing counties with higher rates of HIV and non-HIV STIs ranked by county without a predefined cutoff. We also reviewed the National Center for Health Statistics urban-rural classification scheme focusing on rural counties, as well as those designated as small (<250,000) or medium (<1 million) metropolitan areas [45-47]. We refer to all locations where STI services are offered as *clinics* or *STI clinics*; however, these locations may also include extensions of clinic services, such as mobile testing or service delivery within other outreach events.

Clinics were contacted with information about the study and an invitation to participate. The study team met with clinics who responded; clinics that decided to participate provided signed letters of support indicating commitment to collaborate and outlining expected roles and responsibilities. At the time of study launch, none of the initial 15 participating STI clinics offered PrEP navigation services or had “in-house” providers prescribing PrEP. Only 7% (1/15) of the participating clinics offered referral to a colocated primary care clinic that could prescribe PrEP. Of the remaining 14 initial collaborating clinics that did not offer in-house PrEP services, a minority provided patients with passive referral to services in the community (eg, the clinic shared the name or names of private practice providers that may offer PrEP services). Starting in March 2024, a total of 6 more clinics were added as collaborating sites under protocol version 3.0. None of these clinics offered PrEP navigation services or had “in-house” providers prescribing PrEP.

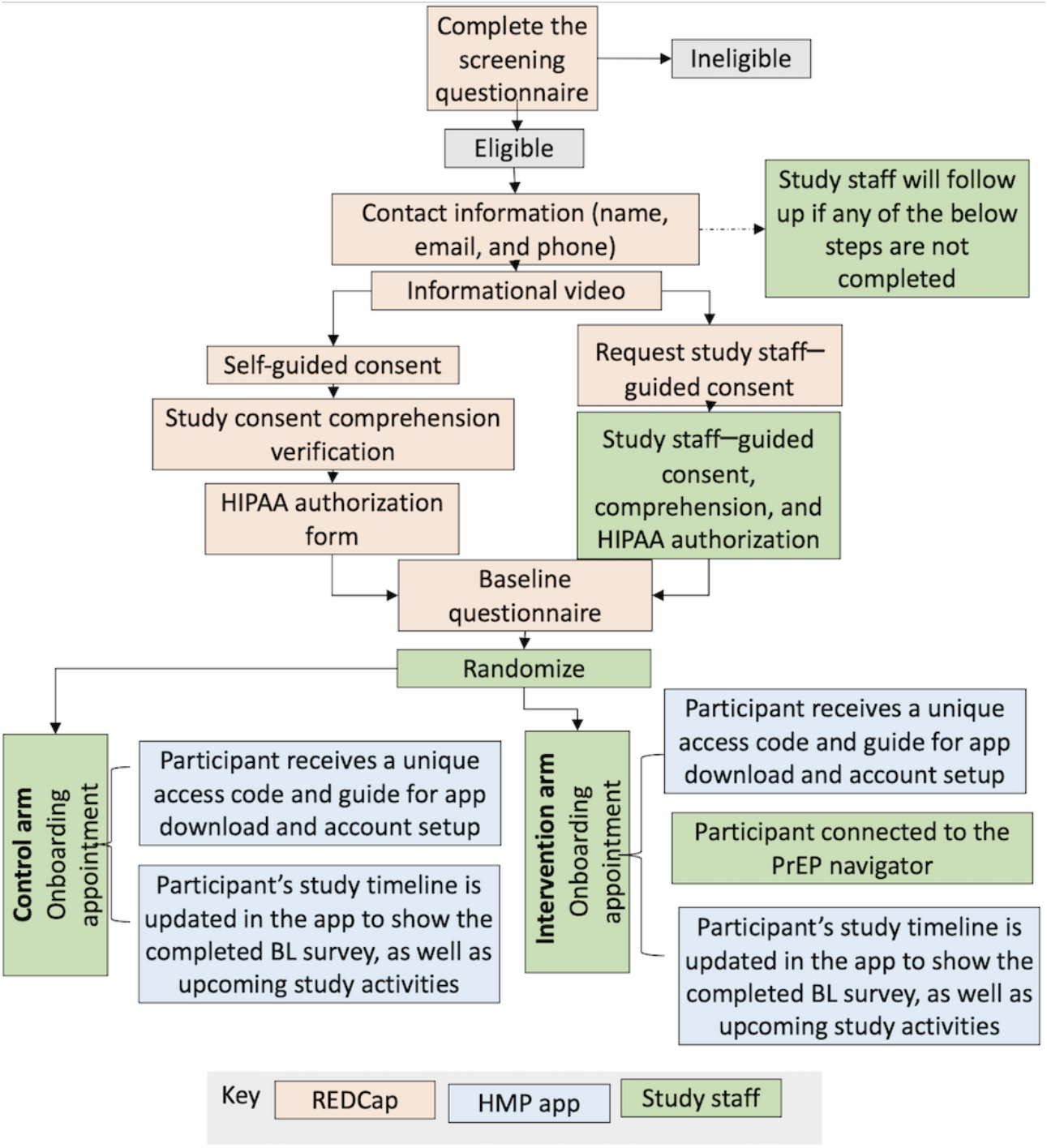
Sample Size and Statistical Power

On the basis of historical clinic volumes and patient demographics, we expect that >7400 patients will present for care across the sites during the study enrollment period, with 20% to 35% being study eligible. Power calculations were based on the study’s primary outcome (PrEP uptake within 3 months of STI clinic visits). PrEP use among the target population has not been estimated previously as there is currently little to no availability of PrEP in rural NC settings. Assuming that 2.5% of eligible patients start PrEP within 3 months in the control arm, we calculated statistical power to detect a range of small to large effect sizes from 5% to 15% increases in PrEP uptake under a range of possible sample sizes and assuming 10% missing data or attrition at 3 months. At a total sample size of 336 given our design and assumptions, we will have >88% statistical power to detect medium (10%) and large (15%) effect sizes and 80% statistical power to detect a moderate (7.5%) effect size with a 5% type-I error rate (SAS; version 9.4 [SAS Institute]).

Randomization and Enrollment

After providing written informed consent electronically and completing baseline surveys, participants will be randomly assigned 1:1 to the control or intervention condition at enrollment using blocked randomization stratified by county, with randomly ordered blocks of sizes 4 and 6 (Figure 2). There will be no masking to assigned arms. Randomization assignments will be automated through the study database. Arm assignment is then disclosed to participants by study staff during study onboarding. The onboarding session includes orientation to study app features for all participants and, for those randomly assigned to the intervention arm, an introduction to the remote PrEP navigator.

Figure 2. Participant enrollment flow. (Note: Dependent on their enrollment date, only a subset of participants will be asked to complete 6 and 12-month study activities.) BL: baseline; HIPAA: Health Insurance Portability and Accountability Act; HMP: HealthMpowerment; PrEP: pre-exposure prophylaxis; REDCap: Research Electronic Data Capture.

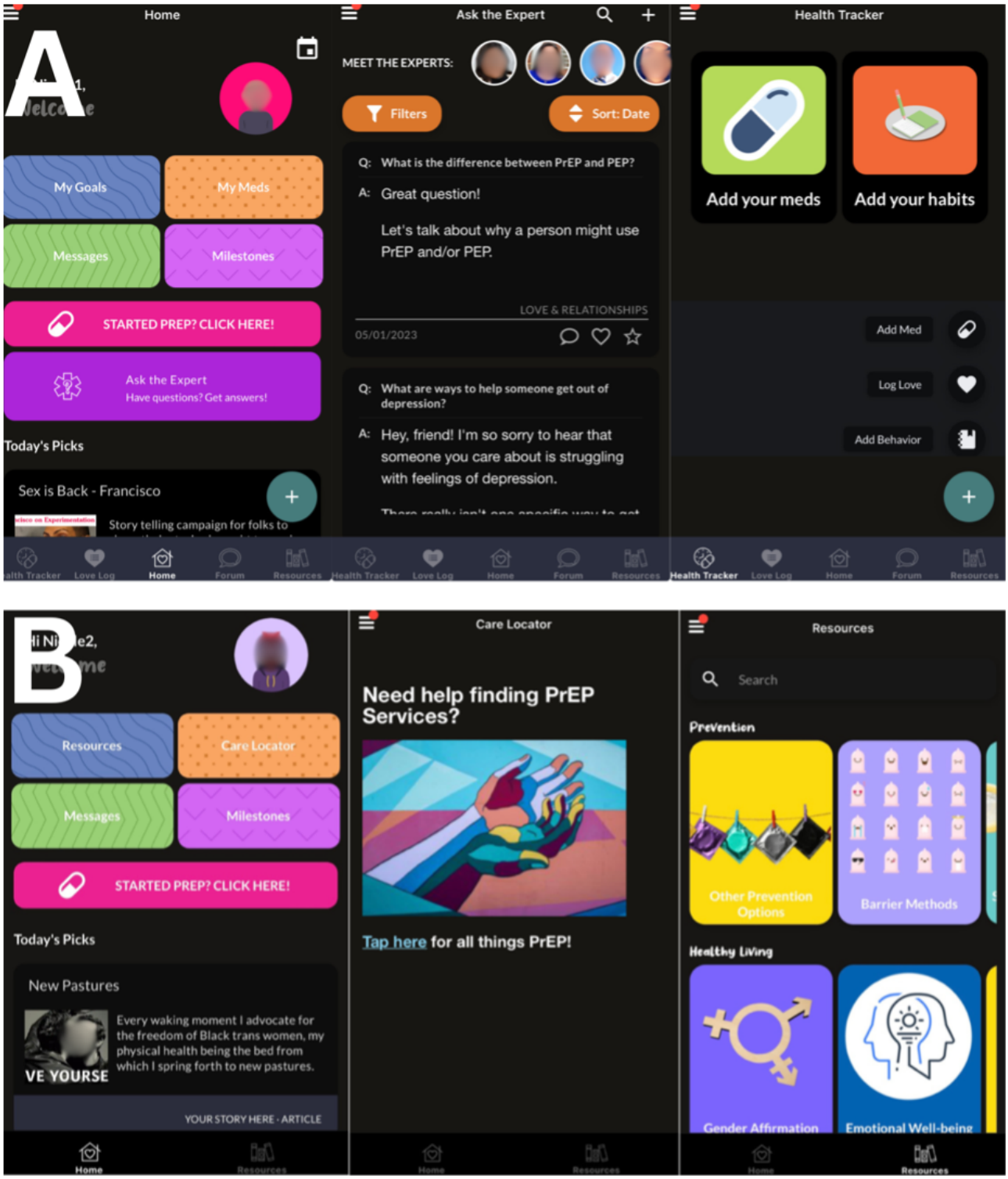


Intervention Arm

Overview

Participants randomly assigned to the intervention arm will receive standard PrEP referral services identical to those available to persons in the control condition (see the following sections), as well as a multilevel intervention with 3 components, all of which they engage with remotely: a PrEP navigator to address potential barriers to PrEP uptake and use and facilitate linkage to PrEP services if interested, referral to telehealth PrEP services as an option for linking to PrEP care, and a Health Insurance Portability and Accountability Act (HIPAA)–compliant web-based digital health intervention app (see additional information regarding app privacy in the *Ethical Considerations* and *Data Quality and Monitoring* sections; Figure 3A).

Figure 3. Screenshots from the HealthMpowerment app—(A) enhanced version of the HealthMpowerment app for the intervention condition and (B) limited version of the HealthMpowerment app for the control condition. PEP: postexposure prophylaxis; PrEP: pre-exposure prophylaxis.



PrEP Navigation

PrEP navigators will connect with participants immediately following app onboarding. Navigator services are available to participants for the first 6 months of participation (active intervention period) and include assessing participant awareness of an interest in PrEP, referral to PrEP care, helping participants engage in PrEP care (including assisting with appointment scheduling, reminders, and other provider access issues), and assisting with completing necessary paperwork for insurance and application for drug assistance programs as needed. PrEP navigators undergo study- and navigator-specific trainings.

PrEP navigators were recruited through relevant recruitment channels and listserves commonly used by professionals in the HIV prevention sector. Preference was given to applicants with experience in sexual health; lesbian, gay, bisexual, transgender, and queer health; health insurance; digital health or telehealth; and patient navigation. In addition, candidates with experience

collaborating with regulatory bodies and research study teams and in academic-community partnership settings were preferred.

PrEP Linkage

PrEP navigators can link interested participants to preexisting local or telehealth PrEP services, although neither are provided, financed, or staffed by the study. Participants referred to telehealth services will receive these PrEP services via the technology platform or service that the provider typically uses. PrEP clinical eligibility, visit frequency, monitoring of laboratory tests, and all other PrEP management will be at the discretion of the PrEP provider. Before enrollment, all participants will sign a HIPAA authorization form permitting study staff to access their medical records pertaining to PrEP care delivery.

Digital Health Intervention App

HealthMpowerment is an HIV status–neutral, theory-informed, HIPAA-compliant digital health intervention that supports sexual health and risk reduction among young, sexual and gender minority men [52-54]. HealthMpowerment is guided by the Integrated Behavior Model [55], facilitating examination of the individual and structural determinants of health (eg, stigma and discrimination, health literacy, and poverty) and psychological distress (eg, depression, anxiety, and loneliness) that hinder adoption of HIV-preventive behaviors. The app provides a range of resources addressing these social determinants for persons at all stages of readiness to initiate PrEP, as well as ongoing support and resources for those who do initiate PrEP. All information on the app is available to all participants. The app also recommends specific content to individuals based on their voluntary responses to questions and activities within the app. As part of PrEP-monitoring features, participants can indicate how PrEP was prescribed (ie, daily oral, event-driven oral, or injectable), as well as indicate the dates on which PrEP was taken or, in the case of injectable PrEP, received. HealthMpowerment was first found effective in a statewide RCT [42,53] in NC, which found that greater HealthMpowerment engagement was significantly associated with fewer episodes of condomless anal sex; stigma reduction; and greater provider communication, HIV status disclosure to partners, and HIV care outcomes (eg, engagement in care and adherence) [53,56].

The content included in this version of the app was selected from a broader content library developed and used in previous studies involving similar populations. The app's design, interface, and features were developed and user tested by a community advisory board comprising racially and ethnically diverse, young, sexual and gender minority groups. In addition, the app's content is dynamic, with updates made based on user engagement analytics and ongoing developments in the field.

Control Arm

Persons randomly assigned to the control arm will receive an enhanced standard of care, pairing existing referral systems with access to the core educational resources of the HealthMpowerment app. For this study, access to publicly available PrEP locator resources and tailored information on PrEP and HIV prevention will be accessible from within the app (Figure 3B). This comparator condition of an enhanced standard of care control was selected to balance the dual goals of establishing effectiveness and ethical obligations to provide all participants with information regarding available PrEP services and basic PrEP education.

Study Procedures

All study staff will be trained in and follow a detailed study-specific procedure manual and topic-specific standard operating procedures (SOPs) that were informed by the Division of AIDS Site Clinical Operations and Research Essentials Manual [57].

Recruitment

The protocol uses clinic-based recruitment at participating STI clinics. Posters, 1-page flyers, and palm cards with scannable QR codes will be posted throughout the clinic waiting areas, on bulletin boards, and in patient rooms. The study will also be promoted through word of mouth via health professionals, administrative staff, and community outreach personnel associated with each site. Clinic and study staff may also bring recruitment materials to community-based events they attend on behalf of the clinic (eg, health fairs and blood drives) with information about the study.

Scannable QR codes will lead to a web-based screener, which allows potential participants to learn about the study and their eligibility discretely. As of July 17, 2024, prospective participants that complete the screening questionnaire are offered a US $5 e–gift card. Individuals who are not eligible based on screening criteria, duplicate entries, or choosing not to proceed will be thanked and rerouted to a public web page. Prospective participants will be asked to grant permission for study staff to contact them and to provide preferred contact information before they are routed to a brief video describing the research basics and specific study objectives.

Participant Management and Retention

We will collect multiple forms of participant contact information and study-related communication preferences (eg, email and phone or SMS text messaging) as part of study enrollment. The HealthMpowerment app supports participant retention through a timeline that displays upcoming study activities and a 2-way secure messaging feature for participants and study staff. All participants will receive compensation throughout the course of their participation.

Data Sources and Collection Methods

Data sources and collection methods are described in this section and summarized in Table 2. The study will use electronic data capture tools (REDCap [Research Electronic Data Capture; Vanderbilt University]) hosted at Florida State University for all primary data collection and participant management purposes [58,59]. REDCap is a secure, web-based software platform designed to support data capture, audit, monitoring, and export for research studies. Study screeners, assessments, and in-depth interviews will all be completed remotely via secure HIPAA-compliant platforms for survey administration and phone and videoconferencing.

Table 2. Data sources and collection methods.

Data source and collection method	Primary effectiveness	Cost-effectiveness
CASI[a] surveys—in the clinic or web-based	✓	
Whole blood collection samples—self-collected blood sample	✓	
Qualitative notes and transcripts—interviews and intervention mapping	✓	✓
Digital health intervention paradata—entered into the app by participants, study staff, and PrEP[b] navigators	✓	
Clinic observations—project receipts and personnel salary		✓
Time-and-motion logs		✓
HIV and STI[c] test results—electronic health record and data or Lapcorp or Quest or CELR[d] or participant-provided records	✓	
PrEP care history—electronic health record data or participant-provided records	✓	✓

[a]CASI: computer-assisted self-interview.

[b]PrEP: pre-exposure prophylaxis.

[c]STI: sexually transmitted infection.

[d]CELR: Clinical and Environmental Laboratory Results.

HIV and STI Result Abstraction From Electronic Health Records

Participants will be encouraged to receive HIV and STI testing at intervals consistent with CDC recommendations (quarterly testing for men who have sex with men and annual testing for sexually active women) [50]. HIV and STI testing will be completed as part of participants' routine care at the STI clinic site, not administered through the study or by study staff. Collaborating clinics or PrEP providers will be responsible for specimen collection, processing, and handling of indicated treatment and treatment referral as appropriate. Proof of a nonreactive (negative) HIV assay is required for study enrollment, but no prospective testing is required, nor are participants incentivized to complete these tests. Participants who receive an HIV diagnosis while enrolled in the study will be study stopped. Individuals may choose to keep the digital health app installed on their phone. All test results will be extracted from clinical records. Clinics will either provide study staff with direct access to the participant's HIV and STI results or upload the results to a secure survey via REDCap.

Specimen Collection

Dried blood spot (DBS) specimens will be used to detect the presence of PrEP metabolites in participants' blood and will be administered at months 3 and 6 depending on participants' enrollment date. Participants can choose to have a DBS kit mailed directly to them (at an address of their choice) or opt for the kit to be mailed to their local health department and pick it up in person. Following an illustrated step-by-step instruction card, participants use a single-use lancet to collect blood onto specialized paper cards, and then they return the sample using a preaddressed, prepaid shipping envelope. DBS specimens will be tested for the presence and levels of tenofovir diphosphate and emtricitabine triphosphate to inform PrEP exposure and prevention-effective use as correlated with survey and available medical record data regarding PrEP medication and intended dosing strategy [60,61].

Study Assessments

Computer-assisted self-interview survey assessments from REDCap will be sent to participants via the HealthMpowerment app at baseline and 3 and 6 months, with a 12-month brief assessment for a subset of participants. Participants enrolled in approximately the final quarter of enrollment will only complete the 3-month survey, reflecting the shorter follow-up period for this group. Survey domains include sociodemographic data, sexual behaviors, PrEP use, self-reported STI and HIV testing outcomes, and perceived or experienced PrEP stigma.

Clinic Assessments

Understanding the organizational environment from which participants will be recruited is crucial to interpret outcomes and potential for scale-up and sustainability. We will conduct assessments of all participating clinics to evaluate staffing, patient volume, hours of operation, and available services. These assessments will be conducted using a combination of in-person and remote interactions. We will also ask relevant stakeholders about intervention acceptability and organizational factors that may influence PrEP provision and integration of services, including organizational readiness for change, support climate, and intervention value fit [62-64]. We will also monitor relevant policy changes, such as those pertaining to insurance, PrEP coverage, or recommendations for use that may serve as external influences relevant to our observed outcomes.

Qualitative In-Depth Interviews

Up to 50 participants will complete an in-depth interview following their 3- or 6-month assessment contextualizing their experience with study participation, perceived accessibility of PrEP before and after study enrollment, evaluation of the acceptability of this enhanced PrEP access model (if randomly assigned to the intervention arm), unmet PrEP-related health service needs and barriers, experience initiating PrEP (if relevant), experience using the study-related intervention components (app, PrEP navigator, and telehealth for PrEP), and other topics as raised by participants (Multimedia Appendix 1).

Participant interviews will be conducted remotely via phone or videoconference platform. Participants will be purposively sampled to ensure diversity in areas such as PrEP initiation status, recruitment clinic, age, and race.

In addition, we will engage up to 50 other stakeholders, including health department–affiliated clinic staff, health care providers, and other stakeholders relevant for PrEP services, for in-depth interviews. Interview topics may include experiences and challenges with being part of a participating clinic for this study, perceived accessibility of PrEP for the target patient population before and after study implementation, perceived strengths and drawbacks of this PrEP access model, suggested changes to this strategy, and unmet PrEP-related health service needs and barriers among the participant population. Stakeholder interviews will be conducted in person or remotely via phone or videoconference platform after consent by trained research staff using a semistructured interview guide (Multimedia Appendix 2). Each interview will be digitally recorded and transcribed for analysis.

Cost-Effectiveness

We will build a decision model to estimate the budget impact and compare the cost-effectiveness and population outcomes of our multilevel PrEP intervention to those of the standard of care.

Specifically, costs will be collected prospectively in 2 ways: microcosting and time-and-motion logs. Microcosting involves "direct enumeration" for consumed inputs [65], an ingredient-based approach. We will further quantify resources associated with the development and implementation of our intervention (eg, costs associated with the adaptation of the HealthMpowerment app and personnel training). Following established methods, we will measure non–research-related costs associated with the intervention and control arms to estimate the incremental cost per additional person starting PrEP. Cost data will be available through contractual information with developers, clinic and project receipts, and NC Department of Health and Human Services supply chain partners. We will also extract data from project expenditure and management records, including purchase logs and human resource records. Time-and-motion assessments record how the involved parties (eg, navigators and providers) divide time among PrEP-related tasks, reliably apportioning effort relevant to implementing the intervention.

Outcomes and Data Analysis

Our primary outcome (PrEP uptake) is assessed through self-reported PrEP use (oral or injection) on a follow-up survey or on the app and verified by at least one of the following: (1) an uploaded photo or image demonstrating a PrEP prescription, (2) any indication of the presence of tenofovir diphosphate or emtricitabine triphosphate in DBS, or (3) staff-abstracted electronic medical record of PrEP prescription issued or prescriber notation of PrEP being initiated (Multimedia Appendix 3).

Outcome Analysis

Analyses will be conducted for all primary and secondary outcomes using the following general procedures. Basic descriptive statistics will be calculated. Frequency tables will be presented for the categorical variables, and means, SDs, and percentiles (25th, 50th, and 75th) will be provided for the continuous variables. For each binary outcome, we will estimate the probability of achieving the event (eg, PrEP uptake) in each arm and a probability difference and the corresponding 95% CI to compare the intervention versus control arms at each time point (3-, 6-, and 12-month follow-ups). For continuous end points, we will use a nonparametric Wilcoxon rank sum test to compare the intervention and control arms. For count data variables (eg, number of unprotected sex acts), we will use small analysis methods for count data (eg, exact Poisson regression).

To address missing data, we will review the frequency of missing and nonmissing values for all variables at baseline and the 3-, 6-, and 12-month follow-ups. We will conduct missing value analyses to determine whether persons with missing values are systematically different from those without missing values and whether the probability of having missing values differs by arm. If this assessment of the frequency and imbalance of missing data suggests that bias may be introduced, we will use inverse probability of observation weights or multiple imputation to address the missing data. If there is chance imbalance in the measured baseline covariates between those randomly assigned to the intervention and control groups, we will conduct sensitivity analyses applying stabilized inverse probability treatment weights.

The primary outcome of PrEP uptake is measured at the 3-month follow-up. The effectiveness of the intervention will be estimated as the difference in probability of starting PrEP within 3 months of an index STI clinic visit comparing patients randomly assigned to the intervention and control groups.

Secondary effectiveness outcomes include PrEP uptake at 6 months, PrEP care engagement, PrEP use, PrEP adherence [66-68], incident STIs, incident HIV, and PrEP stigma [69,70] (all at both 3 and 6 months). All analyses will follow the specifications described previously.

PrEP adherence at 3 and 6 months will be assessed using PrEP metabolite levels and self-reported 30-day adherence as 2 separate outcomes. We will use standard-of-care quarterly STI and HIV testing results to examine differential rates of incident STIs adjusting for testing frequency given potential increased testing frequency among PrEP initiators [71,72].

Exploratory outcomes will report the effectiveness of the intervention (defined previously) as measured using PrEP uptake at the 3-month follow-up stratified by sex assigned at birth.

We will also examine additional exploratory implementation outcomes, including process indicators to inform intervention implementation, optimization, and scale-up. We will measure acceptability of the implementation strategies for providers and clinic directors, feasibility of the intervention, and intervention satisfaction among patients and providers using validated scales [73-76] for outcome assessment, as well as measuring cost-effectiveness.

To measure the acceptability [73,77,78] of the intervention and explore clinic-level influences on implementation feasibility at each clinic, we will interview providers and clinic directors. We will assess factors such as provider burden of intervention, adequacy and timing of training, supervision or support structure, organizational readiness for change (quantitative scale and qualitative interviews) [62], management support (qualitative interviews), implementation climate (quantitative scale and qualitative interviews) [63], and intervention value fit (quantitative scale and qualitative interviews) [64]. We will use facility audit data, including county population, patient panel size and demographics, number and training level of clinic staff, staff-to-patient ratio, daily patient volume, opening hours, and local access to PrEP to contextualize determinants.

Feasibility measures will assess patient engagement with the intervention, including uptake of elements (ie, linkage to insurance if not durably insured at enrollment, use of telehealth PrEP, and interactions with PrEP navigators). We will examine the percentage of enrolled participants in the intervention arm who are engaged by the PrEP navigator within 2 weeks of enrollment. We will also examine app-specific engagement, including successful app installation, account creation and log-in, total number of log-ins, and time spent on the app.

Measurement of patient satisfaction [74,79,80] with the intervention includes qualitative (in-depth interview data) and quantitative (eg, System Usability Scale [75]) assessments. We will conduct interviews with a subset of patients regarding their experiences with the intervention. This sample will include a mix of persons with variable HealthMpowerment engagement and PrEP uptake. We will ask about satisfaction with clinician interactions as part of STI or PrEP care. As a quantitative assessment, all participants will complete a satisfaction scale at quarterly follow-up visits [81].

Analysis of implementation outcome measures will include qualitative analysis. Transcripts from participants and providers or clinic staff members will be analyzed separately and reviewed for quality. Interview transcripts will be thematically analyzed following a combination of deductive and inductive analytic approaches. An initial codebook will be developed based on a priori concepts driven by the theoretical underpinnings used to develop the interview guide. All textual data will then be read thoroughly to summarize first impressions. Emerging themes will be incorporated into the codebook. Preexisting codes may be modified based on interview transcripts. Transcripts will be coded iteratively using qualitative analysis software. In total, 2 researchers will code the interviews separately to assess intercoder reliability. The codebook will be revised and updated. Analysis of the coded data will include investigation of relationships between codes, coding matrices, and mapping of codes and themes. Data from qualitative interviews will be triangulated with the quantitative data to gain a more complete understanding of the factors underlying implementation. For example, if our survey data show that clinics with lower fidelity tended to score low on the implementation climate scale, we will examine our qualitative data for indications of what aspects of the leadership or climate may have contributed.

Our primary cost-effectiveness outcome is the incremental cost per additional person started on PrEP (the primary study outcome) in the intervention versus control condition.

We will conduct a budget impact analysis of the cost in US dollars of the intervention overall, providing decision makers with estimates of the financial feasibility of the intervention [82,83].

All models will include sensitivity analyses to examine the potential impact of varying cost and effectiveness assumptions, accounting for parameter uncertainty [84] and capturing input uncertainty (eg, PrEP adherence and intervention cost and effectiveness). The upper and lower bounds will be based on trial data, literature, or expert opinion. The results represent an average across simulated model runs with an estimated uncertainty range.

We will report incremental cost-effectiveness ratios. The analyses will take the perspective of the health system and public payers.

Study Monitoring and Adverse Event Reporting

The purpose of study monitoring is to verify that the rights and well-being of human participants are protected; the reported trial data are accurate, complete, and verifiable from source documents; and the trial is conducted in compliance with the currently approved protocol and amendments, with good clinical practice, and with all applicable regulatory requirements. This study will follow a detailed clinical quality monitoring plan that specifies the frequency and types of data that will be reviewed (case report forms, regulatory documents, study staff training records, and medical and laboratory records) to accomplish these monitoring activities. External monitoring for this study will be conducted biannually through the North Carolina Translational and Clinical Sciences Institute monitoring service in accordance with established International Conference of Harmonization Good Clinical Practice Guidelines and Title 21 of the Code of Federal Regulations. This review includes quality assurance (QA) and study monitoring, such as regulatory file review, informed consent review, patient eligibility confirmation, protocol compliance review, assessment of safety reporting requirements, and review of training records.

In addition, a study monitoring committee (SMC) will be constituted before initiation of the study. This committee will include, at a minimum, 2 HIV clinicians or research investigators not directly involved in the study and a community representative. At least one representative from the National Institutes of Health (NIH; study sponsor or funder) will be invited to attend the biannual meetings. SMC members will review cumulative study reports, including reports of adverse events (AEs), social harms, and unanticipated problems. The SMC will assess study conduct, adequacy of the delivery of the intervention package, ascertainment of PrEP uptake outcomes, and other related data to ensure adequate collection of primary and key secondary outcome data.

There are no plans for additional interim analyses beyond standard monitoring and reporting, and there are no explicit, prespecified stopping guidelines for the trial. The study sponsor and funder retain the right to terminate the trial.

As a behavioral intervention that does not include an investigational product, standard AE reporting will not be undertaken for this study. The study team will monitor for and track serious and nonserious AEs related or possibly related to study procedures or participation in the study. Study participants will be instructed on how to contact the study staff to report any AEs they may experience at any time between enrollment and the follow-up assessments. AEs will also be actively assessed in all follow-up quarterly assessments. Should a participant report experiencing an AE that they perceive to be related to their study participation, research staff will contact the participant to assess the severity and appropriate resolution action.

Ethical Considerations

This study, including the protocol, the informed consent documents, and all participant-facing materials, has been reviewed and approved by the University of North Carolina (UNC) Biomedical Institutional Review Board (IRB; 22-3058), who is responsible for the oversight of the study. Any subsequent modifications will be reviewed and approved by the UNC IRB before implementation. Annual IRB reporting and review is required for the duration of the study.

Eligible participants will have the choice to complete a self-guided electronic informed consent form following the informational video before enrollment or complete a staff-guided electronic informed consent form (via a HIPAA-compliant videoconferencing platform or phone call) before enrollment (Multimedia Appendix 4). All participants will be required to complete comprehension questions to ensure that they adequately understand the research, risks, and benefits and that they can opt out of study participation at any time before providing an electronic signature. All prospective participants who provide informed consent will be required to review and digitally sign a HIPAA release form (Multimedia Appendix 5).

All participants will be assigned a unique participant ID number. Participant-related study information will be identified only through the participant ID on all participant case report forms, audio files, transcripts, and computer-assisted self-interview files. Participant names and other personally identifying information will not be used on any study documents and will be redacted from interview transcripts.

Participants will receive digital cash incentives through the Tango payout platform for completing study visits (surveys, DBS kits, and interviews) as follows: US $60 for enrollment activities (baseline survey and enrollment), US $40 for the 3-month survey, US $50 for the 3-month whole blood self-collection kit, US $40 for the 6-month survey, US $50 for the 6-month whole blood self-collection kit, US $40 for the 12-month survey, and US $50 for the qualitative exit interview. Participants can choose their preferred gift card from a reward catalog.

We will secure study data with all appropriate physical, electronic, and operational protections following our data collection and handling SOP. All data files will have encryption and strong password protection, and files will be stored and managed using HIPAA-compliant, secure servers and cloud-based participant management software. Participant names and their participant IDs will be stored in separate tabs in REDCap accessible only to designated study staff and site monitors. Any files that are not specific to a single participant (eg, laboratory sample manifest) will be stored securely on a university-managed, HIPAA-compliant server. Original source documents for individual participants will be maintained at the UNC study site and will be accessible only to the study staff.

Data Quality and Monitoring

The clinical quality monitoring plan outlines the regular quality control (QC) and QA checks that are completed by the study team and external study monitor. Internal quality management activities ensure that research staff perform the study-required work correctly per the protocol requirements and in real time. Quality management activities also support good clinical practice compliance, human participant protection, and adherence to protocol requirements and site SOPs. Internal QC and QA monitoring and reporting consists of standardized methods and tools for QA and QC checks, as well as mechanisms for summarizing and disseminating the gathered information. Quality management checks will be implemented throughout the data collection process to quickly identify and rectify potential problems. Survey instruments will use skip patterns and built-in checks to minimize discrepant and unrealistic answers. Standard data-cleaning procedures will be used before analyses, including outlier detection and graphical representation of the data.

Data Dissemination

The results of this research will be disseminated via publication in peer-reviewed journals; conference presentations; and direct presentation to other interested stakeholders involved in HIV prevention and STI care provision, programming, and policy generation. The protocol is available for public review at ClinicalTrials.gov (NCT05984030).

Written publication guidelines for authorship eligibility will follow the criteria recommended by the International Committee of Medical Journal Editors (substantial contribution, participation in writing, approval of final version, and accountability) [85].

Lay summaries and infographics of study findings and implications will also be created for a general public audience and distributed via social media channels, as well as to participating clinics. When participants are asked for consent for the study to maintain their preferred contact information, they are informed that this information may be used to inform them of the study results. Thus, primary results and lay summaries will be individually shared back with participants unless they opt out of receiving this communication.

No participant names or other identifying information will be used in any dissemination materials, published or otherwise. The final deidentified dataset will be maintained by the study primary investigators and may be shared with other investigators for the completion of secondary data analysis following the establishment of acceptable data-sharing or data use agreements per the requirements of the US NIH (funder or sponsor) and UNC at Chapel Hill (grantee).

Results

Enrollment opened on August 31, 2023, at 15 health department–affiliated clinics in NC and subsequently expanded to 21 facilities in 20 counties by July 2024. Completion of the enrollment and data collection phase is expected by May 2025. As of January 2, 2024, a total of 17 persons have been enrolled. We have conducted 13 PrEP trainings, reaching a total of 106 providers and clinic staff members, as well as organizing 15 refresher trainings to promote continued understanding and study engagement among clinics. We have conducted 33 qualitative interviews among study participants, clinicians, and stakeholders. In addition to the customized HealthMpowerment study app, we have developed a PrEP navigation manual that also includes a compiled list of county-specific resources. The conclusion of phase I of this study is expected by May 2025, with results to be published thereafter.

Discussion

Novel Strategies to Address Barriers to PrEP Uptake

This study hypothesizes that leveraging STI clinics as an on-ramp to PrEP will serve as an effective opportunity to capitalize on STI service encounters and address disparities in PrEP access across rural and periurban environments in NC. As infrastructure for providing PrEP in rural NC STI clinics is currently extremely limited, no previous published studies have assessed PrEP uptake in these settings. In some settings, the diverse needs of potential PrEP recipients may exceed what can be reasonably provided by rural STI clinic staff in stand-alone, frequently understaffed clinics. Developing and testing a pathway to PrEP that complements clinic resources and workflow, including linking to remote PrEP navigation and offering high-quality STI testing services or monitoring for PrEP users, is an appealing strategy that could leverage rural STI clinics as a cost-effective on-ramp to sustained PrEP services. We believe that hybridizing components of multiple-effect PrEP uptake strategies, such as access to PrEP navigation and implementation of a virtual PrEP strategy supported by digital health interventions such as HealthMpowerment, may help support PrEP initiation in patient populations that would otherwise face barriers to obtaining and pursuing in-person PrEP service referrals [36,37].

In NC, men assigned male sex at birth who have sex with other men continue to represent a disproportionate majority of new HIV acquisitions. However, as we expanded within rural NC communities and engaged with the rural providers who staff the participating clinics, we recognized the disconnect between this focused recruitment strategy among persons seeking services at STI clinics and the importance of discussing HIV prevention, and PrEP specifically, with all patients. Our expansion to women will offer unique insights into the challenges and opportunities of engaging with this population within rural STI clinics.

Importantly, in this phase of the study, we are screening persons into a research study, not a PrEP referral process or pathway. As such, challenges with the implementation of the study, including recruitment, do not necessarily reflect barriers to linkage to remote navigation and digital health applications that would be implemented were this model to be scaled. Furthermore, although the randomized nature of our approach offers a more robust evaluation of potential efficacy, this design could influence willingness to enroll or engage with study materials. However, the process of referring all persons seeking STI services to PrEP navigation services using a scannable code or offering access to an informational app for those interested, as reflected in the study recruitment process, may indeed be a strategy used in future implementations if our intervention is shown to be effective in improving uptake of PrEP.

Potential Limitations and Future Directions

The external validity of the intervention may be challenging to establish when implemented outside the context of the research study. Participants are provided with a modest monetary incentive for initial engagement, which could influence their motivation to take part initially. In addition, the provision of ongoing incentives for study activities may impact their continued willingness to participate. This potential limitation will be further investigated through qualitative research aimed at exploring the motivation behind participants' decision to engage in the study. Importantly, this study was designed explicitly to address challenges related to PrEP access for persons accessing STI services in rural areas in which PrEP providers and general PrEP services are scarce, and thus, the generalizability, including the acceptability of this approach, may not be immediately relevant to other contexts with more concentrated service delivery options and more widely available, robust PrEP referral and linkage opportunities. The potential expansion or modification of this approach to other similarly resource-constrained settings within and outside the United States will be an important next step but is beyond the scope of this pilot. Incorporating PrEP services into STI clinics presents unique implementation challenges. Barriers at the provider (eg, knowledge and self-efficacy), clinic (eg, budget constraints and understaffing), and structural (eg, limitations in capability for long-term follow-up) levels complicate PrEP scale-up in rural STI clinic settings [86]. However, per CDC recommendations, screening for bacterial STIs should occur at least every 6 months for all sexually active patients and every 3 months among men who have sex with men or persons with ongoing risk behaviors [50,51]. By including budget impact analyses, this study informs program planning and sustainability of the proposed intervention strategy. As public health agencies and providers endeavor to increase PrEP uptake, understanding of the comparative value of alternative strategies, particularly among populations with high HIV incidence and low PrEP use, is urgently needed. Successful implementation and scale-up of the proposed intervention relies on understanding the main drivers of clinic-level costs and demonstrating that an integrated strategy for PrEP and STIs may be more cost-effective than providing these services separately, particularly if optimized models of centralized resources (eg, PrEP navigation and telehealth) and local services (eg, regular HIV and STI testing) can be identified. Ultimately, this study will assess the effectiveness, acceptability, feasibility, and cost-effectiveness of a model to colocate STI services and PrEP access in rural and periurban settings and provide critical information about ways to tailor this service delivery model. A pilot study to assess feasibility

was not conducted before the full-scale RCT, as the R61 mechanism of the NIH is designed to be informative. This study builds on existing preliminary research that supports the use of PrEP navigators, remote provision of PrEP delivery, and DBS monitoring and draws from extensive literature examining the challenges of HIV care among this population. Further directions of this work will include engaging with state and local stakeholders to refine the PrEP intervention and expanding the refined implementation strategy to all persons who enroll at a participating clinic.

Acknowledgments

This trial is supported by funding through the National Institutes of Health (NIH) National Institute of Allergy and Infectious Diseases Division of AIDS (R61AI174285) and the Center for AIDS Research (P30AI50410). The content of this publication is solely the responsibility of the authors and does not necessarily represent the official views of the NIH. SER received additional support from Doris Duke Charitable Foundation grant 2020143. Staff at the NIH National Institute of Allergy and Infectious Diseases (sponsor) reviewed and provided feedback on the study protocol, including the study design, and reviewed this manuscript. The sponsor will continue to provide study oversight without any role in study data collection, management, or analysis.

Data Availability

The datasets generated and analyzed during this study are available from the corresponding author on reasonable request.

Authors' Contributions

SER was the principal investigator and contributed to study concept and design, protocol development and writing, manuscript drafting and revision, lead and oversight over all study activities, and lead for telehealth pre-exposure prophylaxis (PrEP) service development and implementation.

EF was the study coordinator and contributed to protocol development and writing, and manuscript revision; served as the lead for the development and coordination of all partnering clinic activities; and the lead for the development and implementation of participant recruitment, enrollment, and retention activities.

OM was the research assistant and contributed to manuscript drafting and revision.

NB was the data manager and contributed to the design, programming, and implementation of data collection tools; ongoing data analytic monitoring reports and data quality control procedures; participant recruitment, enrollment, and follow-up; and manuscript drafting and revision.

JS was the data system designer and served as the lead for the conceptualization and design of fully integrated data systems for participant screening, enrollment, and follow-up; contributed to the design, programming, and implementation of data collection tools; design of integrated data–monitoring reporting tool; and manuscript revision.

AW was the PrEP navigator and served as lead for the development and implementation of PrEP navigation protocols and intervention components, the development and maintenance of tracking procedures for clinic-based PrEP services and referral procedures, and manuscript revision.

VM was the HIV and Sexually Transmitted Disease state medical director and contributed to the study concept and design, ongoing expert consultations to align study-specific procedures with state-level HIV and sexually transmitted infection services and PrEP expansion initiatives, and manuscript revision.

SD was the chief medical officer of North Carolina Medicaid and contributed study concept and design, ongoing expert consultations to align study-specific procedures with state-level HIV and sexually transmitted infection services and PrEP expansion initiatives, and manuscript revision.

JE was a coinvestigator and contributed to the study concept and design; served as lead study statistician and epidemiologist for informing randomization scheme, statistical methodologies, sample size estimation, and scientific rigor; and contributed to protocol development and manuscript revision.

LBH-W was a coinvestigator study concept and design, protocol development, original creation of the HealthMpowerment digital health intervention, and manuscript revision.

CBH was a coinvestigator and contributed to the study concept, design and protocol development; served as lead for the development, implementation, and evaluation of clinic-based PrEP service training and technical support; and contributed to survey design and manuscript revision.

BP was a coinvestigator and contributed to the study concept and design; served as lead for implementation science design and evaluation components; and contributed to manuscript revision.

KEM was the principal investigator and contributed to the study concept and design; served as lead and oversight over all study activities, protocol development and writing; contributed to manuscript drafting and revision; and served as lead for qualitative research methodology components.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Patient in-depth interview guide.
[PDF File (Adobe PDF File), 258 KB - resprot_v14i1e68085_app1.pdf]

Multimedia Appendix 2
Clinic stakeholder consent form.
[PDF File (Adobe PDF File), 266 KB - resprot_v14i1e68085_app2.pdf]

Multimedia Appendix 3
Primary and secondary study outcomes.
[DOCX File , 27 KB - resprot_v14i1e68085_app3.docx]

Multimedia Appendix 4
Informed consent form.
[PDF File (Adobe PDF File), 266 KB - resprot_v14i1e68085_app4.pdf]

Multimedia Appendix 5
Health Insurance Portability and Accountability Act authorization form.
[PDF File (Adobe PDF File), 432 KB - resprot_v14i1e68085_app5.pdf]

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Abbreviations

AE: adverse event
CDC: Centers for Disease Control and Prevention
DBS: dried blood spot
HIPAA: Health Insurance Portability and Accountability Act
IRB: Institutional Review Board
NC: North Carolina
NIH: National Institutes of Health
PrEP: pre-exposure prophylaxis
QA: quality assurance
QC: quality control
RCT: randomized controlled trial
REDCap: Research Electronic Data Capture
SMC: study monitoring committee
SOP: standard operating procedure
STI: sexually transmitted infection

UNC: University of North Carolina

Edited by A Schwartz; submitted 01.11.24; this is a non–peer-reviewed article;accepted 13.01.25; published 21.03.25.

Please cite as:
Rutstein SE, Ferguson E, Mansour O, Brown N, Stocks JB, Washington A, Mobley V, Dowler S, Edwards J, Hightow-Weidman LB, Hurt CB, Pence B, Muessig KE
Multilevel Intervention to Support Tailored and Responsive HIV Pre-Exposure Prophylaxis Care in Rural North Carolina: Protocol for a Randomized Controlled Trial
JMIR Res Protoc 2025;14:e68085
URL: https://www.researchprotocols.org/2025/1/e68085
doi:10.2196/68085
PMID:

Protocol

Improving Early Dementia Detection Among Diverse Older Adults With Cognitive Concerns With the 5-Cog Paradigm: Protocol for a Hybrid Effectiveness-Implementation Clinical Trial

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Abstract

Background: The 5-Cog paradigm is a 5-minute brief cognitive assessment coupled with a clinical decision support tool designed to improve clinicians' early detection of cognitive impairment, including dementia, in their diverse older primary care patients. The 5-Cog battery uses picture- and symbol-based assessments and a questionnaire. It is low cost, simple, minimizes literacy bias, and is culturally fair. The decision support component of the paradigm helps nudge appropriate care provider response to an abnormal 5-Cog battery.

Objective: The objective of our study is to evaluate the effectiveness, implementation, and cost of the 5-Cog paradigm.

Methods: We will enroll 6600 older patients with cognitive concerns from 22 primary care clinics in the Bronx, New York, and in multiple locations in Indiana for this hybrid type 1 effectiveness-implementation trial. We will analyze the effectiveness of the 5-Cog paradigm to increase the rate of new diagnoses of mild cognitive impairment syndrome or dementia using a pragmatic, cluster randomized clinical trial design. The secondary outcome is the ordering of new tests, treatments, and referrals for cognitive indications within 90 days after the study visit. The 5-Cog's decision support component will be deployed as an electronic medical record feature. We will analyze the 5-Cog's implementation process, context, and outcomes through the Consolidated Framework

for Implementation Research using a mixed methods design (surveys and interviews). The study will also examine cost-effectiveness from societal and payer (Medicare) perspectives by estimating the cost per additional dementia diagnosis.

Results: The study is funded by the National Institute of Neurological Disorders and Stroke of the National Institutes of Health (2U01NS105565). The protocol was approved by the Albert Einstein College of Medicine Institutional Review Board in September 2022. A validation study was completed to select cut scores for the 5-Cog battery. Among the 76 patients enrolled, the resulting clinical diagnoses were as follows: dementia in 32 (42%); mild cognitive impairment in 28 (37%); subjective cognitive concerns without objective cognitive impairment in 12 (16%); no cognitive diagnosis assigned in 2 (3%). The mean scores were Picture-Based Memory Impairment Screen 5.8 (SD 2.7), Symbol Match 27.2 (SD 18.2), and Subjective Motoric Cognitive Risk 2.4 (SD 1.7). The cut scores for an abnormal or positive result on the 5-Cog components were as follows: Picture-Based Memory Impairment Screen ≤6 (range 0-8), Symbol Match ≤25 (range 0-65), and Subjective Motoric Cognitive Risk >5 (range 0-7). As of December 2024, a total of 12 clinics had completed the onboarding processes, and 2369 patients had been enrolled.

Conclusions: The findings of this study will facilitate the rapid adaptation and dissemination of this effective and practical clinical tool across diverse primary care clinical settings.

Trial Registration: ClinicalTrials.gov NCT05515224; https://www.clinicaltrials.gov/study/NCT05515224

International Registered Report Identifier (IRRID): DERR1-10.2196/60471

(JMIR Res Protoc 2025;14:e60471) doi:10.2196/60471

KEYWORDS

cognitive assessment; cognitive screening; cognitive impairment; mild cognitive impairment; dementia; dissemination and implementation science; clinical trial protocol; randomized controlled trial; hybrid implementation-effectiveness trial

Introduction

Background and Rationale

Problem and Progress

Alzheimer disease and related dementias (ADRD) affect approximately 57 million people globally, a figure projected to rise to 152 million by 2050 [1,2]. Studies have long noted deficiencies and delays in individuals receiving a dementia diagnosis [3-12]. The World Health Organization's Global Action Plan on Dementia includes a focus on the right to a timely dementia diagnosis to enable better planning, treatment, care, support, and quality of life [13]; for example, timely diagnosis can help individuals avoid preventable accidents and injuries leading to care escalation and can reduce distress for patients and caregivers [9,14-16]. In addition, several studies have estimated a potential cost saving of approximately US $10,000 per timely diagnosis because of delayed institutionalization, with the expectation that improved health and quality of life related to early diagnosis could result in even more cost savings [17].

Studies have repeatedly noted that delay and deficiency in diagnosis disproportionately impacts individuals from historically minoritized racial and ethnic groups as well as those from socioeconomically disadvantaged backgrounds [3-12]; for example, a recent nationally representative study found that a higher proportion of non-Hispanic Black and Hispanic individuals had a missed or delayed clinical dementia diagnosis compared to non-Hispanic White individuals (46% and 54% vs 41%; P<.001). This is thought to be an underestimate of the impact because the study relied on claims-based data, and non-Hispanic Black and Hispanic individuals may be less likely to access care that generates claims [18].

Experts recommend robust, multifaceted strategies to close these diagnosis gaps [15,17,19-24]; interventions must address implementation ("the actively planned process of putting evidence to use or integrating new interventions within a specific setting." [25]) and dissemination ("the targeted distribution of information and intervention materials to a specific public health or clinical practice audience" [26]) challenges as much as they aim to achieve high clinical accuracy and quality [20,21,27-31]. The Consortium for Detecting Cognitive Impairment, Including Dementia, a collaborative research effort directed and funded by the National Institute of Neurological Disorders and Stroke and the National Institute on Aging of the National Institutes of Health (NIH), has produced promising paradigms to meet this need. As part of this effort, our team at the Albert Einstein College of Medicine and Montefiore Medical Center (hereinafter Montefiore Einstein clinics) in the Bronx, New York, United States, developed the 5-Cog paradigm [32,33]. In a randomized controlled trial (RCT) of 1200 older adults with cognitive concerns at an urban primary care clinic in a primarily Black and Hispanic community, we showed that the 5-Cog paradigm improves dementia care, most notably by increasing the rate of diagnosis of mild cognitive impairment (MCI) and dementia [33]. This detection and diagnosis increases opportunity for primary care providers (PCPs), patients, and patients' families to intervene to potentially slow or prevent progression to dementia or, for individuals who do progress, to prepare in advance to meet the complex caregiving and clinical challenges to come [34].

Hence, our research questions for this cluster randomized trial were as follows:

- Can a brief cognitive assessment paired with a clinical decision tree (5-Cog paradigm) increase the rate of new diagnoses of MCI syndrome or dementia in primary care patients presenting with cognitive concerns in real-world settings, across broad patient groups (hence its categorization as a pragmatic trial [35])?

- What are the determinants of the 5-Cog's impact in these settings?

Updates to the 5-Cog Paradigm for This Trial

The 5-Cog paradigm (brief cognitive assessment battery and decision support tool) worked well in our initial trial. However, building on implementation reflections from that trial [27] as well as feedback from local primary care stakeholders, we have made 2 refinements to the 5-Cog paradigm to improve clinical utility and aid future dissemination. We substituted the gait speed measurement component of the 5-Cog with a questionnaire that assesses mobility and cognition. In addition, we modified the 5-Cog decision support component to capitalize on electronic medical record (EMR) capabilities and better align the 5-Cog paradigm with existing care provider workflows. All these modifications are described in detail in the following subsection (The 5-Cog Paradigm) and in the Interventions section.

The 5-Cog Paradigm

The 5-Cog paradigm is composed of a 5-minute brief cognitive assessment (the 5-Cog battery) combined with an EMR-embedded clinical decision support tool. The 5-Cog battery was granted US copyright registration effective December 14, 2023.

Clinical decision support provides timely information, usually at the point of care, to inform and improve decisions about a patient's care [36].

The first of the 3 items in the 5-Cog battery is the Picture-Based Memory Impairment Screen (PMIS), created by Verghese et al [37], which uses 4 pictures to test free and cued recall after a delay of at least 2 minutes. Administration and scoring have been previously described [38]. This screener was selected because of ease of use (simple to administer after minimal training and does not require specialized technology), freedom from literacy bias (uses photographs of items instead of words), and cultural fairness (photographs were chosen and validated for consistent recognition by patients in the relevant cultural milieu). In our validation study, PMIS was shown to have high validity for distinguishing older adults with cognitive impairment from those without, regardless of age, sex, education, or presence of depression (sensitivity and specificity >90%) as well as excellent reliability (intraclass correlation 0.91) [37,38].

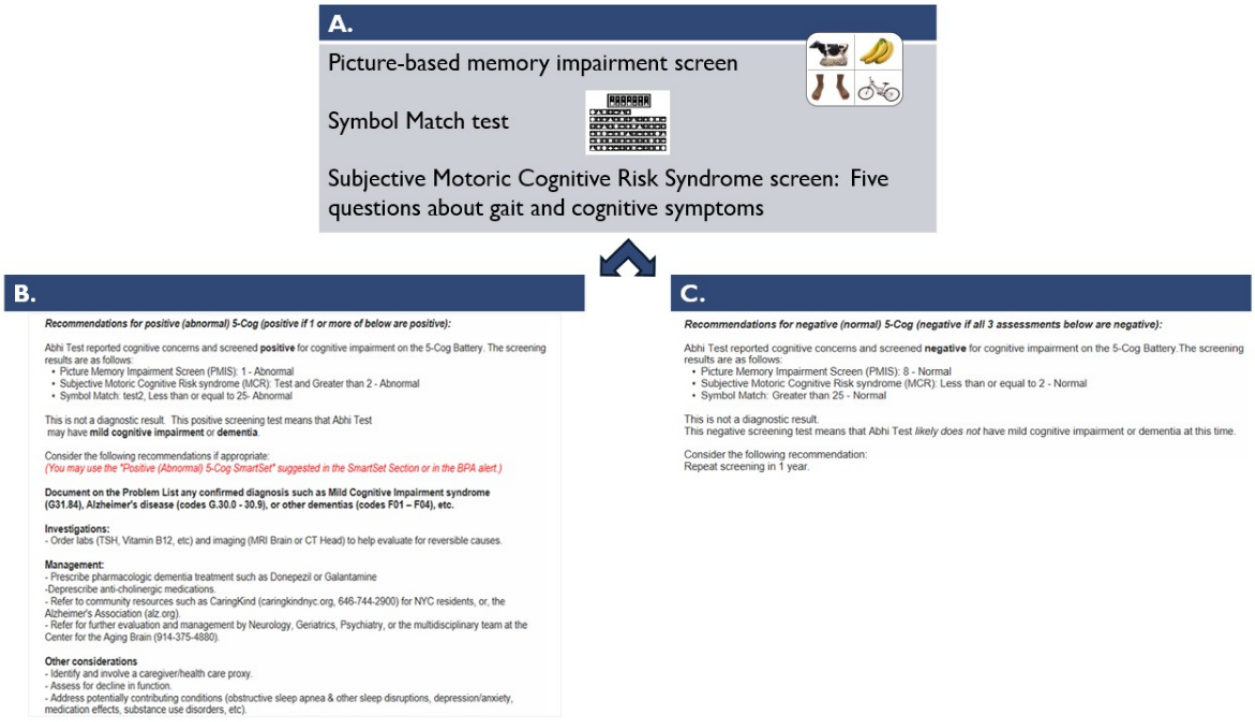
The second item in the 5-Cog battery is the Symbol Match [39], developed by one of our coinvestigators (EFW). It is an oral timed transcription task created to identify difficulties with divided attention, visual scanning, tracking, and motor speed. It requires individuals to quickly substitute (verbalize) numbers for an array of symbols using a key provided at the top of the page. After a practice run with 7 symbols, individuals are given 90 seconds to correctly name as many items as they can as quickly as they can without making a mistake. The number of correct oral substitutions at the end of 90 seconds is the participant's score. Individuals who complete the task before the time limit receive a ceiling score of 65. Internal validation within our study population suggested 25 as the optimal cutoff score to identify cognitive impairment (refer to the Results section for details). The Symbol Match was chosen because of ease of use (requires no specialized equipment and minimal training to administer) [39]. The 90-second Symbol Match correlates highly with the established Symbol Digit Modalities Task [40,41], which can detect nonmemory impairments and functional changes [42]. This feature allows Symbol Match to detect patients with nonmemory impairments that may not be identified by the PMIS [39].

Finally, the 5-Cog incorporates an assessment of gait. The motoric cognitive risk (MCR) syndrome, first described by Verghese et al [43], and defined as slow gait in the presence of cognitive concerns, has been extensively validated to predict an elevated risk of dementia independent of other cognitive assessments [43-47]. Traditionally, the MCR syndrome assessment involves the measurement of gait speed. Given that gait speed is not routinely tested in current primary care environments and that it may present a barrier for 5-Cog implementation, we modified this assessment. For this study, we will be assessing the Subjective MCR (sMCR) screening tool, developed by Ayers et al [48], which uses the patient's subjective reports of mobility and cognitive concerns via a 5-item questionnaire, rather than having a tester measure gait speed. Responses to these 5 questions are used to derive a weighted score that is used to define sMCR. Administration and scoring have been previously described [48]. We found the sMCR approach to have excellent discriminative validity versus objective MCR (defined using gait speed) and excellent predictive validity for incident dementia; in our validation study, participants who met the sMCR criteria had a >2-fold increased risk of developing dementia [48].

The 5-Cog paradigm's EMR-based decision support tool includes 2 components: documentation of the patient's 5-Cog battery result and recommended next steps that may be appropriate for further diagnosis or management of the patient's cognitive concerns (clinical decision support). This "nudge" supports and supplements the provider's own clinical decision–making process [49,50]. In this study, the decision support tool incorporates 3 additional features that make it resemble other EMR-based decision support systems: first, the 5-Cog result will be listed among other clinical practice advisories that contain information tailored to each patient regarding time-sensitive care needs. Second, providers will receive 5-Cog results through an interruptive alert when they access the patient's chart (as they do in cases of other clinical issues that can impact patient safety). Finally, the decision support tool will include a direct link to orders for the next steps in care. This reduces clinician cognitive load by providing a menu of options (such as appropriate laboratory, imaging, and referral orders) and minimizes clicks by consolidating these options in one place.

Our 5-Cog 1.0 protocol [32] can be referenced for additional detail on the development and design of the 5-Cog paradigm. Figure 1 depicts the 2 components of the 5-Cog paradigm.

Figure 1. (A) The 5-Cog battery (5-min cognitive assessment). (B) Decision support for a patient with a positive 5-Cog result. (C) Decision support for a patient with a negative 5-Cog result. EMR: electronic medical record.



Implementation Study

The United States Institute of Medicine (now the National Academy of Medicine) estimated a 17-year gap from when a clinical innovation is proven effective to when it is routinely implemented in clinical care [51]. Given that cognitive impairment detection paradigms are not adopted widely in primary care, it is important to systematically identify and address potential factors that influence implementation outcomes, that is, implementation determinants [52]. Our implementation measurements for the 5-Cog will be guided by the Consolidated Framework for Implementation Research (CFIR). The CFIR is an established implementation science theoretical framework for identifying implementation determinants [53,54]. We chose the CFIR because it facilitates the identification of implementation determinants that influence implementation outcomes either positively as facilitators or negatively as barriers [55-58]. Each CFIR construct is well defined, has established measures, and can be depicted in rich qualitative detail. The CFIR is practical because it is often used to both explore and subsequently optimize future implementation contexts and processes [59]. As with many implementation science frameworks, the CFIR does not mandate a specific data collection methodology [53]; studies applying the CFIR have used quantitative only, qualitative only, or mixed methods approaches [59]. We have chosen a mixed methods strategy to examine implementation contexts, processes, and outcomes. The study approach is based on the broader epistemology of critical realism [60] and more specifically the realist evaluation framework [61] wherein quantitatively measured implementation outcomes are explained by analyzing the relationships between implementation context and process factors. We will use the CFIR to identify implementation determinants through qualitative processes (interviews). We will use quantitative measures—the Acceptability of Intervention Measure (AIM), the Feasibility of Intervention Measure (FIM), and the Intervention Appropriateness Measure (IAM) [62]—to measure implementation outcomes. We will then analyze all findings using the CFIR as a lens to examine the relationships between these outcomes and implementation context and process factors [54,59].

Cost-Effectiveness Assessment

Currently, Medicare reimburses cognitive impairment assessments for older adults as part of their annual wellness visit (AWV) [22]. However, there is no standardized required form and output for this assessment. For health systems that would like to implement the 5-Cog for the AWV, questions may arise regarding its impact on costs. The 5-Cog battery is a low-cost intervention, requiring simple paper-and-pencil tools that are easily adapted to digital formats and minimal training to administer. For the 5-Cog decision support component, we anticipate programming and workflows to be translatable between EMR systems with a 1-time, upfront customization and without recurring software or staffing costs. Thus, the 5-Cog's direct expenses predominantly include staffing costs (eg, salaries, benefits, and travel expenses for workers administering the 5-Cog). Given the short duration and minimal supplies cost of the 5-Cog, indirect expenses (eg, scheduling, record keeping, facility overhead, and equipment depreciation) and opportunity costs (eg, forgoing other billable care) are anticipated to be minimal. Investigators have previously reported costs associated with both community health workers (CHWs) and practice facilitators throughout Indiana and the Midwest in the United States [63]. There may also be costs associated with dementia care actions resulting from the use of the 5-Cog. However, these follow-up costs may be offset by cost savings resulting from earlier dementia care intervention [64].

The goal of our budget impact analysis (BIA) [65-67] and cost-effectiveness analysis (CEA) [68] is to understand the cost per cognitive case identified from a societal and payer (eg, Medicare) perspective to facilitate informed dissemination (per the CFIR model). The study design for estimating the financial effects involves addressing several issues, many predetermined by BIA and CEA best practices and the Consolidated Health Economic Evaluation Reporting Standards [65-68]. The BIA will determine financial planning and affordability, and the CEA will determine the effectiveness and value of the 5-Cog compared to enhanced usual care. The BIA can be used to determine financial adoption and scalability for national implementation.

Trial Design

Given the problems of underdiagnosis and undertreatment of dementia, which are expected to worsen with the growing number of aging adults globally [69], we chose a hybrid type 1 effectiveness-implementation design for this trial. In this design, the primary emphasis is on testing the intervention, with a secondary emphasis on exploring implementation-related factors [55]. We chose this design because it would be premature to conduct an implementation-only trial, given that the 5-Cog has previously been studied in 1200 individuals in only 1 urban primary care setting. The hybrid type 1 effectiveness-implementation design allows us to confirm the effectiveness of our intervention, while also hastening its potential to make needed impact in the "real world" through incorporating implementation examination prospectively [55]. The clinical effectiveness (in this case, meaning the degree of beneficial effect [70]) component of the trial will be completed using a pragmatic, cluster randomized design (randomized at the level of the clinic) with intervention clinics receiving the 5-Cog paradigm and control clinics receiving enhanced usual care (cognitive concern information and cognitive impairment detection education provided but no detection approach or clinical decision support tool implemented).

Objectives

This trial's three aims are to (1) test whether the 5-Cog paradigm used in primary care patients with cognitive concerns in diverse urban and rural environments and including individuals from racial and ethnic minority groups and those with socioeconomically disadvantaged backgrounds leads to an increased rate of MCI and dementia diagnoses; (2) explore the implementation context, process, and outcomes of the 5-Cog paradigm in diverse primary care clinics using mixed methods guided by the CFIR; and (3) assess the cost-effectiveness of the 5-Cog paradigm.

We hypothesize that this trial will demonstrate the 5-Cog paradigm's effectiveness in increasing the diagnosis of MCI in dementia and primary care, its cost-effectiveness in achieving this outcome, and the range of factors shaping its successful implementation across diverse primary care settings.

Methods

Participants, Interventions, and Outcomes

Study Setting

The study is being carried out at primary care clinics affiliated with 2 large academic health systems: Montefiore Medical Center and Albert Einstein College of Medicine (hereafter referred to as Montefiore-Einstein) in the Bronx, New York, and Indiana University Health (IUH) in Indiana.

The Montefiore-Einstein clinics serve an urban population primarily composed of individuals from historically minoritized racial and ethnic groups (Hispanic/Latino and Black populations). Of note, these clinics serve Bronx County, which ranks last (62 out of 62) among New York State counties on health-related indicators [71] and has a significant poverty rate, affecting 1 in 4 older adults [72]. The IUH clinics are situated across both urban and rural settings. Within this network, 12 (75%) of the 16 selected clinics are located in regions scoring >60 on the national area deprivation index (score range 0-100; higher scores indicate higher deprivation) [73,74]. Notably, 2 (17%) of these 12 clinics are in areas with an area deprivation index score of >91, underscoring the profound level of need of these communities. Indiana health-related indicators show higher premature death, lower life expectancy, lower PCP and mental health provider availability, and lower median household income than the US average [74].

The study procedures are completed by research assistants (RAs), who are trained as CHWs and embedded in the clinics. This approach was chosen for its pragmatic value, reflecting reality in primary care settings in which CHWs are incorporated into clinical teams and may complete other screening questionnaires with patients [75,76] and because the 5-Cog components have been shown to be practical and feasible for administration by individuals who are not medical professionals and with minimal training [37,44,77]. The RAs at Montefiore-Einstein are bilingual in English and Spanish because of the high proportion of Spanish-speaking participants at this site. All study materials were translated from English into Spanish and back translated to ensure language fidelity.

Eligibility and Screening

Clinics are eligible to participate if they provide primary care (internal medicine or family medicine), not specialty care. Clinics primarily serving as residency teaching sites are excluded.

In keeping with the pragmatic nature of the trial, our individual-level eligibility criteria are designed to ensure that enrolled patients are those who would receive this intervention if it were part of usual care [78-80]. The 5-Cog intervention was designed to improve dementia diagnosis in ambulatory primary care settings. Individuals are excluded if they have a prior diagnosis of dementia or reside in a nursing home. Nursing home residents are excluded because they already have a high prevalence of diagnosed dementia (60%-90%) [81] and largely do not receive primary care from ambulatory clinics because of their mobility and cognitive limitations [82]. To be eligible

for our 5-Cog effectiveness study, individuals must be aged ≥65 years, have no prior diagnosis of dementia, speak English (Montefiore-Einstein or IUH) or Spanish (Montefiore-Einstein only), have a scheduled primary care office visit, and endorse a cognitive concern via a subjective cognitive concern questionnaire (SCQ) [32,83]. Initial screening is completed by RAs via prospective EMR review of patients scheduled at each clinic and confirmed through screening telephone calls.

Implementation study participants will be recruited from among patients, caregivers, clinicians, clinic staff, clinical leaders, clinical informatics staff, and administrative leaders. The exclusion criteria are the same as those for the effectiveness study.

Textbox 1 lists the complete individual-level inclusion and exclusion criteria, including the SCQ.

Textbox 1. Inclusion and exclusion criteria.

Effectiveness study

- Individual-level inclusion criteria
  - Aged ≥65 years
  - English or Spanish speaking (Albert Einstein College of Medicine and Montefiore Medical Center will enroll English- and Spanish-speaking patients; Indiana University Health will enroll only English-speaking patients)
  - Have a cognitive concern: subjective cognitive concern questionnaire result is positive (≥1 of the following: "Are you concerned about your memory?"—the chosen response is yes; "Are your loved ones concerned about your memory?"—the chosen response is yes; and "Is your mind as clear as it used to be?"—the chosen response is no)
- Individual-level exclusion criteria
  - Prior diagnosis of dementia (as recorded in the electronic medical record or reported by primary care provider; the prior diagnosis of mild cognitive impairment is not an exclusion criterion, but the effectiveness outcome is only counted if a participant previously diagnosed with mild cognitive impairment is assigned a new diagnosis of dementia)
  - Nursing facility resident

Implementation study

- Individual-level inclusion criteria
  - Patients who have undergone the 5-Cog battery, caregivers of these patients, clinicians, clinic staff, clinical leaders, clinical informatics staff, and administrative leaders at each of the randomized primary care practices
  - Ability to provide informed consent
- Individual-level exclusion criteria
  - Prior diagnosis of dementia (as recorded in the electronic medical record or reported by primary care provider; the prior diagnosis of mild cognitive impairment is not an exclusion)
  - Nursing facility resident

Recruitment of Clinics and Patients

The study team actively recruited clinics in the Bronx and Indiana to participate through contacting their administrative leadership to discuss the study. Generally, 1 to 3 meetings were held with clinic leadership and practicing clinicians to introduce the study and secure the clinic's commitment to participate.

All individual patient recruitment for the effectiveness study is passive. RAs review a clinic's scheduled patients via the EMR to determine which patients seem to meet the eligibility criteria and contact potentially eligible patients by telephone within 1 week before their scheduled office visit. The patient is informed that the caller is working with the patient's primary care practice to assess cognitive concerns. The patient is asked to confirm that they plan to keep their upcoming clinic appointment. If they have decided to change the appointment, cognitive concerns are not assessed. If the patient confirms their scheduled appointment, the RA administers the SCQ (Textbox 1). The patient is free to decline to answer, at which point the call is ended. When the patient answers the questions, the results are documented in the EMR. In the clinics randomized to the control arm, patients who have answered the SCQ are considered recruited; and if their SCQ result is positive, they are considered enrolled once they show up to their scheduled clinic appointment. In the clinics randomized to the intervention arm, patients with a positive cognitive concern are invited to undergo additional cognitive screening (the 5-Cog battery) at the clinic on the day of their office visit, just before they see their care provider. Patients who agree are considered recruited, with enrollment confirmed once they complete their scheduled office visit. In both arms, patients who do not show up to their scheduled clinic appointment after a positive SCQ result are not considered enrolled. If these patients have another scheduled clinic appointment during the study period at their clinic, they are eligible to be rerecruited and enrolled at this time (RAs will call and confirm SCQ responses before this visit).

Implementation study participants will be actively recruited from intervention sites through snowball sampling among different types of key informants mentioned previously. In addition, we will collect quantitative implementation surveys from as many clinicians and staff as possible at the intervention clinics.

Participant Timeline

The 22 participating clinics were randomized in year 1 of the study. These clinics are onboarded in waves throughout the 5-year study period. The time period over which each clinic will experience active study recruitment (with the goal of enrolling 300 patients per clinic) is anticipated to vary from 3 to 12 months, depending on clinic size.

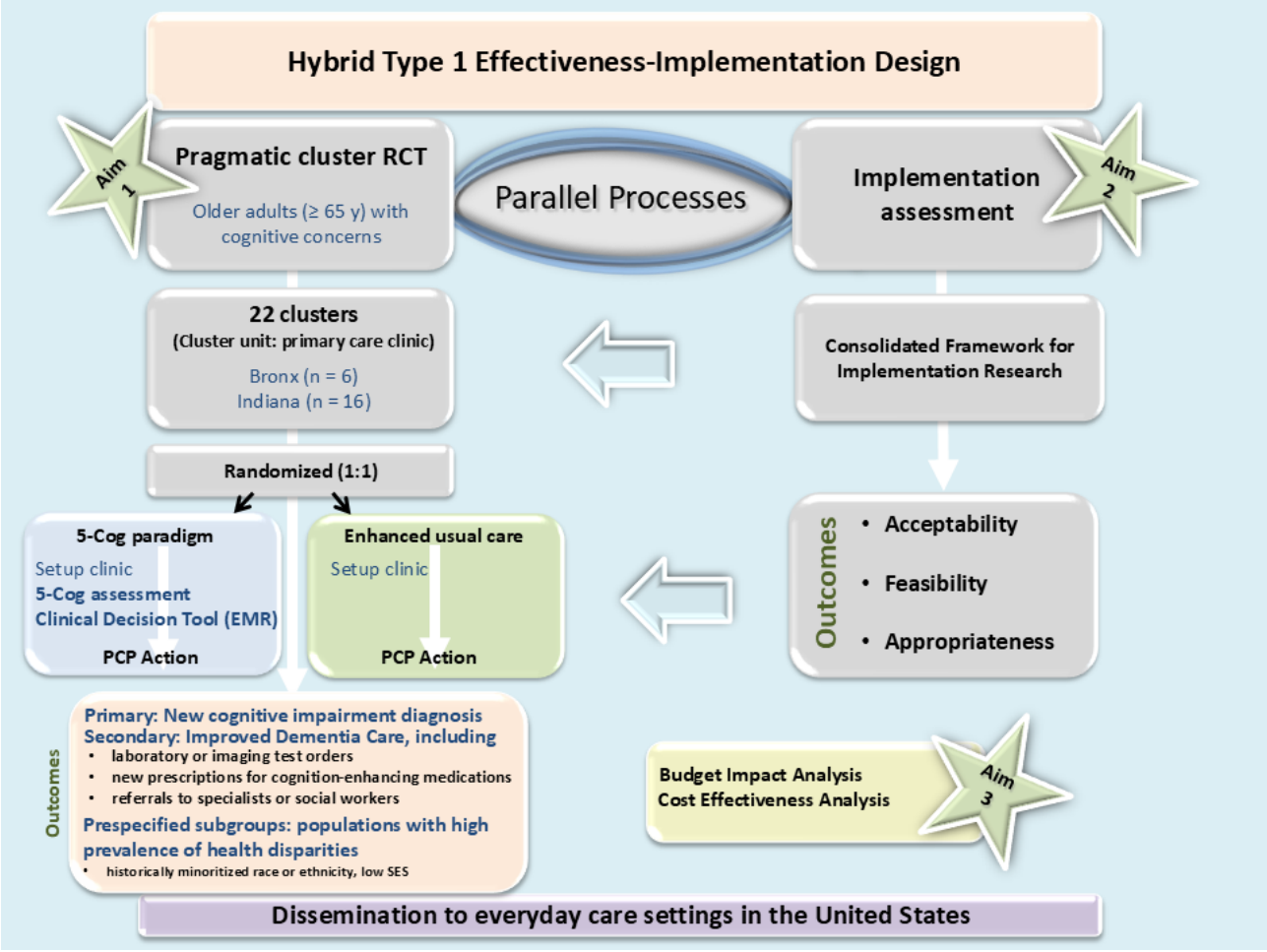
For individual patients in the effectiveness study, the initial screening and recruitment telephone call takes place within 1 week before a patient's scheduled primary care visit and takes 10 to 15 minutes. Patients are then considered enrolled when they complete their scheduled PCP clinic appointment.

At the intervention clinics, participating patients are asked to arrive up to 1 hour early for their scheduled visit to allow sufficient time for undergoing the 5-Cog battery before meeting their care provider. The 5-minute assessment is completed at the clinic before the appointment.

In both intervention and control groups, patients remain enrolled for 90 days. Study outcomes are ascertained at 90 days (primary and secondary end points), at which point the enrolled patients are considered to have completed participation. This time window was selected because >95% of physician actions for dementia care were completed within this period in our initial trial [33].

Implementation study participants are enrolled when they consent to participate in a survey or an interview, and their enrollment is completed at its conclusion. Figure 2 depicts the study flow.

Figure 2. Study flow. EMR: electronic medical record; PCP: primary care provider; RCT: randomized controlled trial; SES: socioeconomic status.



Planned Sample Size

The planned effectiveness study sample size is 6600 enrolled patients, including approximately 300 (4.56%) from each of the 22 participating clinics (Bronx: n=6, 27%; Indiana: n=16, 73%).

For the implementation interviews, we will use snowball sampling to identify the most relevant informants across clinics of different sizes. We anticipate conducting up to 6 implementation interviews per practice for a maximum total sample size of 132 participants or until thematic saturation is reached over the 5-year study period. We will disseminate the quantitative implementation surveys to the clinicians and staff at the intervention clinics.

Interventions in the Intervention Arm (5-Cog Battery With Decision Support Tool)

On the day of the patient's scheduled clinic visit, an RA meets the patient upon their entry into the clinic waiting area in preparation to complete the 5-Cog with them before their PCP visit. The RA escorts the patient through clinic registration. At the same time, the RA communicates with the clinical team to let them know that the patient will undergo the 5-Cog battery before being ready to see their care provider.

The RA administers the 5-Cog (refer to the Introduction section and Figure 1 for more details on the 5-Cog) in a private space within the clinic and then brings the patient back to the waiting area. Next, the RA informs the clinical team that the patient has completed the 5-Cog battery and is ready to be integrated back into the usual clinical workflow. The RA then completes documentation of the battery results in the EMR (and in the study database). The 5-Cog decision support recommendations are harmonized across sites for a positive 5-Cog result, as they are for a negative 5-Cog result (Figure 1).

Montefiore-Einstein and IUH use 2 different EMR systems: Epic (version 100.2412.0.0) and Cerner (version 2024.3), respectively. Unique features within each EMR are used to capture and house the 5-Cog results, create alerts, and present the results and decision support recommendations to the care providers.

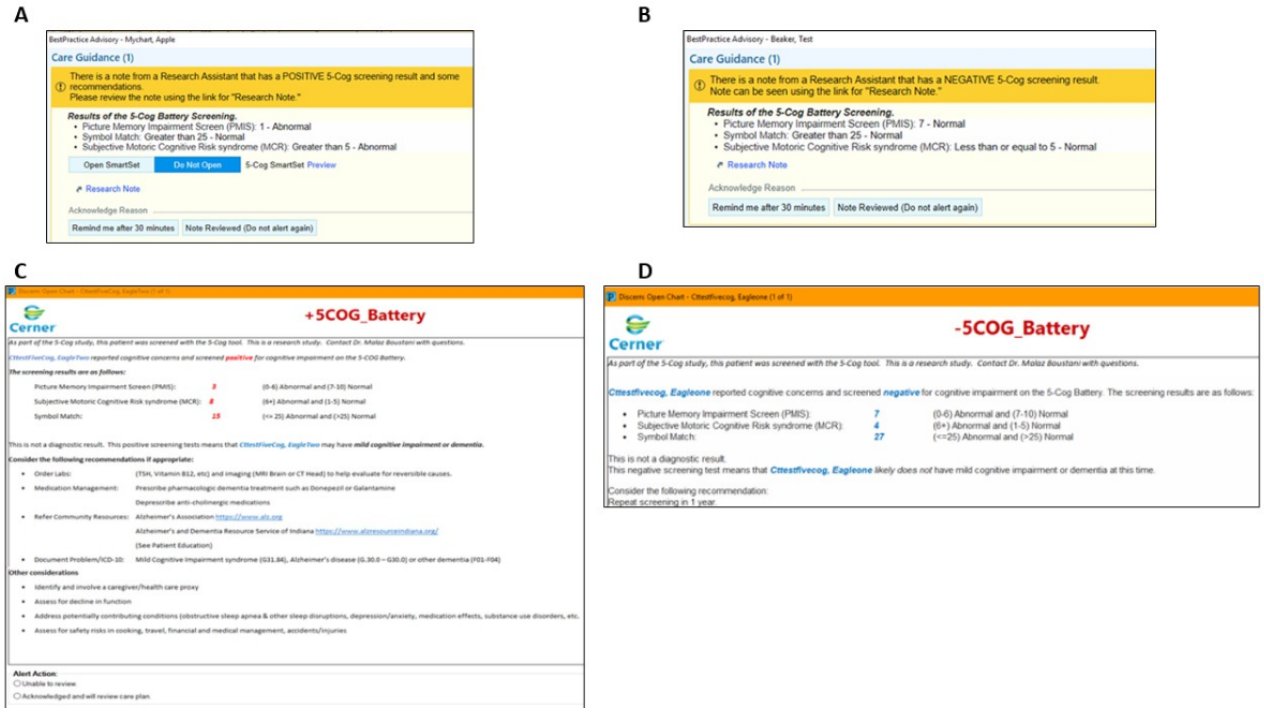
At Montefiore-Einstein, the RA creates a "research note." Here, they input the 5-Cog battery component scores by selecting from a drop-down list for each assessment. They also manually select the appropriate decision support arm (for positive vs negative 5-Cog result) using a quick-text feature. The EMR then responds to the results of the 5-Cog assessments, using structured data elements. Thus, the values that the RA enters for the three 5-Cog battery components trigger a preprogrammed tailored care provider alert, a "best practice advisory" (BPA). If the result of any of the 3 assessments indicates potential cognitive impairment, a "positive 5-Cog" BPA is triggered. If the results do not indicate potential cognitive impairment a "negative 5-Cog" BPA gets triggered. The BPA is "interruptive"; as soon as the care provider accesses the patient's medical record for the current visit in the EMR, they are shown the alert on their screen. The BPA contains the 5-Cog result with a hyperlink to the research note.

At IUH, the RA inputs the 5-Cog battery result into an EMR-based flowsheet through ad hoc documentation. Specifically, these results are entered into the "Results Review - Clinical Assessment" tab. The EMR is programmed to automatically trigger the appropriate decision support content based on the 5-Cog battery result. As at Montefiore-Einstein, a customized, interruptive alert is displayed to the provider. At IUH, the alert itself contains the 5-Cog result, along with all decision support recommendations.

In both IUH and Montefiore-Einstein EMR flows, care providers must respond to the interruptive alert, acknowledging it in some way. The options for this vary by EMR. At both sites, the alert for patients with a positive 5-Cog result also facilitates linking to an order set. This allows the care provider to efficiently and comprehensively select clinical actions that may be relevant to the patient's further cognitive care.

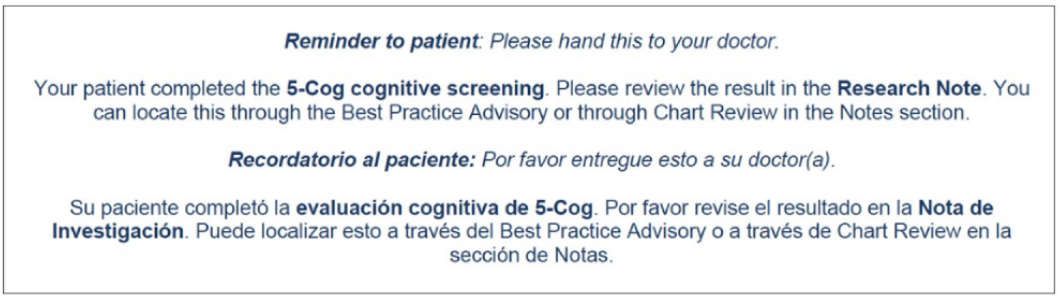
Figure 3 depicts a sample of the Montefiore-Einstein and IUH EMR alerts.

Figure 3. Electronic medical record (EMR)–based provider alerts for the intervention sites at the Albert Einstein College of Medicine and Montefiore Medical Center (Montefiore-Einstein; Epic EMR system) and Indiana University Health (IUH; Cerner EMR system). (A) Montefiore-Einstein: positive 5-Cog result. (B) Montefiore-Einstein: negative 5-Cog result. (C) IUH: positive 5-Cog result. (D) IUH: negative 5-Cog result.



At both sites, a paper token (Figure 4) is used as an additional feature to help ensure that care providers review the patients' 5-Cog results. Patients are handed this token after they complete the 5-Cog battery and are asked to hand it to their care provider at their scheduled visit, generally within 30 minutes after the 5-Cog battery administration.

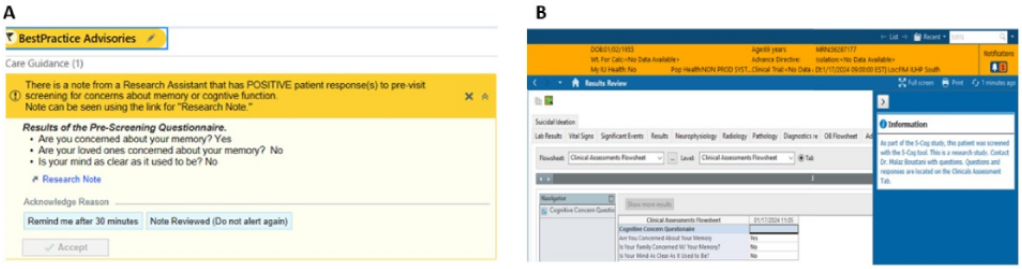
Figure 4. Token to alert care provider for patient's 5-Cog participation.



Interventions in the Control Arm (Enhanced Usual Care)

Patients are screened via telephone using the SCQ, as described in the Recruitment of Clinics and Patients subsection. RAs input results into the EMR. Care providers receive positive SCQ results through noninterruptive alerts. Figure 5 presents images of the alerts at Montefiore-Einstein and at IUH. We are calling this arm "enhanced usual care" because care provider are informed about the presence of a cognitive concern in their patient in this group. In addition, as at the intervention sites, care providers at the enhanced usual care sites receive preparatory education (described in the next subsection). The care providers at the control and intervention sites do not overlap.

Figure 5. Electronic medical record (EMR)–based care provider alerts for the control sites at the (A) Albert Einstein College of Medicine and Montefiore Medical Center (Epic EMR system) and (B) Indiana University Health (Cerner EMR system).



Care Provider Education and Preparation in Both Arms

Care providers at both control and intervention sites receive Microsoft PowerPoint presentations on the 5-Cog study. The presentations review the background to the study and then explain the study interventions that will be carried out at the sites (SCQ and new EMR features at both sites; 5-Cog at intervention sites). The presentations last 10 to 15 minutes at the control sites, and 25 to 30 minutes (to allow education about the 5-Cog battery) at the intervention sites. These presentations are provided 2 to 4 weeks before study start at a regularly scheduled clinic staff meeting. In addition to this education, care providers are given brochures that review cognitive impairment detection, diagnosis, treatment, and billing and invited to contact study staff at any time with questions. Finally, they are given tip sheets summarizing the new EMR features. At the intervention sites, care providers are updated on study progress via a monthly email or an informal in-person check-in by a study leader.

Of note, at both intervention and control sites, members of the interprofessional clinic leadership team (administrative and nursing managers) are provided with education on the study procedures and flow so that they can be prepared to assist and appropriately direct any patients who have questions about the study. At the intervention sites, members of the interprofessional clinic leadership team are also engaged in a session to plan clinic-customized logistical workflows to minimize interruptions to the clinic's operations during the course of the study. These workflows, along with a background to the study, are presented to the full interprofessional clinic staff before study initiation.

Interventions for the Implementation Study

From the intervention sites, a subset of patients (after the completion of study procedures and clinic visit) and providers will be invited to complete interviews to assess implementation issues. We will adapt the semistructured CFIR interview question guide. Interviews will be conducted, recorded, and analyzed by study staff trained in qualitative interviewing. We will aim to include patients with both positive and negative 5-Cog results. PCPs and clinical staff at the intervention sites will be asked to complete quantitative surveys containing 3 standardized 4-item measures: the AIM, FIM, and IAM [62]. The implementation outcomes measures are written at a fifth grade reading level; therefore, no specialized training is needed for administration, scoring, or interpretation. Finally, we will retain and later analyze recordings and field notes from our preimplementation stages (initial conversations with clinics and readiness presentations) through the completion of the project. This analysis will assess the barriers and facilitators to primary care sites' buy-in for study engagement. We will also use

summary reports to discern trends in care provider responses to the EMR-based alerts.

Interventions for the Cost-Effectiveness Study

Billing and actuarial data will be extracted from the EMR for cost estimation. In parallel fashion to the intervention sites, costs are also collected at the control sites. Standardized cost calculators previously developed by investigators [67,84] will also be used to facilitate microcosting (measuring detailed resource use and unit costs to obtain precise estimates [85]) applicable to the 5-Cog paradigm. We will evaluate the cost of implementing and sustaining the 5-Cog paradigm by accounting for and itemizing specific program characteristics. We will evaluate differences in 5-Cog costs of care on the desired study outcomes compared to enhanced usual care.

Effectiveness Study: Primary Outcomes

The primary outcome is a new diagnosis of MCI or dementia within 90 days after study enrollment. Patients who enter the study with a known diagnosis of MCI will only be counted as meeting the primary outcome if they receive a new diagnosis of dementia. We chose diagnosis as the primary outcome for 2 reasons. First, a new diagnosis was a common outcome in our 5-Cog 1.0 study, and we want to validate this finding [33]. Second, this outcome is highly relevant to patients and PCPs: knowing their cognitive diagnosis has been shown to be important to patients and family members [34,86,87]; moreover, diagnostic clarity facilitates appropriate psychoeducation, resource connections, tailored medical treatment, and caregiver activation [88,89].

Effectiveness Study: Secondary Outcomes

The secondary outcome is a composite: “improved dementia care” within 90 days after study enrollment. “Improved dementia care” is defined by any of the following actions that are relevant to dementia diagnostic assessment and care: orders for dementia-related laboratory or imaging tests; a new prescription for cognition-enhancing medication or the deprescribing of anticholinergic medication; or referrals to a dementia specialist clinician, a nurse navigator, a social worker, or a community-based organization for related supports. We are including this composite outcome because a new diagnosis without subsequent action is less likely to improve patient outcomes. The aforementioned components are highly relevant to both PCPs and patients [90,91]. The actions described are only counted as an outcome if a cognitive indication (eg, memory loss or MCI) is entered as the indication in the EMR. Tests or referrals without indications entered or performed for any other medical reasons are not counted as outcomes. Prescription of dementia medications will always be counted because these medications inherently indicate cognitive impairment. For anticholinergic deprescribing, actions will be counted via a comparison of EMR-extracted medication lists from the 90 days before and after study enrollment. Charts will be reviewed for clinician notation on whether deprescribing (discontinuation or nonrenewal) was due to a cognitive indication [92]. We will consider the medications listed under “Drugs with strong anticholinergic properties” in the American Geriatrics Society Beers Criteria [93].

All primary and secondary outcomes are collected prospectively from the EMR. Textbox 2 presents a summary of the primary and secondary outcomes.

Textbox 2. Study outcomes.

Primary outcome: new cognitive diagnosis (with associated International Classification of Diseases, Tenth Revision, code [94])

- Vascular dementia with or without modifiers (F01)
- Dementia in other diseases with or without modifiers (F02)
- Unspecified dementia with or without modifiers (F03)
- Mild cognitive impairment or minor neurocognitive disorder (unless patient entered study already having this diagnosis; G31.84)
- Alzheimer's disease with late onset (G30.1)
- Other Alzheimer's disease (G30.8)
- Alzheimer's disease, unspecified (G30.9)
- Frontotemporal dementia (G31.09)
- Lewy body dementia (G31.83)
- Dementia associated with alcoholism (F10.27)
- Unspecified with psychoactive substance–induced persistent dementia (F19.97)
- Variant Creutzfeldt-Jakob disease (A81.01)
- Creutzfeldt-Jakob disease, unspecified (A81.00)
- Other Creutzfeldt-Jakob disease (A81.09)

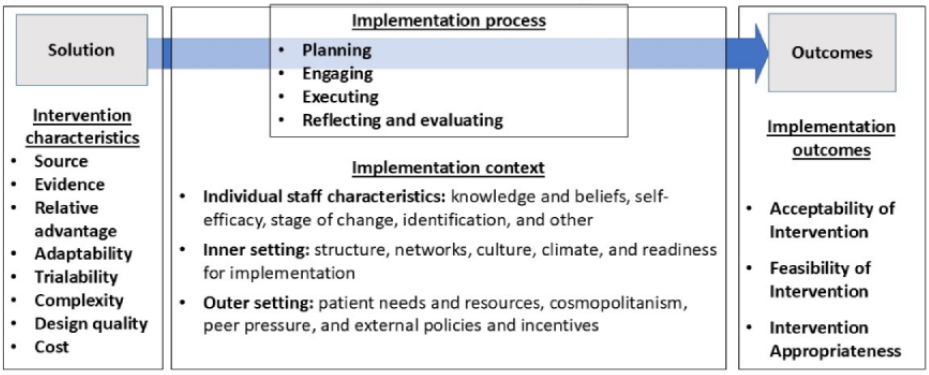
Composite secondary outcome: "improved dementia care" through relevant actions

- Medications: donepezil, rivastigmine, galantamine, memantine, donepezil-memantine, antiamyloid monoclonal antibody infusions, and any other Food and Drug Administration–approved medications for dementia
- Deprescribing anticholinergic medications: discontinuation or nonrenewal of any of the 41 medications in table 7 ("Drugs with strong anticholinergic properties") of the American Geriatrics Society Beers Criteria [93]
- Laboratory tests (cognitive indication only): thyroid-stimulating hormone, vitamin B12, glycated hemoglobin, complete blood count, basic metabolic panel, liver tests, HIV antigen and antibody combination, and syphilis immunoglobulin G and immunoglobulin M antibody with reflex
- Imaging tests (cognitive indication only): computerized tomography (head without contrast) and magnetic resonance imaging (brain without contrast)
- Specialist referrals for cognitive evaluation: geriatrics, neurology, neuropsychology, psychiatry, geriatric psychiatry, and social work
- Community referrals: Alzheimer's Association or local support organization

Implementation Outcomes

We will begin recruiting implementation study participants after approximately 1 month of patient involvement at each study site, once a "steady state" has been established. We will vary time points for the collection of implementation outcomes throughout our engagement at each clinic in anticipation that informant responses may shift with varied exposure to the 5-Cog. Surveys will assess the implementation outcomes of acceptance, feasibility, and appropriateness, which are considered "leading indicators" of implementation success. These will be measured using the AIM, FIM, and IAM, as noted in the Interventions for the Implementation Study subsection [62,95]. The results of the surveys will be computed using descriptive statistics (central tendency and variability) and, after checking for assumptions (eg, high interclass intraclass correlation), aggregated at the clinic level across all respondents. We will also collect and analyze EMR engagement data (eg, the rates and types of responses to alerts and the use of order sets) to assess the acceptance of EMR tools. In addition, we will collect field notes with observations about the study sites and observations from informal conversations with clinic staff during the study period to better understand the implementation context. Figure 6 summarizes the implementation constructs and the CFIR outcome measurement model for the study.

Figure 6. Consolidated Framework for Implementation Research (CFIR) Measurement Model.



Cost-Effectiveness Outcomes

The cost calculator includes parametric models of cost inputs; cost model outcomes from this study will thus allow scenario analyses [67,84]. The proposed calculator will incorporate both the direct costs of the intervention (test administration, staffing costs, etc) and costs associated with interventions prompted by the 5-Cog (brain imaging, specialist referral, laboratory tests, etc). The cost calculator will thus enable others to determine 5-Cog delivery costs and implementation specifics such as the cost of hiring at future implementation sites. Data collected for the BIA will determine financial planning and affordability, while data collected for the CEA will determine the effectiveness and value of the 5-Cog paradigm compared to enhanced usual care.

Exploratory Outcomes

Medical billing for cognitive impairment detection paradigms may be an important component of sustainability [22] because PCPs often lack sufficient resources to support the effort required to care for patients with complex needs [96]. The 5-Cog may have benefit in enhancing billing opportunities because it incorporates 5 minutes of cognitive testing and may add to the level of medical complexity of a visit. As noted, one of the 5-Cog 2.0 study interventions—implemented at both 5-Cog and control sites—is provider education on billing for cognitive impairment detection, diagnosis, and treatment. Although the 5-Cog study does not include PCP billing interventions as part of its aims, we will monitor and compare the rates of use of "cognitive" billing codes (eg, Medicare AWV and current procedural terminology codes 96136 and 96138 [97]) between the 5-Cog and enhanced usual care sites. At the 5-Cog sites, we will examine whether the use of "cognitive" billing codes is associated with 5-Cog paradigm administration.

Assignment of Interventions

Sequence Generation

As in other pragmatic cluster randomized trials [98], we randomize at the clinic level. Commitment to join the study was sought from clinics. Once an adequate number of clinics (n=22) were identified, they were randomized. Computer-generated randomization assigned primary care practices in a 1:1 ratio within each site (the Bronx and Indiana) to either the 5-Cog paradigm or control arm. Randomization was stratified within each arm by clinic size (number of PCPs).

Allocation Concealment Mechanism

Randomization is central, computer generated, and not vulnerable to researcher influence. The study statisticians are blinded to interventions and other aspects of the trial.

Implementation

The 22 clinic clusters will be phased in gradually for logistical reasons, following a standardized procedure at each clinic: an overview presentation for leadership, a readiness presentation for providers and staff, and then study initiation.

Masking

Blinding of patients or PCPs at 5-Cog sites will not be feasible due to the nature of the intervention. However, the outcome is EMR based, and data abstractors will be blinded to allocation. Standardized checklists will be used for outcome measurement to further minimize bias. Statisticians will not be involved in the intervention delivery.

Data Collection, Management, and Analysis

Data Collection Methods

Data will be collected from 2 sources (refer to the following subsections).

EMR Data

We will collect EMR data on trial-enrolled patients aged ≥65 years receiving care in the participating practices after obtaining consent from the practice leadership and receiving a waiver from the institutional review board (IRB). Outcomes will be extracted and aggregated from the EMR. Deidentified analytic databases will be created and analyzed by investigators.

Feedback From Care Providers, Staff, and Patients

Data on clinician and practice staff perceptions of the intervention and factors that facilitated or impeded implementation and sustainability will be obtained through digital surveys and in-person interviews with key informants. Data on patient perceptions and experiences with the 5-Cog will be obtained through in-person, telephone, and video call platform interviews. Data collection will be the responsibility of the clinical trial staff at the site under the supervision of the site investigators. The investigator will be responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported. All source documents will be completed in a neat, legible manner to ensure accurate interpretation of

data. Hard copies of the study visit worksheets will be provided for use as source document worksheets for recording data for each participant consented and enrolled in the study. Data recorded in the electronic case report form derived from the source documents will be consistent with the data recorded on the source documents. All effectiveness and implementation data will be entered into REDCap (Research Electronic Data Capture; version 14.0.31; Vanderbilt University), a 21 CFR Part 11–compliant data capture system provided by the Albert Einstein College of Medicine through an NIH grant (UM1TR004400). The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that seem inconsistent, incomplete, or inaccurate.

Data Management

Data collected for this study will be analyzed and stored at the Albert Einstein College of Medicine via REDCap. These data will be available through web-based registration to researchers for future analyses after the completion of our pragmatic clinical trial and publication of the main results. For resource-sharing approval, collaborators—both internal and external—will be required to register on the web and submit a resource transfer agreement. Requests can be submitted electronically to expedite research progress. Requests will also be reviewed by the steering committee at regularly scheduled meetings.

Effectiveness Study: Statistical Plan

The baseline characteristics of the clinical sites as well as individual enrolled patients will be examined after the baseline measurement time point at the halfway point of target enrollment. It is possible that baseline differences between the groups or missing data will limit the value of data analysis of measurements. Effects on the power to detect differences in the primary outcome will be evaluated and communicated to the principal investigators (PIs), data safety monitoring board (DSMB), and NIH. Given the monitoring plans outlined in the Monitoring subsection, it is exceedingly unlikely that there will be baseline differences between the groups of a magnitude that could threaten the validity of the study.

We will evaluate the clinical effectiveness of the 5-Cog paradigm on new cognitive impairment detection by comparing the proportion of “new MCI and dementia diagnoses” by PCPs within 90 days after the clinic encounter in the 5-Cog paradigm group versus the enhanced usual care group using generalized linear mixed effects (GLME) models with a logit link to account for clinic-clustered data [99]. Using these models, odds ratios of new MCI and dementia diagnoses between the 5-Cog paradigm and enhanced usual care arms will be calculated and tested. We chose a 90-day cutoff because the majority of PCP actions occurred within the first 30 days in our recent RCT [33]. The 22 clinics are cluster randomized to either the 5-Cog paradigm or enhanced usual care arm, which can result in correlated data due to clustering of patients within clinics. This issue will be handled using random effects in the mixed models. Proportions of new MCI and dementia diagnoses for each treatment group will also be reported. We will perform an intention-to-treat analysis. As a secondary approach, we will also perform a per-protocol analysis. All estimates will be reported together with their 95% CIs. The same method will be used for the secondary outcome (“improved dementia care”).

Stratified analyses across the 22 sites will be performed for groups impacted by health disparities, as designated by the NIH, including those from racial and ethnic minority groups (Black and Hispanic individuals) and individuals from socioeconomically disadvantaged backgrounds. Interactions between race and ethnicity and socioeconomic status (SES) will also be explored by stratified analyses by the combination of the 2 factors and by including the 2 factors and their product as well as interactions with the treatment groups in the GLME model for all enrolled patients. We will compare 5-Cog results by location in sensitivity analyses to detect any health care system–based variations.

All sample size and power calculations were performed using 2-tailed tests with a significance level of α=.05. The within-cluster intraclass correlation in this cluster randomized trial is assumed to be 0.05 based on prior studies [100]. On the basis of our RCT data, the proportions of “new MCI and dementia diagnoses” are expected to be 14% and 2% among the 5-Cog and control arms, respectively. The proportions of “improved dementia care” are expected to be 21% and 7% among the 5-Cog and control arms, respectively. In our total sample (N=6600), we have >99% power to detect the overall effectiveness of the 5-Cog paradigm on “new MCI and dementia diagnoses” and the secondary outcome of “improved dementia care.” Sample size determination was based on the primary outcome among individuals from racial and ethnic minority groups (2112/6600, 32%) and those with low SES (3750/6600, 56.82%). Assuming that 80% (1400/1800) of the participants in the 6 Bronx clinics are from racial and ethnic minority groups, and 75% (1350/1800) have low SES, as well as 14% (672/4800) and 50% (2400/4800), respectively, in the 16 Indiana clinics, 300 patients per cluster (clinic) will enable the detection of the effect of the 5-Cog paradigm on new MCI and dementia diagnoses with 81% power among individuals from racial and ethnic minority groups and 99% power among those with low SES.

Our outcomes are ascertained from the EMR by blinded assessors and do not require repeat in-person assessments. This will minimize missing data issues. We will implement robust EMR-based data management processes to further minimize missing data. Cluster sites are not contiguous, and patients within a cluster are assigned to specific PCPs who do not work across sites. Any intentional or unintentional contamination will be monitored by the data team, including by comparing enrolled patient lists across the sites.

Implementation Study: Statistical Plan

Interview data will undergo content analysis to identify and score implementation barriers or facilitators. Qualitative content analysis will be performed primarily using a deductive approach, starting from a developed theoretical model—the CFIR—and its associated hypotheses and then examining data to disconfirm or confirm these hypotheses [101]. The analysis will also allow for the inductive development of new themes, categories, and relationships as they arise from the data [102]. Deductive data analysis will be guided by the CFIR constructs and their

definitions such that units of qualitative data (sentences or passages) are assigned to ≥1 codes reflecting the CFIR constructs [102]. We will use NVivo 15 (Lumivero) to manage and code qualitative data. For each implementation interview, there will be an artificial intelligence–generated transcript that will be manually reviewed by study staff before it is moved into NVivo. To guide systematic coding, a codebook will be developed. A multiple-analyst team will be trained and tested on its application. Analysts will code a random subset of interviews together during training and then assigned at a ratio of 2 to 3 per transcript for either all or a subset of transcripts, depending on the original level of coding agreement (ie, interrater reliability) [103,104]. Subsequent coding discussions will be held intermittently for the calibration and discussion of difficult cases and disagreements. Interrater reliability will be computed in NVivo at the start, middle, and end of coding, with retraining and adjustments to the plan depending on the results. Inductively, we will allow for the emergence of new codes and subcodes [104]. We will also use applied thematic analysis [105] to identify patterns within and between codes. As much as possible, data analysis will occur in parallel with data collection, enabling us to adjust data collection procedures to capture emerging and unexpected phenomena, as well as perform member checking with informants willing to complete follow-up interviews to review and validate our coding of their initial interviews. Within each CFIR code, for each implementation context or process element, the assigned analyst will add a rating on a scale ranging from +3 (strong facilitator) to −3 (strong barrier) [54]. Analysts will be trained to use evidence from interviews and not personal opinions to rate each driver [102].

RAs in Indiana and the Bronx will be trained by coinvestigators to reliably collect implementation process data from a combination of documents, field notes, and interviews, with select staff responsible for the implementation process. To capture implementation data monthly, while minimizing staff burden, we will use the Prospectively Reported Implementation Update and Score [106]. The analysts will reconstruct these data into process maps or workflow diagrams depicting key historic moments, process variations, and players [54,59,102].

Linking Implementation to Effectiveness Analysis

Examining how stakeholder-level factors impact and are impacted by the 5-Cog implementation is critical because implementation can be influenced by stakeholders' characteristics, attitudes, intentions, and motivations. Stakeholder-level factors are also shaped by organizational factors [107]. Following the guidance of Damschroder and Hagedorn [58], we will link identified and rated (+3 to −3) context and implementation process drivers to implementation outcomes. Our analytical approach is as follows: we will derive clinic-level mean and variability measures of the AIM, FIM, and IAM scales and examine whether these implementation measures are associated with cognitive impairment detection by using GLME models with a logit link, treating the mean and variability measures of the AIM, FIM, or IAM as independent variables [108]. This analysis will determine how detection rates are associated with the levels or variabilities in implementation acceptance, perceived feasibility, and appropriateness within each clinic. We will explore whether and how context variables account for 5-Cog effects on outcomes by including quantitative context measures and interactions with the intervention group as independent variables in the GLME models from the effectiveness analysis [108]. We will then develop a thematic matrix that includes characteristics derived from stakeholder surveys and emerging themes from our qualitative data for each 5-Cog clinic site and conduct side-by-side comparisons—at system, organizational, and staff levels—of the factors that were identified as facilitating or hindering 5-Cog implementation. We will note common and unique factors for each clinic or location. This will generate a list of relevant system-, organizational-, and staff-level factors and processes organized by level of consensus (ie, identified by >1 source) and operational salience (ie, identified as critical for implementation). We will use this list to generate a heuristic model to inform future implementation strategies [54,55].

CEA and Economic Impact

Using data from the BIA cost-tracking tool, the cost-effectiveness ratio [109,110] "numerator" will account for site personnel and other costs at both intervention and control sites. The denominator will represent the number of cognitive impairment cases identified at the 5-Cog and control sites. In summary, the cost-effectiveness ratio represents the incremental cost of the 5-Cog intervention compared to enhanced usual care to achieve a clinically meaningful change, divided by the difference in effectiveness, to determine the cost per cognitive impairment case identified. This is expressed as follows:

Cost-effectiveness ratio = intervention costs + Δ (health care costs) / Δ health outcomes (5-Cog) – Δ health outcomes (enhanced usual care comparison group)

To assess uncertainty in our analysis, we will follow the recommendations of the International Society for Pharmacoeconomics and Outcomes Research and the Society for Medical Decision Making Modeling Good Research Practices Task Force [63,65-68,111]. Variability of inputs across study sites with differing levels of social determinants of health will be included in analyses [112]. Differences in intervention and health care costs due to secondary procedures will be assessed individually using negative binomial regression and reported with a 95% CI. Only statistically significant differences from the regression analyses will be incorporated into the cost-effectiveness ratio. Differences in health outcomes will be assessed as described in the Effectiveness Study: Statistical Plan subsection, and the estimate of the GLME model, if significant, will be incorporated into the cost-effectiveness ratio. Costs will be discounted at a 3% annual rate for the trial period, as recommended by the Second Panel on Cost-Effectiveness in Health and Medicine [113].

Monitoring

Data Monitoring

Each clinical site will perform internal quality management of study conduct, data collection, documentation, and completion. All sites will follow a common quality management plan. Before we began data collection, the PIs and the DSMB chair reconfirmed that our sites have appropriate safety measures in

place. The DSMB met with the entire research team to review the study protocols. Particular attention was paid to outcome definition, study design, procedures for recording and reporting adverse events (AEs), informed consent procedures, and documentation. At its initial meeting, the DSMB approved the protocol and formulated its operating procedures (eg, meeting schedule, report deadlines for the study statistician, unblinding policy, and guidelines for releasing interim data to the investigators). At this meeting, the plans for interim monitoring for efficacy and futility were presented to the DSMB to aid in trial oversight. We will train competent staff to conduct the assessments and ensure that they understand the data collection procedures and process as well as AE reporting requirements.

Effectiveness Study: Monitoring for Harms

Patients who receive care at the practices randomized to implement the 5-Cog paradigm may experience minimal risk through their participation. It is possible that patients may feel shame, anxiety, and some emotional discomfort when completing the cognitive assessment; however, this may be the case with the standard of care cognitive assessment as well and may not be specific to the intervention arm. In addition, in our ADRD screening trial that evaluated the potential benefits and harms of ADRD screening, there were no differences between the screened and control groups in quality of life, depressive symptoms, or anxiety [114,115]. That trial also assessed the impact of this early diagnosis on participants' quality of life and care and found no negative impact on quality of life, depression, anxiety, health care use, or independence at home [114,115]. The risk of potential harm such as stigma is not known. However, the early detection of ADRD is considered part of the standard of care, and screening for ADRD is part of the AWV covered by Medicare because of the significant potential benefits.

Implementation Study: Monitoring for Harms

Answering questions on surveys and participation in interviews with trained personnel involve minimal psychological, social, or other risks. We do not expect any AEs during these noninvasive assessments.

Full Study: Monitoring for Harms

Safety oversight will be under the direction of a DSMB composed of individuals with the appropriate expertise. We will set up a data safety monitoring plan, which will be monitored by the PIs and DSMB. The PIs will also conduct data and safety monitoring and will regularly monitor study progress, goal achievement, and overall research direction in consultation with the coinvestigators. Members of the DSMB will be independent from the study conduct and free of conflicts of interest. The DSMB, which will meet at least semiannually to assess safety and efficacy data from each study arm, will operate under the rules of an approved charter that was written and reviewed at its organizational meeting. The DSMB will provide its input to the National Institute of Neurological Disorders and Stroke and NIH staff.

AEs will be monitored on an ongoing basis by the study managers through self-initiated reports from participants or patients, observations of research and clinic staff at the intervention sites, biannual review of acute care use among enrolled patients, and review of EMR data at 90-day outcome collection for any medical records or notes of medical, psychological, or stress symptoms possibly related to the administration of the 5-Cog battery. In addition, a list of hospitalizations and emergency department visits (for any reason) occurring within 90 days after the clinic visit will be generated by the EMR system, which will be reviewed by the PIs and study investigators. All AEs not otherwise precluded per the protocol will be captured on the appropriate case report form. Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study procedures (assessed only by those with the training and authority to make a diagnosis), and time of resolution or stabilization. All AEs occurring during the study will be documented appropriately regardless of their relationship to the intervention and followed until adequately resolved. Any preexisting medical or psychiatric conditions at screening will be considered baseline and not reported as an AE. However, any deterioration in a patient's clinical or psychological condition during the assessment will be recorded as an AE. Changes in AE severity will be documented to assess the duration of the event at each severity level. For AEs characterized as intermittent, the onset and duration of each episode will be documented. New diagnoses of MCI or dementia may result in psychological stress for patients that may not be captured in the EMR. Hence, we will also assess these more subtle psychological symptoms during the implementation interviews.

Auditing

Quality control procedures will be implemented. In the implementation study only, regarding informed consent, study staff will review both the documentation of the consenting process and a percentage of the completed consent documents to evaluate compliance with good clinical practice, accuracy, and completeness. Feedback will be provided to the study team to ensure that proper consenting procedures are followed. To assess data accuracy (the level of correctness of stored information [116]), site staff will compare a representative sample of source data against the database, focusing on key data points. The study team will review protocol deviations on an ongoing basis and implement corrective actions if deviations reach a concerning level. Should independent monitoring become necessary, the PIs will provide direct access to all trial-related sites, source data and documents, and reports for monitoring and auditing by the funding agency and inspection by local and regulatory authorities.

Ethical Considerations

The Albert Einstein College of Medicine IRB approved this study (2022-14144) and serves as the IRB of record for both sites under a reliance agreement with the Indiana University IRB. This study will be conducted in accordance with federal publication and data-sharing policies and regulations. Regarding consent for participants, we received a waiver of informed consent from individual patients from the IRB to maintain the pragmatic design of the clinical trial. For the implementation part of the study, consent is obtained from all participants before

completion of any study measures. Participants who consent for the implementation study receive US $25 in compensation for completed interviews. Outcomes will be extracted and aggregated from the EMR and will be deidentified. After the study is completed, the deidentified, archived data will be transmitted to and stored in a data repository with protections in place for patient confidentiality.

Results

The grant was funded, and the protocol received IRB approval, in September 2022.

Effectiveness Study

A validation cohort of 76 older patients (mean age 76.5, SD 7.72 y; n=50, 66% women) from dementia centers at Montefiore Einstein was evaluated with the 5-Cog battery to determine optimal cut scores. This was completed by July 2023. Among these 76 patients evaluated by the multidisciplinary care provider team at these centers (neuropsychology, neurology, and geriatrics), the resulting clinical diagnoses were as follows: 32 (42%) had a diagnosis of dementia, 28 (37%) MCI, 12 (16%) subjective cognitive concerns without objective cognitive impairment, and 2 (3%) had no cognitive diagnosis assigned. The mean scores on the PMIS were 5.8 (SD 2.7), Symbol Match 27.2 (SD 18.2), and sMCR 2.4 (SD 1.7). We correlated performance on the individual 5-Cog battery tests with the Blessed Information-Memory-Concentration Test scores (range 0-32; higher scores indicate worse performance), an omnibus test of general mental status (mean 10.3, SD 6.8). The PMIS (Pearson r=−0.76; P<.001) and Symbol Match (r=−0.69; P<.001) showed excellent correlation with Blessed scores. While the sMCR was not correlated with Blessed scores (r=0.008; P=.95), it was correlated (r=−0.34; P=.007) with walking speed (mean 72.3, SD 25.3 cm/s) in this sample. The PMIS was correlated (r=−0.59; P<.001) with the 5-item memory recall subtest on the Blessed Information-Memory-Concentration Test (mean 2.9, SD 1.84; higher scores indicate worse performance). Symbol Match was correlated (r=0.88; P<.001) with the Symbol Digit Modalities Task score (mean 21.2, SD 14.6; lower scores indicate worse performance).

As we examined the sensitivity and specificity data to choose cut scores, we chose to favor sensitivity to minimize missing individuals with true disease in this sample of patients considered high risk because of their cognitive concerns. The cut scores for a *positive* result on the 5-Cog components were as follows: PMIS ≤6 (range 0-8), Symbol Match ≤25 (range 0-65), and sMCR >5 (range 0-7). There was a high rate of completion of the PMIS (75/76, 99%), Symbol Match (76/76, 100%), and sMCR (74/76, 97%) tests on the 5-Cog battery, indicating high acceptability and feasibility of administration of the 5-Cog battery in populations with cognitive impairments.

The DSMB met in July 2023, approved the protocol and data safety monitoring plan, and authorized study enrollment. By October 2023, all 22 clinics had agreed to participate and been randomized. By November 2023, decision support tool integration into the EMRs had been finalized. As of December 2024, a total of 12 clinics had completed onboarding processes (refer to the Methods section, Care Provider Education and Preparation subsection), and 2369 patients had been enrolled.

Implementation Study

We have completed 6 implementation interviews and 23 implementation surveys over 12 clinic sites.

Cost-Effectiveness Study

5-Cog 2.0 investigators have already collected procedure and health care cost estimate data for Montefiore-Einstein for a 5-Cog 1.0 CEA. Preliminary results suggest that the 5-Cog paradigm is a cost-effective option compared to “enhanced usual care” for the early detection of cognitive impairment in primary care (H Congivaram, BS, unpublished data, December 2024). Investigators have begun collecting cost estimates for 5-Cog procedures and resulting health care costs in the IUH system, as these were not previously collected.

Discussion

Anticipated Findings

The results of this 5-Cog 2.0 RCT will provide additional evidence that the 5-Cog paradigm is effective in improving dementia diagnosis. At the same time, the implementation portion of this study will provide critical information about the context, facilitators, and barriers to using the 5-Cog successfully, while the cost-effectiveness portion of this study will offer a practical analysis of the cost implications of the paradigm. Taken together, these study outcomes will allow informed, tailored, and rapid adaptation and dissemination of the 5-Cog paradigm to diverse primary care environments.

Meeting the ongoing and anticipated growing need for timely dementia diagnosis and care has been a focus of much study. Despite the availability of high-quality tools for dementia detection [22], significant gaps remain in real-world application, and the rates and timeliness of diagnosis remain unacceptably low [28,117,118]. This translates to clinical “blind spots” for care providers and missed opportunities for patients. These gaps are even more pronounced among individuals from historically minoritized racial and ethnic groups [5,119]. The 5-Cog paradigm is poised to effectively bridge these gaps. The 5-Cog itself is designed for widespread applicability, with characteristics that make it appropriate for individuals from various cultural, linguistic, and literacy backgrounds [32,33]. The 5-Cog’s simple, fast format also makes it easily adaptable in resource-limited environments in contrast to some cognitive assessment tools that require specialized training or equipment to administer [120,121]. Although the evidence for decision support systems to improve clinical practice is mixed [50,122], the 5-Cog paradigm does build on prior evidence of the efficacy of decision supports in dementia detection [123,124].

Strengths and Limitations

This study has several strengths. Its results are anticipated to have improved generalizability compared to prior studies for several reasons: its large sample size; the racially and ethnically diverse patient population being enrolled; and the pragmatic nature (using local CHW staff, colocation in patients’ usual sites of care, and a waiver of written informed consent), which

may help reduce the hesitancy of individuals from historically marginalized groups to participate in the trial [125]. While the characteristics and specifications of primary care clinic sites will vary, the urban and rural primary care clinic sites in the 5-Cog study are typical of primary care clinics in the United States, especially those that serve underserved individuals from historically minoritized groups. Prior studies of decision supports in dementia were limited by a small sample size and a lack of active control groups [50,122]. The 5-Cog 2.0 study overcomes these limitations. Another strength of this study is that the BIA will form the basis of a tool that can be used to tailor financial adoption and scalability in different practice settings for national implementation. Finally, this study's unique hybrid effectiveness-implementation design will rapidly generate actionable data to advance progress in closing dementia care gaps. This study is anticipated to have a few limitations. Although the inclusion criteria are intentionally liberal in this pragmatic trial, the trial may not address dementia care gaps for the subset of patients who lack insight into their cognitive impairments and deny having them and are therefore not eligible for the trial. Implementation analyses will allow an exploration of whether and how the 5-Cog can support PCPs' clinical approach to this subset of patients who do not recognize their own cognitive decline. A limitation of the CEA is that the time horizon is relatively short, and long-term sustainability will need to be assessed in future studies.

Anticipated Dissemination Strategy

The information gained about the 5-Cog paradigm, including details of the EMR-embedded clinical decision support and incorporation into medical billing systems, in this pragmatic trial will enable future implementation in everyday clinical settings across the United States for routinely detecting cognitive impairment, including dementia. For dissemination, this trial has been registered at ClinicalTrials.gov (NCT05515224), and results information from this trial will be submitted to ClinicalTrials.gov. Every attempt will be made to publish the results in peer-reviewed journals. Final research data will be shared openly and in a timely manner: data from this study may be requested from other researchers 1 year after the completion of the primary end point by contacting Albert Einstein College of Medicine. For dissemination of the 5-Cog paradigm itself, the 5-Cog forms and administration instructions will be made available on a publicly facing website. 5-Cog team members anticipate making presentations at national conferences of clinical, educational, and administrative leaders in dementia care to facilitate the dissemination of the paradigm.

Future Directions

Although there will not be a "one-size-fits-all" solution to detecting cognitive impairment across the country, we anticipate that elements of the 5-Cog battery can be adapted in distinct sites and further studied; for instance, pictures in the PMIS may need to be updated to account for local cultural and ethnic factors. We also anticipate that, as new knowledge regarding MCI and dementia and treatments emerges in the future, we will have to update the 5-Cog decision tree and adapt to other EMR systems. Finally, the results of this study will provide the foundation for further study of the 5-Cog assessment for use in the increasingly common collaborative dementia care models [15,30,126-128], as a screening paradigm for population health models [129,130], and to evaluate the impact of early detection on clinical care and outcomes.

Acknowledgments

The authors wish to acknowledge the IT specialists from the Indiana University Health Cerner team and the Montefiore- Einstein Epic team who helped integrate the 5-Cog battery into the respective EMRs; the community health workers and research assistants from both sites who provided input and refinement to anticipated study procedures and processes; Indiana University Health team members Andrea Burkhardt and Julie Maier who contributed substantially to protocol development before moving to other departments; and the study data safety monitoring board members Alexia Mary Torke, Amy Ehrlich, and Claudene George. This work is funded by a grant from the National Institute of Neurological Disorders and Stroke of the National Institutes of Health (2U01NS105565).

Data Availability

The data that support the findings of this study will not be publicly available due to reasons of confidentiality. On reasonable request to the corresponding author, individual deidentified participant data (including data dictionaries) will be made available via a REDCap (Research Electronic Data Capture) web-based database, after review and approval of a methodologically sound proposal, with a signed data access agreement, in line with ethics committee requirements.

Authors' Contributions

JV and MB were responsible for conceptualization and funding acquisition. EA, DA, AH, and PY were responsible for data curation. CW and HX were responsible for formal analysis. JV, MB, JZ, RBRC, AT, EA, EFW, AA, KF, CW, DA, DDF, JMW, HC, NRF, DS, HX, AH, RJH, MM-V, CN, and PD were responsible for methodology. EA, MM-V, PY, NRF, AH, RBRC, EFW, AA, and CN were responsible for project administration. JV, MB, and AA were responsible for resources. RBRC, DS, and PD were responsible for software. JV, MB, NRF, JZ, EFW, and RJH were responsible for supervision. RBRC, PY, EA, EFW, and DS were responsible for visualization. RBRC, EA, JV, and MB wrote the original draft. EA, JV, MB, NRF, EFW, AT, AA, PY, CW, JZ, KF, DS, RJH, HX, DDF, JMW, HC, MM-V, CN, PD, AH, and DA reviewed and edited the manuscript.

Conflicts of Interest

JV serves on the editorial boards of the Journal of the American Geriatrics Society and the Journals of Gerontology, Series A: Medical Sciences. He serves as a scientific adviser for Catch U, Inc, and MedRhythms, Inc. JV, EA, and EFW hold a copyright for the 5-Cog battery (TX9340781). MB serves as chief scientific officer and cofounder of Blue Agilis, Inc and chief health officer of DigiCare Realized, Inc. He has equity interest in Blue Agilis, Inc and DigiCare Realized, Inc (he sold his equity in Preferred Population Health Management, LLC and MyShift, Inc [previously known as RestUp, LLC]). He serves as an advisory board member for Eli Lilly and Company, Eisai Inc, Merck & Co, Inc, Biogen, Inc, and Genentech, Inc. MB's conflicts have been reviewed by Indiana University and have been appropriately managed to maintain objectivity. All other authors declare no conflicts of interest.

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Abbreviations

ADRD: Alzheimer disease and related dementias
AE: adverse event
AIM: Acceptability of Intervention Measure
AWV: annual wellness visit
BIA: budget impact analysis
BPA: best practice advisory
CEA: cost-effectiveness analysis
CFIR: Consolidated Framework for Implementation Research
CHW: community health worker
DSMB: data safety monitoring board
EMR: electronic medical record
FIM: Feasibility of Intervention Measure
GLME: generalized linear mixed effects
IAM: Intervention Appropriateness Measure
IRB: institutional review board
IUH: Indiana University Health
MCI: mild cognitive impairment
MCR: motoric cognitive risk
NIH: National Institutes of Health
PCP: primary care provider
PMIS: Picture-Based Memory Impairment Screen
RA: research assistant
RCT: randomized controlled trial
REDCap: Research Electronic Data Capture
SCQ: subjective cognitive concern questionnaire
SES: socioeconomic status
sMCR: Subjective Motoric Cognitive Risk

Edited by T Leung, D Khajee; submitted 15.05.24; this is a non–peer-reviewed article;accepted 31.12.24; published 03.04.25.

Please cite as:
Chalmer RBR, Ayers E, Weiss EF, Fowler NR, Telzak A, Summanwar D, Zwerling J, Wang C, Xu H, Holden RJ, Fiori K, French DD, Nsubayi C, Ansari A, Dexter P, Higbie A, Yadav P, Walker JM, Congivaram H, Adhikari D, Melecio-Vazquez M, Boustani M, Verghese J
Improving Early Dementia Detection Among Diverse Older Adults With Cognitive Concerns With the 5-Cog Paradigm: Protocol for a Hybrid Effectiveness-Implementation Clinical Trial
JMIR Res Protoc 2025;14:e60471
URL: https://www.researchprotocols.org/2025/1/e60471
doi:10.2196/60471
PMID:

Protocol

Web-Based Human Papillomavirus Education and Professional Skills Intervention for Health Care Providers: Protocol for a Randomized Controlled Trial

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Abstract

Background: The human papillomavirus (HPV) vaccine is an effective way to prevent HPV and its associated cancers. Provider recommendation has been shown to be one of the most successful strategies for increasing the uptake of the HPV vaccine; however, more training and resources are needed to help boost health care providers' confidence and communication skills in recommending the HPV vaccine to their patients, particularly in underserved Hispanic communities where vaccination rates among all ages are lower.

Objective: This study aims to compare HPV educational and professional skills intervention effectiveness on improving provider recommendations and patient communication strategies with health care providers serving the El Paso United States–Mexico border region.

Methods: We will conduct a randomized, blinded, multiple posttest-only controlled behavioral trial using a parallel group design that will examine the effectiveness of a fully automated, web-based, culturally tailored HPV education and professional skills intervention containing unique reading material and video role-play, as compared to a standard Centers for Disease Control and Prevention fact sheet and video about general communication skills. Participants were recruited using a purposive sampling technique, both internet-based and in-person outreach events. Study data are being collected and managed using REDCap (Research Electronic Data Capture; Vanderbilt University) hosted at the University of Texas at El Paso. Chi-square analyses, ANOVA, and other statistical tests will be used with 2-tail α to reject null hypotheses at .05 to analyze the self-assessed outcome data. The Mauchly test of sphericity for each ANOVA and the Huynh-Feldt epsilon test or Greenhouse-Geisser correction to the degrees of freedom of the F-ratio will be reported for each significant effect. We may use multiple imputation procedures to handle the missing data (if applicable). This study is being conducted in the west Texas or southeast New Mexico region of the United States. Chi-square analyses will be used to assess associations between variables reported on the baseline provider knowledge, attitudes, and practice scales. We seek to examine self-assessed changes in provider attitudes and behaviors regarding HPV vaccine recommendation 1 month after receiving our unique multimedia and culturally tailored intervention.

Results: Research and data collection for this clinical trial began in December 2023. Participant recruitment was closed by May 2024 (N=128), with final data collection expected to be completed by December 2024.

Conclusions: This study team decided to report on the intervention protocol to help ensure transparency in the research process and facilitate the improvement of the research design. Tailored web-based educational programs for health care professionals, designed to address regional and patient population characteristics, may be a promising approach to enhancing the real-world implementation of clinical practice guidelines.

Trial Registration: ClinicalTrials.gov NCT05120869; http://clinicaltrials.gov/ct2/show/NCT05120869

International Registered Report Identifier (IRRID): PRR1-10.2196/60790

(JMIR Res Protoc 2025;14:e60790) doi:10.2196/60790

KEYWORDS

human papillomavirus; randomized controlled trial; HPV knowledge; HPV vaccine; health care provider; provider recommendations; communication strategies; Hispanic

Introduction

Overview

The human papillomavirus (HPV) is a primarily sexually transmitted infection that affects approximately 40 million Americans and is associated with 6 types of cancer [1]. A total of 3 HPV vaccines (nonvalent, quadrivalent, and bivalent) have been developed, licensed, and shown to be effective in preventing high-risk HPV infection. Current immunization guidelines recommend that children aged 11-12 years initiate a 2-dose HPV vaccine series but can begin as early as 9 years of age. Young adults older than the age of 15 years with no previous history of HPV vaccination can start a 3-dose series; the 9-valent HPV vaccine is also approved to protect against 73% of HPV-associated cancers for adults older than 26 years of age [2]. Although national vaccination rates in the United States have steadily increased over the years, vaccination rates for adolescents remain well below the 80% designated target goal set forth by Healthy People 2030 [3]. The need for this vaccine is particularly salient considering the high direct and indirect costs of HPV and associated cancers in the United States; for example, Ong et al [4] found that the average cost of HPV-related cancer and other diseases was approximately US $38,056 per case.

HPV Health Care Provider Recommendation Practices

Recent studies reveal that receiving a recommendation from a health care provider is a crucial factor influencing HPV vaccine uptake among parents of vaccine-eligible children and adults themselves [5-8]. However, in a study currently under review, many health care providers have reported that while they have sufficient knowledge and understanding about HPV and its treatment and prevention, they often lack the confidence to effectively communicate about HPV and recommend the vaccine to their patients. Similarly, some populations, such as adults, men, and sexual minority individuals (members of the LGBTQ+ [lesbian, gay, bisexual, transgender, and queer/questioning] community), are less likely to be encouraged to get vaccinated and tend to have inaccurate perceptions of the importance of vaccination [9]. Due to the need to improve training and resources for health care providers concerning HPV vaccine recommendation (in addition to the recommendation of other salient vaccines such as influenza and meningococcal vaccines [10,11]), researchers have explored the effectiveness of several approaches, theories, and foci when recommending HPV vaccination. The combined use of the presumptive approach (in which the provider assumes parents will vaccinate their child rather than communicating that the HPV vaccine is optional), along with motivational interviewing and a fact sheet for vaccine-hesitant clients, results in higher perceived levels of parental HPV vaccine acceptance [5]. Furthermore, studies [6,7] emphasize the importance of providing recommendations that "announce" the need for the HPV vaccine in a manner that is brief, easy to understand, and focused on cancer prevention.

Beyond the need for improved HPV vaccine recommendations among health care providers' nationwide, enhancing communication strategies is particularly important for health care providers practicing with racial minority populations, such as predominantly Hispanic populations residing along the United States–Mexico border. Recent literature has identified both barriers and facilitators that exist in trying to increase HPV vaccine uptake in a diverse and predominantly Hispanic community [12]. Similarly, a recent quantitative study revealed that HPV vaccine acceptability in Hispanic young adults is associated with several factors, including the number of HPV informational sources, number of HPV discussions, health care provider recommendations, having a health care provider with similar characteristics, and family vaccine perceptions [12]. Another study found that culture-based factors such as familism and trusted sources of information can predict HPV vaccine acceptance [13]. Additionally, Xu et al [14] demonstrated that patient-provider health communication strategies aimed at enhancing HPV vaccine uptake among racial minority patients must be culturally tailored for the intended population, while including approaches that increase provider self-efficacy, use persistent language, reframing vaccine conversation focus from sex to cancer, and working with the community to culturally sensitize vaccine-related language. All these findings highlight the importance of receiving HPV vaccine recommendations from health care providers in a culturally competent manner, as well as the importance of family in shaping perceptions and behaviors related to vaccinations.

Web-Based Health Care Professional Educational Interventions

To improve patient care and population health outcomes, health care providers rely on clinical practice guidelines (CPGs) to stay current with evidence-based recommendations [15]. However, the dissemination and implementation of guidelines, such as those for HPV vaccination and screening, vary across health professionals. While traditional print-based delivery methods for CPGs have largely shifted to digital platforms, digitizing guidelines on medical authority websites (eg, the Centers for Disease Control and Prevention [CDC]) have improved the access for health professionals. Despite improved access, time constraints often make it difficult for providers to actively search for and apply these guidelines without additional support. The absence of supportive modules that assist with real-world implementation, such as HPV recommendation practices, creates barriers to addressing gaps in care. Notably, research has shown that web-based medical educational modules can be as effective as in-person training in helping health care providers implement CPGs more efficiently [16].

Intervention Theoretical Framework

Elements of the Health Belief Model have been examined as predictors of HPV vaccine acceptance and uptake among adults in the United States–Mexico border region in a previous study conducted by the researchers [13]. This model demonstrates that a broad range of intersectional factors play a role in an individual's health choices and behaviors, such as perceived benefits (in this case, the belief that the HPV vaccine will prevent infection and cancer) and perceived severity, which have both been associated with HPV vaccine acceptance [13]. Frietze et al [13] also studied perceived safety and perceived harm as predictors of acceptance and uptake. Therefore, the proposed intervention has incorporated 4 tenets of the Health Belief Model (perceived benefits, severity, safety, and harm) into the intervention to increase provider vaccine recommendation practices and strategies. The tailored intervention also builds on educational models including HPV biology, epidemiology, and disease morbidity, coupled with role-played conversations in clinical video vignettes using the "announcement" approach, in which the health care provider works from the presumption that patients or parents will accept the vaccine. The research question is, will health care providers receiving a web-based, culturally tailored, HPV-specific professional skills intervention report stronger HPV prevention recommendation behaviors at 0-3-6 months post intervention, compared to health care providers receiving a web-based intervention using publicly available CDC HPV provider materials and general communication skills modules?

Research Aims and Hypothesis

This study is guided by 2 aims. Aim 1 is to assess the knowledge, practices, and beliefs of emerging and current health care providers in the Paso del Norte Region related to HPV prevention, HPV vaccine, and HPV-associated cancers. Aim 2 is to facilitate the prevention of HPV-associated cancers in the Paso del Norte Region through strengthened recommendation of the HPV vaccine and screening by health care providers.

It is hypothesized that health care providers receiving a web-based, culturally tailored, HPV-specific professional skills intervention will report higher between-group changes in proportions on the HPV health care provider (HCP) practices scale at 0, 3, and 6 months post intervention, compared to health care providers receiving the standard web-based CDC HPV provider materials and communication skills active control intervention.

Methods

Ethical Considerations

This study was approved by the University of Texas at El Paso institutional review board (#1441487). Participation in the study was voluntary and confidential. All potential participants who were screened and met eligibility were invited to join the study and provided informed consent. Informed consent covered primary and secondary data collection procedures and data analysis and dissemination following the completion of the study. Participants consented to relinquish the ownership of anonymous data to the research team for dissemination (primary and secondary analysis). All study data will be deidentified and survey responses will be anonymous. Participants are compensated in the form of a US $30 electronic gift card for the completion of the initial survey and a US $10 electronic gift card for the completion of each of the follow-up surveys (US $50 total throughout the course of the study). The study information sheet made clear to participants that they were free to withdraw from the study at any time with no consequence to them, and withdrawal protocols with contact information were included.

Study Trial Design

We will conduct a mixed (within-between) subjects longitudinal design in which participants are randomly assigned to 1 of the 2 conditions and will be assessed over 3 time points using a parallel group design to examine the effectiveness of a tailored versus a standard HPV education and professional skills intervention. Emerging and current health care providers will be randomly assigned to 1 of the 2 conditions. (1) Treatment condition in which they will receive a tailored Education and Professional Skills Intervention and (2) control condition in which they will receive general, publicly available (ie, CDC) information about HPV and communication skills. Participants will then be followed over 3- and 6-month time frames, and group differences will be assessed. Furthermore, this clinical trial protocol will follow the CONSORT-EHEALTH (Consolidated Standards of Reporting Trials of Electronic and Mobile Health Applications and Online Telehealth) to report the internet-based educational modules (behaviorally based treatment) [17]. The completed itemized checklist instrument is provided in Multimedia Appendix 1.

Study Setting

The intervention is internet based, and participants will complete the survey using personally owned computers, tablets, or cell phones. This study is based on, deployed in, and will reach health care providers primarily in the Paso Del Norte Region, which includes El Paso County, Texas, and Southern New

Mexico, including Dona Ana County, and the cities of Alamogordo, Hobbs, Artesia, Roswell, and Lovington. The population is predominantly Hispanic, with 82.9% (718,964/867,239) of the population of El Paso County, Texas, identifying as Hispanic or of Latin ancestry, and 50.2% (1,061,413/2,114,371) of the population of the State of New Mexico identifying as Hispanic or of Latin ancestry [18,19].

Community Advisory Board

A community advisory board was formed, as community advisory boards have previously demonstrated to be effective when planning health-related programs and interventions to facilitate meaningful and structured engagement with local community members [20]. Our community advisory board consisted of a formalized collective of community members, research stakeholders, regional clinical partners, and other academics from several institutions, including The University of Texas at El Paso, Texas Tech University Health Sciences Center El Paso, and New Mexico State University. The community advisory board was instrumental in providing insight into the local community while providing insight to develop equitable partnerships with the community. The community advisory board has been involved in all phases of the intervention development, from the reconnaissance phase to the intervention's development, and will remain a vital component of the intervention until the study has concluded and results are evaluated. To date, the community advisory board has met periodically and has been provided with a report of ongoing project-related activities and project progression. All community advisory board feedback and suggestions have been taken into consideration and retro fed back into project-related activities.

Acceptability, Pretest, and Pilot

All components of the clinical trial (survey, control and experimental intervention modules, recruitment plan, and communications) underwent multiple rounds of review and revision by members of the research team. In addition, the intervention and survey were pilot-tested with a small group (n=7) of health care providers in training or in practice, and feedback from those individuals was incorporated into the final products. For example, demographic questions such as participant gender were changed to reflect participant's concerns on gender identity (to include nonbinary and gender nonconforming individuals). For example, "Which of the following best describes your gender identity: male, female, transgender male, transgender female, gender variant/nonconforming, prefer not to answer," and an "other" option which permits text entry. In addition, the pilot test helped to clarify questions regarding previous HPV infections: "How likely do you think it is that you have ever been infected with HPV?" and "How likely do you think it is that your current or recent partner(s) has (have) ever been infected with HPV?" A question was added to elicit the zip code in which the participant primarily practices or trains in, and the amount of time it would take to complete the study was adjusted.

Consolidated Standards of Reporting Trials Flow Diagram

Progress through the phases of this planned randomized trial (ie, enrollment, intervention allocation, follow-up, and data analysis) will be visually represented using the CONSORT (Consolidated Standards of Reporting Trials) flow diagram [17]. A participant is considered to have completed the study if they have completed the initial postintervention assessment and the 3-month and 6-month follow-up assessments.

Intervention Materials

The intervention materials and survey were developed and produced by members of the research team based on, and in alignment with, a health care provider survey and a community needs assessment conducted under the larger parent study [13,21]. HPV knowledge, practices, and beliefs will be assessed, as was done previously in formative research, with additional questions that further assess in-depth provider recommendation behaviors for HPV vaccination that is inclusive of vaccine-eligible age groups and genders. We will also inquire about provider comfort in communicating with patients about sexual health topics, vaccines, and cancer.

Participants will be randomly assigned to 1 of the 2 conditions: (1) the treatment condition, in which they receive the tailored HPV Education and Professional Skills Intervention, and (2) the control condition, in which they receive the General Education and Professional Skills Intervention. An internet-based platform will be developed to deploy the HPV Education and Professional Skills Intervention to emerging or current health care providers. The platform will be comprised of training modules divided into 3 sections paralleled among control and experimental groups—a document to be read, a video to be watched, and an activity to complete. Participants will take 15-30 minutes to complete all 3 sections of the module.

Control Group Materials

The control group (active comparator) will receive the General HPV Education and Communication Skills Intervention materials, which will be comprised of a 3-page PDF document, a web-based video, and 4 rank-order multiple-choice questions to answer. The PDF document will be a standard, publicly available HPV fact sheet from the CDC. The video contains information on improving basic communication skills as would occur in a business or interpersonal setting. The multiple-choice questions will ask the participant to select their preferred mode of communication (ie, email, text, phone call, or face-to-face) in different scenarios.

Experimental Group Materials

The experimental treatment group will receive the tailored HPV Education and Communication Skills Intervention materials, which comprised the same categories of content as in the control intervention. In this case, the 3-page PDF document is modeled after the CDC HPV fact sheet but includes data from the first phase of our program and informs the reader of important and relevant research findings from our region. The video was produced in-house and scripted to focus on improving provider communication with patients, specifically regarding HPV, the HPV vaccine, and addressing vaccine hesitancy. The

multiple-choice questions are presented as clinical vignettes with response options that address patient concerns, and participants will rank them in terms of their perceived effectiveness.

Thus, the control module will engage participants to improve general communication skills and increase baseline knowledge about HPV, HPV vaccine, and HPV-associated cancers. The experimental intervention module, in contrast, will specifically engage participants to improve patient-provider communication and strengthen HPV vaccine recommendations through (1) identifying critical points of discussion regarding the HPV vaccine and patient health; (2) encouraging discourse on vaccines that are optional (eg, influenza) for patients; (3) sharing best practices for discussing vaccines with patients or parents who are vaccine-hesitant; (4) increasing provider understanding about generalized and region or culture-specific reasons for vaccine hesitancy among patients; and (6) facilitating increased knowledge about HPV, the vaccine, and its cancer relevance.

Surveys are to be delivered 3 and 6 months after the initial intervention, and the survey will again evaluate provider knowledge, practices, and beliefs regarding HPV, HPV vaccine, and cancer and will also specifically assess changes in provider behavior since the intervention. Uptake of the HPV vaccine by the provider or their children, assuming eligibility, will be tracked, as will provider recommendation behaviors and levels of comfort in interacting with patients when issues of sexual health, vaccine hesitancy, or cancer prevention arise.

Study Outcome Measures

Provider Practices

The primary outcome of interest is between-group changes in proportions of provider practices. This will be measured on the 8-item HPV HCP practices scale (HCP vaccine recommendations, HCP screening recommendations, and HCP communication practices) scored on a Likert scale from never (1) to always (5). A composite score is developed that creates an average score for HCP vaccine recommendations, HCP screening recommendations, and HCP communication practices. Postintervention practices of health care providers will determine change in both strength and frequency of recommending the HPV vaccine to patients.

The secondary outcomes of interest include understanding provider beliefs and provider knowledge. These will be measured on previously validated scales adapted from the Vaccine Attitudes and Knowledge Survey (VAKS) [13,21].

Provider Beliefs

Provider beliefs (ie, attitudes toward HPV vaccine) will be measured using the 9-item HPV vaccine attitudes scale (perceived safety, perceived harm, and perceived effectiveness) scored on a Likert scale from strongly disagree (1) to strongly agree (5). A composite score is developed which creates an average score for perceived safety, perceived harm, and perceived effectiveness.

Provider Knowledge

Provider knowledge about HPV and the HPV vaccine will be measured using a previously adapted 14-item HPV knowledge scale scored as true (1) or false (0) [13,21]. A composite score is developed which creates an average score for 14 items and then multiplying by 100 to calculate a percentage.

Participants

Participants will be recruited from the health care provider population in El Paso County, Texas, and Southern New Mexico. Both current (in practice) and emerging (in training) practitioners in the professions of medicine (ie, doctor of medicine, doctor of osteopathic medicine, physician assistant, nurse practitioner, pharmacy, or nursing) are eligible to participate in the study. To qualify, participants must be a current (in practice) or emerging (in training—student, resident, or fellow) health care provider, be between the ages of 18 and 65 years, be working, training, or living in the Paso del Norte Region (ie, El Paso County, TX-Southern New Mexico), have computer or internet literacy and access to an electronic device with internet access (eg, cell phone, tablet, and computer), and have the authorization to recommend the HPV vaccine. Participants will be excluded from the study if they are not affiliated with the El Paso United States–Mexico border region, have not previously participated in phases I or II of the larger parent research project, do not identify as a current or emerging health care provider, decline or are unable to participate in the full intervention and follow-up time points, or are unable to complete participation and activities in the English language.

Recruitment

Recruitment took place over 6 months, from December 2023 to May 2024. No critical secular events fell into this study period. Participants who were eligible and agreed to participate in the study will be active in the project for 7 months post-initial recruitment. This time frame starts at the time of recruitment and ends at the final 6-month follow-up time point. Researchers used a purposive sampling technique to recruit participants through multimedia (ie, print and email) and professional network contacts. The study participants were recruited from (1) the main campus and some regional clinical hubs of the Burrell College of Osteopathic Medicine; (2) the University of Texas at El Paso College of Health Sciences, College of Nursing, and School of Pharmacy; (3) federally qualified health centers in the Paso del Norte Region; (4) private provider clinics; and (5) other health care workers and professional network connections that provide training and services to the Paso del Norte region residents. Special attention will be given to recruit practitioners in the specialties of pediatrics, family medicine, and obstetrics and gynecology due to their increased familiarity with vaccines, HPV, and cancer. All participation is entirely web-based. Once the participant is deemed eligible and agrees to participate, they will be provided with a study information sheet outlining that their participation is voluntary, and they can opt out at any time. Participants will be compensated for their time with a US $30 electronic gift card after completion of the initial training session and surveys (~30 minutes). Participants will receive email reminders to complete each of the 2 follow-up survey sessions at 3 and 6 months after

completing the initial intervention, as well as an additional US $10 electronic gift card for participating in the follow-up survey sessions (~20 minutes per survey questionnaire).

Randomization, Treatment Allocation, and Concealment

Sequence Generation

After determining eligibility, we will randomize participants on a 1:1 basis to intervention groups (experimental vs control) while controlling for the potential bias introduced by factors of sex, age, and career stage. To achieve this goal, we will use a randomization table within the REDCap (Research Electronic Data Capture; Vanderbilt University) platform to create balanced treatment groups based on these factors and reduce the effect of selection bias [22].

Concealment

This study is double masked (ie, participant and outcomes assessor). Participants will be randomly assigned to treatment and control groups; they will not be made aware of other participants' receipt of treatment or control materials. Participants will be asked not to discuss this project outside of the intervention; delivery of the intervention or other educational materials will be internet-based, limiting the ability of participants to interact with one another during the study. Furthermore, to reduce bias in the implementation and assessment of the clinical trial (eg, outcome assessor), participant information and pre-post survey responses will be maintained separately from the assignment and delivery of the intervention.

Measures

All the survey questionnaire measures or instruments will be made available electronically in English.

Screening Questionnaire

Participants completed a screening questionnaire delivered via the REDCap platform to determine their eligibility to participate in the study or intervention [22]. The questionnaire will assess items such as age, geographical location, and health care provider education status (ie, MD, DO, PA, NP, PharmD, or RN) of the potential participant. The questionnaire will also assess their comfort with auditory and visual content in the English language, and if they had prior participation in the earlier phase of this study. The screening questionnaire requires approximately 3 to 5 minutes to complete. Upon successful completion of the screening questions, participants will read and sign the consent form indicating that they agree to participate in the study.

Demographic and Background Questionnaire

The demographic and background questionnaire via the REDCap platform will gather demographic information (eg, age, gender, ethnicity, and income), as well as information about family composition, HPV vaccination status, trusted sources for medical information, general feelings about vaccines, trust in the government, and experiences with the recent COVID-19 endemic [22]. The demographic survey will only be administered at baseline prior to administering the intervention. The demographics survey requires approximately 5 to 8 minutes to complete.

Postassessment

A post-assessment via the REDCap platform will be administered at baseline (immediately following intervention), 3 months, and 6 months [22]. The post-assessment will include a modified version of the VAKS [13,21] to self-assess factors that influence levels of comfort in discussing HPV-related topics, patient-provider communication about HPV, vaccines, cancer risk, and additional questions designed to evaluate the impact of the interventions and the actual changes in practice in terms of vaccine uptake, patient communication, and vaccine recommendation behavior. Moreover, the outcome variables are included in the post-assessments such as the self-assessment of the proportions of provider practices (as indexed by the HCP practices scale), provider beliefs (as indexed by the HPV vaccine attitudes scale), and provider knowledge (as indexed by the HPV knowledge scale). These will be measured on previously published scales adapted from the VAKS [13,21]. In a previous study that administered the VAKS, Cronbach α ranged from 0.70 to 0.90 for the various scales included in the survey [13]. The post-assessment requires approximately 25-30 minutes to complete.

Data Collection and Management

All study data will be collected using REDCap [22], a password-secured internet-based software application system developed to design and manage web-based databases and surveys, hosted at The University of Texas at El Paso. All data collected will be deidentified. REDCap will be maintained by the College of Science at The University of Texas at El Paso [22]. Data will remain stored for up to 5 years after completion of the study. Only the study team will have access to the data, as the team has received training on maintaining research data confidentiality, responsible conduct of research, and research ethics with human participants. Data will be accessed through password-protected and encrypted computers.

Analytical Methods

All statistical analyses will be conducted using SPSS (version 26.0; IBM Corp) and R (version 4.0.3; R Core Team) and will use 2-tail α to reject null hypotheses at .05. Prior to conducting analyses, data will be screened to ensure that statistical assumptions are met and any transformations or adjustments to the model will be used. We may use multiple imputation procedures to handle missing data. Descriptive statistics will be reported for demographic variables including age, sex, gender, and health professional degree or field. A power analysis estimating repeated measures within-between interaction, assuming a small effect size (f=0.15), determined that approximately 110 total participants are required to provide an 80% chance of detecting an effect between the 2 experimental conditions (tailored intervention vs active control) across 3 time points (0, 3, and 6 months postintervention). To account for an estimated 10%-15% attrition, at least 100 participants needed to be recruited.

Study Outcomes

The chi-square analyses will be used to assess associations between variables reported on the baseline provider knowledge, attitudes, and practice scales. Repeated measures mixed ANOVA with α set to .05 will examine whether change in our outcome variables (self-assessment of the proportions of provider practices, as indexed by the HCP practices scale), provider beliefs (as indexed by the HPV vaccine attitudes scale), and provider knowledge (as indexed by the HPV knowledge scale) is the result of the interaction between the experimental condition (tailored intervention vs active control) and time (at 3 time points) [23]. If no interaction emerges, we will conduct follow-up tests to determine whether any change in our outcome variables are due to one of the factors (experimental condition or time). We will calculate the Mauchly test of sphericity for each ANOVA, and the Huynh-Feldt epsilon test or Greenhouse-Geisser correction to the degrees of freedom of the *F*-ratio will be reported for each significant effect [23-25]. We may use multiple imputation procedures to handle missing data (if applicable).

Future Directions and Plans for Dissemination

Plans for the dissemination of our findings include publication in peer-reviewed scholarly journals and presentation at scientific conferences, but we are also committed to sharing our data with the community that supports and contributes to this work. For both providers and patients, it is important to base medical decision-making on relevant and up-to-date information. Our findings will also be shared with health care providers in practice and in training at the institutions and locations in which our participants were included. Data will be reported in aggregate form, with no identifying information shared. This data may further be incorporated into the curriculum followed by providers in training in the Paso del Norte region and beyond.

Results

Overview

A larger parent grant (NIH/NIMHD 2U54MD007592) was funded in October 2019. Data collection of this subproject, a provider-focused randomized controlled trial (RCT), began in December 2023, with a total of 128 participants recruited by the closing of recruitment in May 2024. Primary data collection was completed in December 2024. As of March 2025, data analysis is in progress, with publication of results anticipated in winter 2025.

Study Outcomes

Provider Practices

Results of the ANOVA model assessing the primary outcome of between-group changes in proportions of provider practices will be summarized and presented in tables and visuals.

Provider Beliefs and Provider Knowledge

Results of the ANOVA model assessing secondary outcomes of understanding provider beliefs and provider knowledge will be summarized and presented in tables and visuals.

Discussion

Principal Findings

The goal of this RCT was to develop and deploy an educational and professional skills intervention to increase health care provider HPV prevention recommendation scores. This is a critical factor in cancer prevention, and multiple factors contribute to the observation that, while HPV vaccine uptake in our region is higher than in many other regions, it still falls short of national targets. We anticipate finding that health care providers who receive our experimental intervention materials (culturally tailored videos specifically targeting effective HPV vaccine-related communication strategies) will demonstrate improved and more frequent HPV vaccination recommendation practices and behaviors with their patients, as compared to health care provider participants who receive the control materials (standard CDC-issued materials).

Comparison to Prior Work and Strengths

Our approach to intervention with health care providers is not particularly novel, nor is the intention to increase provider vaccine recommendations since it has been well-established that provider recommendation is one of the most critical factors in patient decisions to get vaccinated [26]. What is innovative in our approach, however, is how we engage with and tailor skills-based training for providers in our region. The initial evaluation of provider knowledge, practices, and beliefs about HPV and the HPV vaccine informed us that HPV-related knowledge among providers is high. An intervention that provides additional education on HPV, the vaccine, and cancer was thus likely to have limited benefit and would not be a valuable use of provider time. In contrast, our intervention focuses on supporting the professional development of providers in the domains of modifying their own behavior and improving communication with patients. Increasing provider awareness of biases in vaccine recommendation and delivery, increasing their comfort in discussions about sexual health topics, and supplying them with tools for addressing patient hesitancy associated with vaccination were determined by our group to be more likely to produce the desired results.

A second way in which our research is innovative is to focus on emerging health care providers. Engaging with this group has the potential to produce multiple positive outcomes, including (1) increased vaccine uptake since many individuals in this group are vaccine-eligible but remain unvaccinated, (2) normalization of vaccine-related discussions in patient care if this becomes a consistent component of provider training, and (3) strengthened vaccine recommendations as the providers themselves serve as role models for vaccination to their patients. Third, we are committed to improving vaccine recommendation behavior by providers that serve a binational, majority-Hispanic population that is medically underserved and faces multiple barriers to vaccination. Previous work has shown that Hispanic women have high HPV vaccine acceptability [27], but this may vary based on age and birth origin [28].

Limitations

This study recruited an internet population of health care providers in the United States–Mexico border region; therefore, findings may not directly translate to other health care provider populations nationally or globally. Furthermore, this intervention did not provide Continuing Medical Education (CME) credit, which would limit uptake outside of an RCT setting. Study participation involved a relatively large time commitment for providers in practice, which worked against recruitment and survey completion. We may, therefore, be somewhat limited in our ability to conduct subanalyses such as comparisons across provider specialties (eg, pediatrics vs family medicine) or other participant characteristics (eg, ethnicity or income level). As we have gathered data from health care providers in medicine, nursing, and pharmacy, different approaches to patient care in these professions may increase variability in the responses obtained. A pretest of HPV and vaccine-associated practices was not done in our study, and the use of solely self-reported data may be incomplete or may contain bias. Our random assignment of participants into control and experimental groups should protect against baseline group differences; however, we will still be able to determine the persistence of any changes in behavior regardless of participant starting point. If any group of providers demonstrates high vaccine recommendation rates at the onset of the study, it will be difficult to determine a statistically significant increase in behavior in response to the intervention. Still, identifying providers with strong recommendation practices will be of benefit to our project. Finally, we anticipate the loss of a limited number of participants through attrition over time for many possible reasons, perhaps reducing the power of our study and our data analysis capabilities at the 3- and 6-month time points.

Conclusions

To improve population health, it is essential to look beyond interventions aimed solely at patient populations. Web-based educational programs for health care professionals are promising tools for enhancing the real-world implementation of CPGs. Tailoring these provider-level interventions to account for regional and patient population characteristics can also improve patient-provider communication as clinical guidelines evolve. Until HPV and other vaccine-preventable infections are eradicated, collaboration between health researchers and providers is critical to delivering accessible and effective professional development interventions. Furthermore, beyond reporting research findings of such studies, reporting specific intervention protocols helps ensure transparency in the research process and facilitates the improvement of population health interventions.

Acknowledgments

The authors would like to thank the university and community partners, especially key representatives from local federally qualified health centers and both The University of Texas at El Paso College of Health Sciences and the College of Nursing, for assisting in the recruitment process. The authors would also like to thank all the members of the advisory committee for their contributions and support of the ongoing project. This paper was completed through funding (grant 2U54MD007592) by the National Institute on Minority Health and Health Disparities (NIMHD), a component of the National Institutes of Health (NIH). A Diversity Supplement supported author JM (grant 3U54MD007592-28S3) from the NIMHD/NIH. One of the authors (JIC) was supported by a research fellowship funded under the University of Texas Health Science Center at Houston (UTHealth) School of Public Health Cancer Education and Career Grant Development Program, National Cancer Institute/NIH Grant (T32/CA057712).

Data Availability

The datasets generated or analyzed during this study are not publicly available as they are stored in the REDCap (Research Electronic Data Capture) repository maintained by the University of Texas at El Paso and subject to institutional access restrictions but are available from the corresponding author on reasonable request.

Authors' Contributions

EMM, KG, and JIC conceptualized the study with critical input from KLL, MW, and JM. JIC, KLL, MW, and JM wrote the first draft, and EMM, KG, and JIC gave critical input throughout the study development and contributed to the paper revisions. All authors contributed and approved the final study. No artificial intelligence was used in any portion of the paper development.

Conflicts of Interest

None declared.

Multimedia Appendix 1
CONSORT-eHEALTH checklist (V 1.6.1).
[PDF File (Adobe PDF File), 1253 KB - resprot_v14i1e60790_app1.pdf]

Multimedia Appendix 2

Peer-review report from the External Advisory Committee for the National Institutes of Health (NIH) Research Centers in Minority Institutions (RCMI) Program - Border Biomedical Research Center at the University of Texas at El Paso (National Institutes of Health, USA).
[PDF File (Adobe PDF File), 171 KB - resprot_v14i1e60790_app2.pdf]

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Abbreviations

CDC: Centers for Disease Control and Prevention
CME: Continuing Medical Education
CONSORT: Consolidated Standards of Reporting Trials
CONSORT-EHEALTH: Consolidated Standards of Reporting Trials of Electronic and Mobile Health Applications and Online Telehealth
CPG: clinical practice guideline
HCP: health care provider
HPV: human papillomavirus
LGBTQ+: lesbian, gay, bisexual, transgender, and queer/questioning
RCT: randomized controlled trial
REDCap: Research Electronic Data Capture
VAKS: Vaccine Attitudes and Knowledge Survey

Edited by T Leung; submitted 22.05.24; this is a non–peer-reviewed article;accepted 21.10.24; published 03.04.25.

Please cite as:
Martinez J, Cordero JI, Whitney M, LaRoche KL, Frietze G, Moya EM, Gosselink K
Web-Based Human Papillomavirus Education and Professional Skills Intervention for Health Care Providers: Protocol for a Randomized Controlled Trial
JMIR Res Protoc 2025;14:e60790
URL: https://www.researchprotocols.org/2025/1/e60790
doi:10.2196/60790
PMID:

Protocol

Effects of Using a Smart Bassinet on the Mental Health of Military-Affiliated Pregnant Women: Protocol for a Randomized Controlled Sleep Health and Mood in Newly Expectant Military Mothers (SHINE) Trial

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Abstract

Background: Postpartum mood and anxiety disorders (PMADs) are higher among pregnant military service women (26%) and military spouses (12.2%) compared to the civilian population (10%-15%). This is partly due to military-specific factors, including deployment, which are known to increase risk. Important risk factors for PMADs include sleep disturbances, defined as sleep deprivation, insomnia, or poor sleep quality, which are more are common among military-affiliated pregnant women.

Objective: This study describes a protocol for a new randomized controlled trial that aims to ameliorate the risk for PMADs through improving infant sleep or maternal sleep during the first 6 postdelivery months in a sample of military-affiliated women.

Methods: This study is a 6-month, parallel-arm, randomized controlled trial. Pregnant women (N=342) in the third trimester will be randomized at 1:1 ratio to use a smart bassinet (SB) or a standard commercially available bassinet (HALO BassiNest Swivel Sleeper 3.0; traditional bassinet [TB]) for up to 6 months after delivery. Participants will have their infants sleep in the bassinet, complete monthly web-based questionnaires, and record sleep data with diary and actigraphy for both the participants and their infants for 1 week each postpartum month. Blood samples will also be collected at baseline (late pregnancy) and at 3 months and 6 months post partum to assess immune functioning. The primary outcomes for this study will be postpartum mood (depressive and anxiety symptoms) and infant and maternal sleep. In addition, we are evaluating whether SB has a significant impact on immune functioning—a marker that physiologically connects sleep and mood symptoms.

Results: Recruitment for this study began in January 2025. Six separate mixed 2 (treatment vs control) × 6 (assessment period) multivariate analysis of variance and analysis of variance models will be conducted to test the hypotheses that SB will have a greater impact on infant and maternal sleep than TB, SB will be associated with a greater reduction in postpartum mood symptoms than TB, and immune system function will be less dysregulated in birthing individuals using SB compared to those using TB. Lastly, we will evaluate whether the elevated risk demonstrated by previously identified postpartum depression epigenetic biomarkers in the *TTC9B* and *HP1BP3* genes can be modified with an SB. We hypothesize that the elevated risk will be reduced in SB compared to that in TB.

Conclusions: At the conclusion of this project, we will have gained a thorough understanding of the capability of SB to positively affect infant and maternal sleep compared to the traditional sleep arrangement and its impact on maternal mood through 6 months post partum in military-affiliated women. The promotion of sleep health in both mothers and infants may be an accessible and amenable method to prevent PMADs.

Trial Registration: ClinicalTrials.gov NCT06544941; https://clinicaltrials.gov/study/NCT06544941

International Registered Report Identifier (IRRID): PRR1-10.2196/66439

(JMIR Res Protoc 2025;14:e66439) doi:10.2196/66439

KEYWORDS

maternal health; postpartum; pregnancy; sleep; infant; depression; anxiety; smart bassinet; intervention; prevention; military

Introduction

Postpartum mood and anxiety disorders (PMADs) are the most common and disabling complications of childbearing. They are often underdiagnosed and undertreated [1]. PMADs are recognized to seriously affect both mother and baby [2,3]. In fact, mental health conditions are a leading contributor to maternal morbidity, with suicide as a major cause of postpartum death. According to the Department of Defense, the number of females in the US military constituted 17.3% of the total force in 2021 [4]. Research indicates that the rate of PMADs in active-duty women can range from 20% to 26% [5-7], with slightly lower rates among military spouses at around 12.2%. Although these rates are similar to that reported in the civilian population (~10%-15%) [8-10], when other factors such as deployment are considered, the rates vary dramatically, reaching as high as 50% [11-16]. Women with spouses who are deployed have more frequent diagnoses of depressive disorders, sleep disorders, anxiety, acute stress reactions, and adjustment disorders compared to women without a deployed spouse. Despite these elevated risks, this segment of our population has been insufficiently evaluated as it pertains to PMAD risk and warrants further attention.

It is well appreciated that sleep disturbance is associated with both new and recurrent depressive and anxiety episodes in all populations, especially perinatal women [17-22]. Sleep disturbance often precedes the development of mood disorders [23,24]. Indeed, sleep issues lasting for at least 2 weeks increase the risk for the future development of mood disorders [25,26] and are a criterion for the diagnosis of depression in the Diagnostic and Statistical Manual of Mental Health Disorders, Fifth Edition, Text Revision (eg, major depressive disorder) [27]. Sleep disturbances, both in prevalence and severity, in military-affiliated women extend beyond what civilian women experience. Active-duty service members and their spouses experience unique stressors that often exacerbate sleep issues [28,29]. Despite this, there are limited empirical data regarding sleep disturbances among military-affiliated women.

Infant sleep problems further contribute to significant maternal sleep issues [30-32] and maternal mental health consequences, regardless of the mothers' depression history [32-34]. Mothers who report poor infant sleep behavior have significantly more depressive symptoms than mothers who report good infant sleep [35-37]. There is some evidence that maternal sleep quality is a mediator of this relationship [35]. Persistent, rather than transient, infant sleep issues contribute to maternal depression, poor sleep, and poor family functioning well into toddlerhood [33,38,39]. We propose that focusing and intervening on infant sleep is a viable pathway to improve maternal sleep and well-being.

Here, we describe the protocol for a randomized controlled trial (RCT; Clinical Trials.gov CT94252410690; Sleep Health and Mood in Newly Expectant Military Mothers [SHINE]) with the following aims.

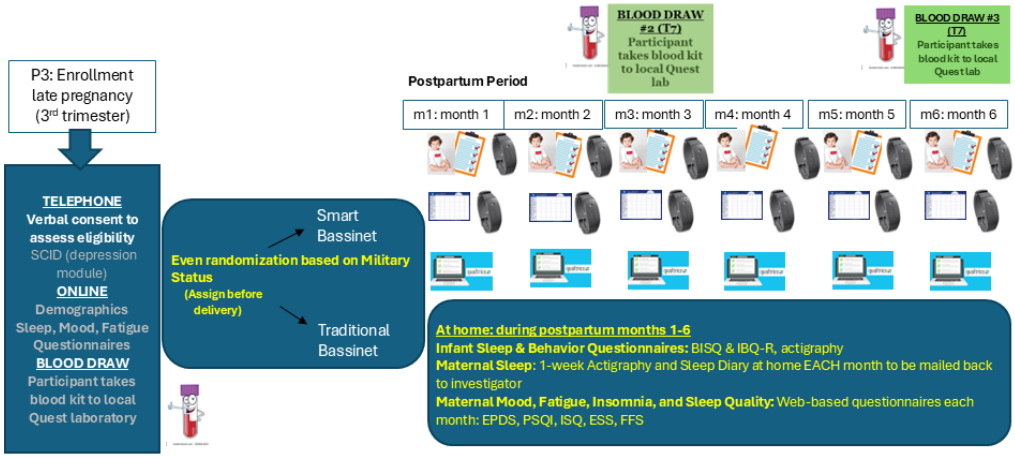
1. Determine whether the use of a smart bassinet (SB) augments infant sleep and improves maternal sleep during the first 6 months post partum compared to the use of a traditional bassinet (TB). (1) Hypothesis 1a: Infants who sleep in SB will have better sleep (ie, diary and Brief Infant Sleep Questionnaire as maternally reported) [40] than those who sleep in TB. Outcomes will include maternally reported sleep duration, awakenings, as well as objectively assessed (actigraphy) wake after sleep onset and sleep onset latency. (2) Hypothesis 1b: Mothers of infants who sleep in SB will have better subjectively reported (ie, diary and Pittsburgh Sleep Quality Index) and objectively assessed (actigraphy) sleep compared to those of infants who sleep in TB. Outcomes will be the same as those for infants.
2. Determine the effect of SB on maternal postpartum depressive and anxiety symptoms and evaluate the model that the association between SB and postpartum depressive symptoms is mediated by both infant and maternal sleep. (1) Hypothesis 2a: Mothers of infants who sleep in SB will have fewer postpartum depressive symptoms over time (ie, Edinburgh Postnatal Depression Scale) compared to those of infants who sleep in TB. (2) Hypothesis 2b: SB improves infant sleep, which then predicts better maternal sleep, and thereby predicts lower maternal depressive symptoms.
3. Compare the trajectory of immune system function from late pregnancy through post partum between participants with and without PMADs and between SB and TB groups. (1) Hypothesis 3a: Peripheral cytokines, immune cells, and stimulated cytokine profiles of women with PMADs assessed in late pregnancy and at 3 and 6 months post partum will indicate greater innate immune activity compared to those of women without PMADs. (2) Hypothesis 3b: Mothers of infants who sleep in SB will exhibit lesser innate immune dysfunction than mothers of infants who sleep in TB.
4. Exploratory aim: Evaluate whether the elevated risk demonstrated by previously identified PMAD epigenetic biomarkers at the TTC9B and HP1BP3 genes can be modified by using an SB. We hypothesize that the elevated risk will be reduced in the SB group compared to that in the TB group.

Methods

Study Design

This study is a 2-arm, parallel-group RCT. Participants will be randomized at 1:1 ratio to either SB group or TB group. Outcomes are assessed at 7 timepoints (Figure 1): late pregnancy (P3) and in postpartum months 1-6 (M1-M6).

Figure 1. Flowchart in this study. BISQ: Brief Infant Sleep Questionnaire; EPDS: Edinburgh Postnatal Depression Scale; ESS: Epworth Sleepiness Scale; FFS: Flinders Fatigue Scale; IBQ-R: Infant Behavior Questionnaire-Revised; ISQ: Insomnia Symptom Questionnaire; PSQI: Pittsburgh Sleep Quality Index; SCID: Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders-5.



Ethics Approval

This study has been approved by the institutional review board of the University of Colorado Colorado Springs (#2024-071) and the Office of Human Research Oversight (US Army Medical Research and Development Command). The SHINE trial was previously registered with Clinical Trials.gov (CT94252410690). This protocol follows recommendations from CONSORT (Consolidated Standards of Reporting Trials) 2010 statement checklist (Multimedia Appendix 1) and guide [41]. All participants will be required to provide informed written consent prior to enrollment. Participation is completely voluntary, and the participant has the right to withdraw at any time. All participants will be assigned a 6-digit ID number to be used so that all data collected will be deidentified. Participants will be compensated for their time. There are 7 timepoints in this study. At baseline (late pregnancy), participants will be compensated US $100; at postpartum months 1, 2, 4, and 5, they will be compensated US $50 for data collection, and at postpartum months 3 and 6, they will be compensated US $100. At baseline and at postpartum months 3 and 6, they will provide a blood sample.

Participants

At the time of recruitment (P3) (third trimester), participants will complete a screening survey to determine their eligibility. Eligible pregnant women (N=342) will be recruited nationwide. The inclusion criteria were pregnant military-affiliated individuals with a singleton gestation; age 18-45 years; ability to communicate in English during the screening process; access to a computer, smartphone, or tablet with internet service; willing to use the bassinet they are randomized to; and willing to travel to a local Quest Diagnostics (an insert description) for blood draw. The exclusion criteria were presence of a depressive or anxiety disorder assessed over videoconference using the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders-5-Clinical Version mood disorders section [42]; current active suicidal ideation, medical or psychiatric instability, or active substance abuse or dependence during the last 90 days; plans to co-sleep with infant; younger than 18 years or older than 45 years; multiple gestations; type 1 diabetes; congenital fetal anomalies; tobacco use (current); self-reported, untreated comorbid sleep disorders, including narcolepsy, periodic leg movement disorder, or obstructive sleep apnea; and current use of psychotropic or sleep medications.

Procedures

Recruitment and Consent

Advertisement for this study will take place primarily online (social media) and through partner advocates (Postpartum Support International and Maternal Mental Health Leadership Alliance). Pregnant military-affiliated individuals who reside in the United States are eligible. Interested participants will contact the study coordinator for additional information and initial eligibility screening, including verification of military status.

Telephone Interview and Screening

Participants who meet initial inclusion criteria and have completed the consent and baseline questionnaires will be contacted for a telephone interview to assess further eligibility. The interview will contain items of the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders-5-Clinical Version [42] and the Structured Clinical Interview for Sleep Disorders-Revised [43]. Eligible participants will be randomly assigned to either SB group or TB group. The SB will be shipped to the participants and returned after M6 at no expense to them. TB group participants will be shipped a standard bassinet (HALO BassiNest Swivel Sleeper) to keep. Mother-infant dyads (up to N=342) will be randomly assigned to conditions by using a random number generating program found on a widely used and reputable website [44]. We will perform 1:1 randomization. Variability in the length of bassinet usage may be impacted by size of infant, parental preference, or infant temperament. However, data will be collected through 6 months post partum.

Data Collection

For each assessment (Figure 1), all participants will receive an email with a REDCap (research electronic data capture) link for web-based data collection. All web-based survey data will be published in accordance with the CHERRIES (Checklist for Reporting Results of Internet E-Surveys) checklist. To mitigate

and minimize the possibility of missing data in the measures, we will program electronic questionnaires to prevent skipping questions. REDCap is a web application and back-end database model designed to support data capture for research studies. REDCap is an open-source tool developed by Vanderbilt University to build and manage web-based forms for data collection. REDCap was developed specifically based on guidance from the Health Insurance Portability and Accountability Act of 1996 security guidelines and contains features such as data encryption. In addition, participants will receive a monthly package containing 2 actigraphs, a baby's day diary, and a prepaid return envelope.

Adverse Events

Adverse events will be monitored monthly via questionnaires and during telephone contact at month 3 and month 6 (phone calls to remind them to get blood drawn). Further, participants will be asked to report to the research team immediately if they experience unwanted adverse effects during participation. These events will be recorded and included in human research ethics reports. The Edinburgh Postpartum Depression Scale [45] has a single item that denotes suicidal ideation. It will be flagged such that if the participant endorses the item, a telephone call from a clinical psychologist (LF) to the participant will be initiated to conduct a risk assessment and assist with triage, as necessary.

Measures and Materials

Table 1 describes the schedule of the study assessments for primary and secondary measures.

Table 1. Assessments and timeline.

Measures	Baseline enrollment	1 month PP[a]	2 months PP	3 months PP	4 months PP	5 months PP	6 months PP
Maternal screening measures							
Consent/inclusion/exclusion	✓						
Demographics	✓						
SCID[b] depression module/sleep SCID	✓						
Infant assessments							
Actigraphy		✓	✓	✓	✓	✓	✓
Brief Infant Sleep Questionnaire		✓	✓	✓	✓	✓	✓
Infant Behavior Questionnaire-Revised		✓	✓	✓	✓	✓	✓
Baby Cry/Fuss chart		✓	✓	✓	✓	✓	✓
Maternal assessments (primary)							
Sleep diary		✓	✓	✓	✓	✓	✓
Actigraphy		✓	✓	✓	✓	✓	✓
Pittsburgh Sleep Quality Index	✓	✓	✓	✓	✓	✓	✓
Edinburgh Postnatal Depression Scale	✓	✓	✓	✓	✓	✓	✓
Generalized Anxiety Scale	✓	✓	✓	✓	✓	✓	✓
Tasso blood collection kit (Epigenetics)	✓						
Blood samples (inflammation)	✓			✓			✓
Maternal assessments (secondary)							
Insomnia Symptom Questionnaire	✓	✓	✓	✓	✓	✓	✓
Epworth Sleepiness Scale	✓	✓	✓	✓	✓	✓	✓
Flinders Fatigue Scale	✓	✓	✓	✓	✓	✓	✓
Treatment expectations	✓			✓			✓
Social support survey	✓	✓	✓	✓	✓	✓	✓
Adherence questionnaire				✓			✓
Delivery information		✓					

[a]PP: post partum.

[b]SCID: Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders-5.

Primary Infant Assessments

The mother will record infant sleep for 1 week per month in the baby's day diary [46]. Boxes are filled in daily for 1 week with symbols that correspond to when the infant is asleep, awake, awake and fussy, sucking, or feeding. This measure has been widely used and exhibits desirable reliability and validity [47,48]. The Brief Infant Sleep Questionnaire [40] is used to assess the infant's sleep during the past week. The Infant Behavior Questionnaire-Revised [49] will be used to allow mothers to report, on a 7-point scale, the frequency with which infants have enacted specific behaviors in common situations during the past week.

Primary Maternal Assessments

The Consensus Sleep Diary [50] will collect subjective sleep, while actigraphy will be contemporaneously used to derive objective sleep data. The Pittsburgh Sleep Quality Index [51] will measure habitual sleep quality. The Edinburgh Postnatal Depression Scale [52,53] will be used to assess changes in the depressive symptoms over time. The Generalized Anxiety Disorder Scale-7 items [54] and the Perinatal Anxiety Screening Scale [55] will be used to assess anxiety symptoms over time.

Participants will have their blood drawn (up to 20 mL) at enrollment, 3 months post partum, and 6 months post partum at a Quest Diagnostics laboratory near them (Figure 1). Briefly, blood collection kits with ethylenediaminetetraacetic acid tubes will be mailed to participants with a requisition form and a laboratory directive (from Quest) that provides the Quest Diagnostics Patient Service Center instructions on how to collect and process the study kit. Blood samples will be shipped in a temperature-controlled fashion to the Psychoneuroimmunology in Pregnancy & Postpartum (PIPPI) laboratory at Weill Cornell Medical College for analysis. Measurements of circulating cytokines, stimulated cell assays, and flow cytometry analysis will be conducted to evaluate the role of immune dysregulation.

Secondary Maternal Assessments

The Insomnia Symptom Questionnaire [56] is a self-report instrument that identifies a clinically relevant case definition of insomnia consistent with widely used insomnia classification criteria. It has 13 items, which identify sleep symptoms, frequency, duration, and related daytime impairment. Scoring indicates positive or negative for insomnia. The Epworth Sleepiness Scale [57] will assess daytime sleepiness. The Flinders Fatigue Scale [58] will assess daytime fatigue.

Measures in Both Mothers and Infants

Actigraphy watches (Phillips/Respironics and ActiGraph, LLC) will be provided to the dyad each month to collect objective sleep data. Data collection and interpretation will be consistent with previous reports [59-61]. For infants, watches will be placed on the right ankle in accordance with suggested guidelines [61-63].

Epigenetic Biomarker Testing

Blood Draw Collection

Upon enrollment, participants will be sent supplies from TruDiagnostic for blood collection, including a Tasso blood collection kit and a prepaid mailing kit to TruDiagnostic. Blood samples will be processed using the Illumina Human MethylEPIC beadchip. Methylation data for the *TTC9B*, *HP1BP3*, and *MS4A7* genes will be sent to Dr Zach Kaminsky who will use the published algorithm for predicting postpartum depression risk to determine if the participant's epigenetic methylation patterns are consistent with increased risk for postpartum depression. Participants will not be informed of their biomarker status, as we are still determining the clinical value of the biomarkers.

Immune Markers

Blood collection kits with ethylenediaminetetraacetic acid tubes will be mailed to participants with a requisition form and a laboratory directive (from Quest) that provides the Quest Diagnostics Patient Service Center instructions on how to collect and process the study kit. Aliquots of plasma and the second tube of whole blood will be shipped overnight to Weill Cornell Medicine. Peripheral blood mononuclear cell (PBMC) suspensions will be prepared within 24 hours of blood collection by low-density gradient centrifugation via Hermle Z300 (K#55085010) to avoid erythrophagy-related activation of the monocytes. PBMCs will be frozen and stored at –80 °C using 10% dimethylsulfoxide, thereby allowing all samples to be analyzed in parallel. Plasma will also be stored at –80 °C. In our prior studies, we have missing biological data (due to incomplete blood draws) in about 7% of the visits; we anticipate similar rates in this study.

Cytokine Analysis

Cytokine analysis will be performed under Dr Osborne's supervision in the PIPPI laboratory at Weill Cornell Medicine. Plasma cytokines will be measured using the Meso-Scale Discovery Ultrasensitive Proinflammatory Multiplex kit (Meso Scale Diagnostics LLC) according to the manufacturer's protocol in duplicate and read using the MS2400 imager (Meso Scale Diagnostics LLC). We will calculate the coefficient of variation for each woman's replicates when both have concentrations above the limit of detection.

Cell Preparation and Stimulation

Maternal PBMCs will be thawed in Roswell Park Memorial Institute 1640 medium and distributed into three 24-well multiplates (5×10^5 cells/well). Remaining cells will be aliquoted into two 5-mL culture tubes (2×10^6 cells/tube). Cells will be maintained in a humidified atmosphere of 95% air/5% CO_2 at 37 °C. After 24 hours, PBMCs in the 24-well plates will be treated with increasing concentrations of cortisol. Hydrocortisone stock solutions will be prepared by dissolving hydrocortisone in ethanol and then diluting with pyrogen-free sterile saline solution (NaCl 0.9%) to achieve equipotent final culture concentrations of 0.2 µg/mL (physiological plasma cortisol level) and 0.4 µg/mL (plasma cortisol level in high-stress status). PBMCs will be treated with a final cortisol concentration of 0, 0.2, and 0.4 µg /mL. Cells in the 5-mL culture tubes will be stimulated with phorbol myristate acetate (Sigma Aldrich) and ionomycin (Sigma Aldrich) in the presence of GolgiStop (Becton Dickinson) for 4 hours in 37 °C under a 5% CO_2 environment to stimulate T-effector cells. Following the

incubation periods, the supernatant from cortisol-stimulated cells will be collected and stored at –80 °C until assayed for interleukin (IL)-6, IL-10, IL-8, and IL-4 by using a commercial enzyme-linked immunosorbent assay. Cellular pellets will be resuspended and prepared for flow cytometry to assess the immune cell phenotype.

Flow Cytometry Analysis

Flow cytometry analysis will be performed on the BD LSRII instrument (BD Biosciences, 3 laser, 14 color) within the Cubillos-Ruiz laboratory adjacent to Dr Osborne's PIPPI laboratory. Additional analyses, as necessary, will occur in the Weill Cornell Flow Cytometry Core, which houses a BD AriaII sorter, 5 laser (355, 405, 488, 561, 640) capable of 4-way sorting; a BD Influx sorter, 6 laser (355, 405, 445, 488, 561, 640) capable of 6-way sorting; a BD Fortessa analyzer, 5 laser (355, 405, 488, 561, 640) 20 parameter and a BD FACSCelesta analyzer, and 3 laser (405, 488, 561) 14 parameter. Panel one will include membrane staining markers and will be performed using thawed PBMCs. Stained cells will be analyzed by 8-color flow cytometry (with anti-CD3 BV786, anti-CD4 Pe-Cy7, anti-CD8 BV605, anti-CD14 antigen-presenting cell, anti-CD25 phycoerythrin, anti-CD16 PerCp-Cy5.5, anti-CD56 fluorescein isothiocyanate, and anti-CD19 BV421; Becton Dickinson). We will use a gating method to measure subsets of monocytes, lymphocytes, natural killer cells, T-cells, B-cells, CD4+ T helper cells, and CD8+ cytotoxic T cells. Samples stimulated with phorbol 12-myristate 13-acetate and ionomycin will be stained using a T-cell specific panel and analyzed by 8-color flow cytometry (with anti-CD3 BV786, anti-CD4 Pe-Cy7, anti-CD45RO BV605, anti-IFN-γ antigen-presenting cell, anti-CD25 PE, anti-FoxP3 PerCp-Cy5.5, anti-IL-4 fluorescein isothiocyanate, and anti-IL-17A BV421; Becton Dickinson).

Process Measures

Treatment Expectation Questionnaire

An adapted version of the Treatment Expectation Questionnaire [64] will be administered at month 3 and month 6 to assess the mother's expectations of benefits, satisfaction with condition, and fears. This measure asks about expectations regarding symptom relief, improvement, and benefits from using the specific bassinet. It allows for comparison of the impact of multidimensional expectations across different conditions. Open-ended comment boxes will be provided for mothers to report experiences, adverse events, or other comments.

Patient Adherence

Various items will be collected to determine patient adherence: (1) self-reported adherence assessed using an adapted survey checklist provided by Dr Stremler, (2) self-report data on bassinet usage, (3) pictures of bassinet use by participants, and (4) comment boxes to explain nonadherence.

Additional Factors to Consider and Use as Covariates

These include (1) presence of spouse/partner and other children at home [36,65-67]; (2) type of feeding [68-70]; (3) infant variables such as acid reflux, colic, and gestational age; (4) consistency of bedtime routine [71-73] and when moved to a crib; (5) history of childhood trauma in the mother via the Childhood Trauma Questionnaire [74], as prior trauma is highly correlated with depressive episodes, especially in new mothers [75,76] and negatively affects sleep [77]; and (6) type of delivery, complications, or time spent in neonatal intensive care unit.

Statistical Analysis

Power

Power analyses were performed using $P<.05$ (2-tailed) at .80 power, based on recommended guidelines [78-80]. The power analyses were conducted for each statistical technique to be pursued in aims 1 to 3: mixed (between-subjects and within-subjects) multivariate analysis of variance (MANOVA), mixed (between-subjects and within-subjects) analysis of variance, independent 2-sided *t* test, dependent 2-sided *t* test, correlation, and the mediational models involving structural equation modeling (based on the β coefficient). The pilot study collected similar measures from pregnant/postpartum women with a history of major depressive disorder who used SB or HALO TB. Hence, the power analyses were based on pilot sleep and mood data. Calculations revealed an average effect size across all postpartum timepoints (T1 to T6) between the treatment and control groups on the following measures: infant sleep (d=0.39), postpartum sleep quality (d=0.27), and postpartum depression (d=0.33). Based on these effect sizes, a sample size of 208 participants is needed for infant sleep, 434 participants for postpartum sleep quality, and 286 participants for postpartum depression to attain statistical significance. Thus, a final sample size of 393 participants will be targeted (allowing for an attrition rate of 15%).

Randomization

AL generated the random sequence by using a random number generating program found on a widely used and reputable website [44]. We performed 1:1 randomization, stratifying for antidepressant use (actively taking or not). The study coordinator is responsible for the assignment based on the random sequence. This is not a blinded study, as there are distinct differences between the 2 bassinets.

Intention-To-Treat Analyses

Intention-to-treat analyses [81,82] will be conducted to understand the extent to which participants who satisfy the inclusion criteria for enrollment and are therefore randomized to one of the two conditions (intention-to-treat population) are similar to participants who provided complete data across the measurement rounds (actually treated sample). The purpose of intention-to-treat analyses is to scrutinize whether the conclusions drawn from the RCT remain robust even after considering participant attrition across time [81]. We will adhere to the recommended guidelines for performing multiple imputation on clinical research data [83].

Mean Differences

Initial analyses will be performed to verify that the random assignment procedure successfully equalized participants between the treatment and control groups on the preintervention variables. Thus, MANOVA will compare these 2 groups on the entire set of preintervention baseline measures. A chi-square

test will verify that both groups have the same distribution of infant boys and girls. As participants will be randomized to groups using a random number generator, baseline equivalency of the 2 groups is anticipated.

Six separate mixed 2 (treatment vs control) × 6 (assessment period) MANOVA models will be conducted. Specifically, to assess hypothesis 1a (aim 1), the model (model 1) will be applied to the infant sleep quality outcome measures. To address hypothesis 1b (aim 1), the analysis (model 2) will be applied to maternal postpartum sleep quality outcome measures. To evaluate hypothesis 2a (aim 2), the model (model 3) will be applied to the maternal postpartum depression outcomes. To examine hypothesis 3a (aim 3), the model (model 4) will be estimated on the measures involving peripheral cytokines, immune cells, and stimulated cytokine profiles. To examine hypothesis 3b (aim 3), the model (model 5) will be undertaken on the measures of T-cell dysfunction. Furthermore, to examine the exploratory aim, the model (model 6) will be estimated on the epigenetic biomarkers.

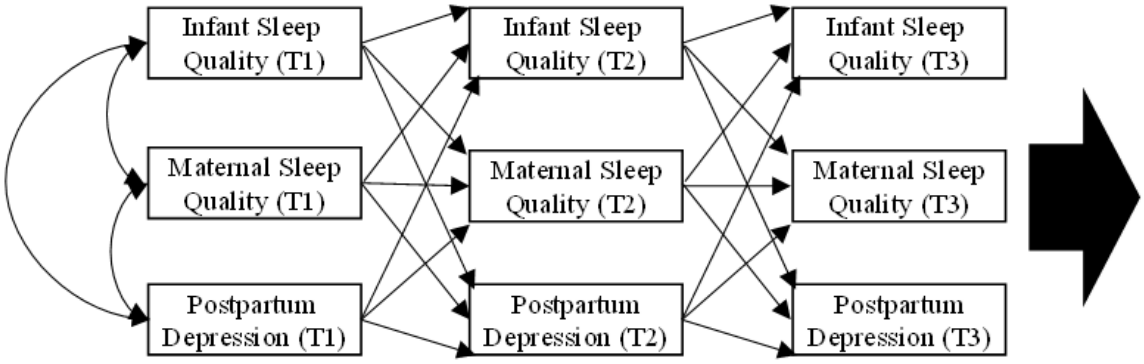
In each of the mixed MANOVA models, several follow-up analyses will be conducted to examine the results. First, a mixed (between-subjects and within-subjects) analysis of variance will be applied on each specific outcome. Second, independent 2-sided *t* tests will assess mean differences between the treatment and control group (at each timepoint) on each outcome. Third, dependent 2-sided *t* tests will permit scrutiny of the temporal change in mean scores between every 2 timepoints on every outcome. Fourth, the longitudinal trajectories across the entire 6-month period for both the treatment and control groups will be graphed using 95% CIs to provide a visual tool to offer insights to understand the effectiveness of the RCT.

Prior to conducting analyses, the normal distribution of all the measures will be inspected. If a variable is evidenced to be nonnormally distributed, then the bootstrapping variant of these statistical techniques instead will be performed to obtain corrected *P* values [84].

Mediational Analyses

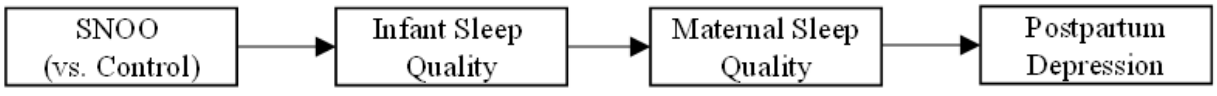
Cross-lagged panel designs will be pursued to make inferences about the temporal priority of a set of measures assessed longitudinally [85-87]. Accordingly, cross-lagged panel models permit the opportunity to determine the temporal precedence of antecedents and consequents in the set of constructs [86]: infant sleep quality, maternal sleep quality, and postpartum depression. The depiction of the proposed cross-lagged panel model to be tested is shown in Figure 2.

Figure 2. Cross-lagged panel model. For diagrammatic clarity, not displayed but will be estimated as part of the model are the constructs for postpartum months 3 (T4), 4 (T5), and 5 (T6), the correlations across constructs in every measurement round, and predictive error terms.



The cross-lagged panel model findings in the above model are expected to help inform how to specify the mediational model for hypothesis 2b. We propose that the cross-lagged panel model will evidence the following significant temporal cross-lagged directions that are consistent with hypothesis 2b: SB versus TB→infant sleep→maternal sleep→postpartum depression. Thus, a longitudinal mediational model, incorporating the intervention factor, will be specified and estimated (Figure 3). This mediational model tests and proposes that following underlying mechanism: SB group (vs the control group) will improve infant sleep quality, which would then predict better maternal sleep quality and finally contribute to lower maternal postpartum depression. All the outcomes of aim 1 are incorporated into the aim 2 mediational model to provide comprehensive and compelling insights that will statistically connect all the psychosocial constructs and understand the underlying process of this RCT.

Figure 3. Mediational model. For diagrammatic clarity, not displayed but will be estimated as part of the model are the predictive error terms. SNOO: smart bassinet.



The cross-lagged panel model and the meditational model each will be estimated with structural equation modeling [88]. The overall adequacy of these structural equation models will be assessed using fit indices [89-91]. A nonsignificant model chi-square test is desired to signify that the model approximates the underlying data, but this index tends to be sensitive to sample size [92]. Thus, additionally interpreted will be the comparative fit index and the Tucker-Lewis index, with higher values, preferably above 0.90, indicative of a good-fitting model [93,94]. The root mean-square error of approximation is sufficiently sensitive in detecting model misspecifications and provides a 90% CI [95]. Values below 0.05 indicate close fit, between 0.05 and 0.08 fair fit, between 0.08 and 0.10 mediocre fit, and above 0.10 poor fit [95].

If the fit indices for a model would be judged satisfactory, then the magnitude of the direct paths and the *P* values of these paths will be interpreted [96]. In the mediational model, the statistical significance of these mediational processes starting from the SB intervention (vs control) to infant sleep quality to maternal sleep quality and finally to postpartum depression with be evaluated in tests of indirect effects to determine whether the mediational process is significant beyond chance [88]. As recommended for structural equation models [96], bootstrapping with bias-corrected CIs will be applied to adjust for potential nonnormality of the variables.

Statistical Analyses for Immune Measurements

The initial statistical approach will include a descriptive cross-sectional analysis at each timepoint, both for quality assurance and to attain a better understanding of the distributions of the immune cell and cytokine profile variables for use in subsequent analyses, including the need for any transformations (ie, logarithmic transformation to symmetrize the residuals). Factor analysis will be employed as a means of data reduction to probe latent cytokine profiles reflected across the manifest indicators (eg, tumor necrosis factor-α, IL-6, IL-1β). We will first compare levels of a combined score of peripheral innate immune cytokines and frequency of maternal immune cells between women who do and do not develop PMADs in separate models to evaluate cross-sectional effects, employing a multivariable linear regression model to adjust for relevant covariates (eg, gestational age, BMI). Similar models will be repeated for maternal cytokines and innate cell recruiting factors as produced by the stimulated cells. Second, we will test whether the magnitude of group difference varies across the study period in a longitudinal analysis. We will fit a generalized linear population-average model estimated using generalized estimating equations with exchangeable working correlation structure to account for within-women correlation of mood measures. The model will include the relevant immune markers identified in the cross-sectional analyses, indicators for visit and group, as well as any relevant interaction terms (immune marker by group or immune marker by visit). The models will adjust for baseline severity of depressive symptoms and psychotropic medication use. Standard model checking will be performed, and the most parsimonious model will be selected based on the Akaike information criterion or quasi-likelihood information criterion for generalized estimating equations models. To test the within-group effects of severity of PMAD symptoms, the dichotomous group variable will be replaced by continuous Edinburgh Postpartum Depression Scale and Generalized Anxiety Disorder Scale-7 item scores in analytic models and restricted to only the subset of women with significant PMAD symptoms.

Missing Data

Attrition in our prior studies has been approximately 15%, and we have accounted for that in our planned sample size. In addition, in our prior studies, we have missing biological data (due to incomplete blood draws) in about 7% of the visits; we anticipate similar rates in this study, which will use the same approach. Given the prospective nature of our study, we will carefully evaluate missingness. If identified, we will employ one of the two strategies to handle missing data. The first approach relies on a technical assumption of missing at random and involves inclusion of covariates related to missingness in all analyses. Full information maximum likelihood performs well under ignorable missing data conditions such as missing at random. A second strategy we will use is multiple imputation. Although this has the potential to yield biased estimates dependent on the nature of missingness [97], we will employ this approach to implement sensitivity analysis under plausible assumption of missing not at random to examine the robustness of our inference [98].

Results

This project was funded in June 2024 and approved by the institutional review board of University of Colorado Colorado Springs (#2024-071) and by the Office of Human Research Oversight in February 2024. Recruitment for this study began in January 2025. We anticipate that the data analysis for the primary and secondary aims will be completed by July 2028. The methodology for the web-based surveys will be reported according to the CHERRIES checklist before the submission of any manuscript. The results from this trial will be used to extend SB efficacy in larger military cohorts and in women experiencing active perinatal mood disorders.

Discussion

Implications of SHINE

At the conclusion of this project, we will have gained a thorough understanding of how SB affects infant and maternal sleep compared to TB and its association with maternal mood through 6 months post partum in military-affiliated women. We will also significantly extend our current knowledge regarding the biological mechanisms associated with PMADs and how they may be modified by behavioral interventions. Future directions will include evaluations of women with current depressive disorders, women with a history of depression but not actively depressed, women with and without a history of trauma, and women who deliver prematurely to determine if SB can mitigate depressive symptomatology over the course of 12 months. This is a primary goal, as PMAD is a serious public health concern.

Limitations

This study will, however, have important limitations that warrant discussion. The study goal is to determine whether SB can prevent or reduce the reoccurrence of PMADs and not for use as an active treatment. Hence, we chose to exclude participants with active psychopathology at enrollment. We focused on at-risk participants. Those with active psychopathology are not at-risk—they have it. Moreover, we felt that it was a matter of safety. Recruiting participants from across the United States restricts the ability of our team to manage or treat an actively depressed mother. Ethically, we believe that we needed to demonstrate that SB can mitigate or prevent PMADs before evaluating whether it can treat active PMADs. However, if a participant develops PMAD at post partum, they will remain in the study and be referred for treatment. To clarify, we are only excluding women with a positive diagnosis of SCID; women with a history of PMAD or who are effectively treated will be included. This decision comes with some concerns. One is that we may have too small of a magnitude or range of mood symptoms to observe a true positive effect of SB on mood symptoms. In other words, the population will be too mentally normal/healthy. We believe, however, that the diverse sample will provide enough variability in mood symptoms, especially since a greater percentage of active-duty women and military spouses experience mental health conditions and at a higher rate than civilians [99-101]. If we notice that the rate of PMAD symptoms is limited or if we are excluding too many participants due to active psychopathology, we may alter the design to include active psychopathology. Another limitation is that the study requires participants to have access to the internet; therefore, individuals of low socioeconomic status and certain racial/ethnic groups may potentially be excluded from the study [102]. However, low-income Americans have made gains in technology and access to the internet, which is likely to continue in the future. A primary goal of this study is to have a diverse sample of racial and ethnic backgrounds. Recruiting and retaining a broad range of participants, particularly those of low socioeconomic status, has been challenging, with recent calls to enhance representation [103,104]. In order to provide an equitable interpretation of the data, the participants need to be diverse and accurately reflect the population of the United States. Therefore, a major emphasis will be on recruiting a diverse and representative sample of military-affiliated participants. Although attrition has been a minimal issue in our studies, we are cognizant of the duration and expectations of the protocol. Thus, our group will maintain regular contact and troubleshoot, if necessary, to enhance retention.

Conclusions

Pregnant active-duty and military spouses are an underserved population. Data suggest that persistent, rather than transient, infant sleep issues contribute to maternal depression, poor maternal sleep, and poor family functioning. We contend that to achieve the goal of reducing PMADs among new military-affiliated mothers, sufficient and efficient sleep is crucial. Understanding that there are few nonpharmacologic interventions that significantly improve infant or maternal sleep highlights the need for these data. This will be the first study to assess sleep methodically and longitudinally from infants who sleep in an SB and their mothers versus those who sleep in a TB and their mothers and how sleep from both individuals interacts to affect postpartum mood. We hypothesize that this study will indicate that SB may indeed reduce PMADs in military-affiliated mothers.

Acknowledgments

This work was supported by the Assistant Secretary of Defense for Health Affairs endorsed by the Department of Defense, in the amount of US $3,800,334.00, through the Peer Reviewed Medical Research Program under award HT9425-24-1-0690 (Multimedia Appendix 2). Opinions, interpretations, conclusions, and recommendations are those of the authors and are not necessarily endorsed by the Assistant Secretary of Defense for Health Affairs endorsed by the Department of Defense (Army Medical Research Acquisition Activity Award; principal investigator, MO; 001207-1533-0001).

Data Availability

Data supporting this study will be openly available from the National Sleep Research Resource, which is a National Heart Lung Blood Institute–supported repository for sharing sleep data (polysomnography, actigraphy, and questionnaire-based) collected on tens of thousands of individuals from cohort studies, clinical trials, and other data sources.

Conflicts of Interest

None declared.

Multimedia Appendix 1
CONSORT (Consolidated Standards of Reporting Trials) 2010 statement checklist.
[PDF File (Adobe PDF File), 253 KB - resprot_v14i1e66439_app1.pdf]

Multimedia Appendix 2

Peer review from the Congressionally Directed Medical Research Programs - Fiscal Year 2023 Peer Reviewed Medical Research Program - Lifestyle and Behavioral Health Interventions Research Award - Clinical Trial (Department of Defense, U.S. Army Medical Research and Development Command, USA).
[PDF File (Adobe PDF File), 382 KB - resprot_v14i1e66439_app2.pdf]

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Abbreviations

CHERRIES: Checklist for Reporting Results of Internet E-Surveys
CONSORT: Consolidated Standards of Reporting Trials
IL: interleukin
MANOVA: multivariate analysis of variance
PBMC: peripheral blood mononuclear cell
PIPPI: Psychoneuroimmunology in Pregnancy & Postpartum
PMAD: postpartum mood and anxiety disorder
RCT: randomized controlled trial
REDCap: research electronic data capture
SB: smart bassinet
SHINE: Sleep Health and Mood in Newly Expectant Military Mothers
TB: traditional bassinet

Edited by A Schwartz; submitted 12.09.24; this is a non–peer-reviewed article;accepted 06.03.25; published 10.04.25.

Please cite as:
Okun ML, Payne JL, Osborne LM, Feliciano L, Lac A
Effects of Using a Smart Bassinet on the Mental Health of Military-Affiliated Pregnant Women: Protocol for a Randomized Controlled Sleep Health and Mood in Newly Expectant Military Mothers (SHINE) Trial
JMIR Res Protoc 2025;14:e66439
URL: https://www.researchprotocols.org/2025/1/e66439
doi:10.2196/66439
PMID:

Protocol

Virtual Reality–Based Psychological Intervention for Young Adults Living With HIV: Protocol for a Randomized Controlled Trial

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Abstract

Background: Young adults (15-24 years old) living with HIV may experience pressure both from HIV infection and social role change problems, resulting in a series of psychological problems such as depression and anxiety. Effective psychological intervention can improve their mental health and quality of life.

Objective: The study aims to explore the effectiveness of VR-based mental intervention on young adults living with HIV. The application and advantages of virtual reality (VR) in children's psychotherapy provide new ideas for psychological intervention for young adults living with HIV.

Methods: We use the qualitative interviews and questionnaire results as well as guided by classical psychotherapy to create a personalized psychological intervention system for young adults living with HIV through VR technology, which is based on the long-term AIDS treatment cohort and infectious diseases cohort of children. We use the mental scales and biochemical indexes as the outcomes, conducting a prospective randomized controlled trial to verify the feasibility and effectiveness of the VR psychological intervention system.

Results: The study began enrollment in September 2023. To date, 160 participants have finished the baseline questionnaires.

Conclusions: The study results might provide a scientific basis for accurate psychological treatment among young adults living with HIV in the future.

International Registered Report Identifier (IRRID): DERR1-10.2196/55633

(JMIR Res Protoc 2025;14:e55633) doi:10.2196/55633

KEYWORDS

HIV; young adults; mental health; virtual reality; VR; psychological intervention; depression; anxiety; living with HIV; privacy; mental health; intervention

Introduction

According to the latest data from the joint United Nations Program on HIV/AIDS (UNAIDS), an average of about 4000 people were newly diagnosed with HIV globally per day in 2021. Young people aged 15-24 years old accounted for 31% of new HIV infections. In the Asia-Pacific region, about 260,000 young people were newly diagnosed with HIV in 2021, accounting for 17.3% of the global increase, second only to Africa [1]. The mental health of people living with HIV/AIDS is an important part of the quality of life, and infection-related stigma makes people living with HIV/AIDS face 2-3 times more anxiety and depression than the general population [2-4]. Young people living with HIV face pressure from social adaptation, such as personal growth and role change, as well as disease pressure caused by the incurability and stigma of HIV infection [5]. Studies on young people aged 10-24 years old living with HIV showed that 21% of them had depression symptoms and 14% had anxiety, and the proportion interval of suicidal ideation was from 4.4% to 24.4%, and those with long-term suicidal ideation ranged from 9.26% to 33.33% [6-9]. So, how to carry out effective psychological intervention for young people living with HIV is very important.

There are many forms of psychological intervention, and numerous interventions are intended to support mental health, mainly by way of face-to-face and group-based intervention, internet intervention, and mobile remote intervention. Regardless of the form of psychological intervention, it is based on the theoretical framework or theoretical basis. Common theoretical bases include cognitive behavioral therapy (CBT) and dialectical behavior therapy (DBT) [10]. Previous studies proved the effectiveness of CBT or DBT in the way of face-to-face intervention. Synder et al [11] conducted a group-based psychological intervention study on people living with HIV aged between 16 and 24 years of CBT. The results showed that the self-perceived social support of the intervention group was higher than that of the control group, but the difference was not statistically significant (P=.20) [11]. Bedics et al [12] conducted a 1-year DBT treatment on 101 women with borderline personality disorder, which showed that DBT therapy could reduce suicidal behaviors and nonsuicidal self-injury behaviors. Burton et al [13] conducted a psychological intervention with DBT therapy, suggesting that the depression clinical scores had improved of the participants in the intervention group. DBT therapy has achieved some effects in helping improve behavioral problems in children [14] and alcohol problems among college students [15]. However, face-to-face and group-based CBT or DBT needs to be carried out by professionals, and the existing qualified health care providers and infrastructures are limited in meeting the challenge in China.

Studies in developed countries have shown the feasibility and efficacy of using mHealth to provide counseling and services to improve mental health in diverse populations. Mohr et al [16] conducted a self-control psychological intervention in the general population by mobile phone, and the results showed that depression and anxiety decreased over time [16]. The research team conducted a randomized controlled psychological intervention trial on 300 adults living with HIV on the WeChat public platform. At 3 and 6 months after the intervention, the depression level and suicide ideation rate of the experimental group were reduced compared with the control group (P=.02) [17,18]. However, there is no study focusing on mental intervention among young people living with HIV. At the same time, studies showed that compliance with remote Internet or mobile phone intervention is poor, and patients are unable to concentrate during the intervention process, which makes it difficult to ensure the effective implementation of the intervention.

Virtual reality (VR) provides a variety of sensory stimuli to people through the computer-generated virtual environment, enabling people to interact with the virtual environment naturally to achieve a sense of immersion and experience in the real environment [19]. Falconer et al [20] used VR technology to set virtual scenes to treat patients with depression and found that the depression decreased after the intervention, and the improvement effect was still maintained one month after the end of the experiment. Based on the mindfulness-based program (MBP), Modrego-Alarcón et al [21] conducted a study on the stress level of 280 college students through VR equipment. The results showed that the experimental group had increased relaxation and decreased stress levels compared with the control group (P=.006) [21]. Navarro-Haro et al [22] combined DBT therapy with VR to guide mindfulness training. The results showed that the impulse to commit suicide, self-harm, give up treatment, and use drugs in the experimental group was reduced after the intervention [22]. However, most of the existing studies are small-scale pilot studies on general adults or adolescents with adverse psychological conditions, and there is little study on young people living with HIV.

In summary, the proposed study intends to address the issues of prevalent mental health problems in young people living with HIV and to innovatively use VR to provide integrated and culturally appropriate intervention for mental health improvement.

Methods

Goal and Objectives

The objectives of the project are (1) using DBT as the theoretical framework, based on VR technology to carry out the individualized psychological intervention for young people living with HIV; and (2) A 1:1 prospective randomized controlled trial (RCT) will be conducted to verify the effectiveness of VR psychological intervention on reducing depression and anxiety in young people living with HIV.

Intervention Design

Development of A VR Intervention System

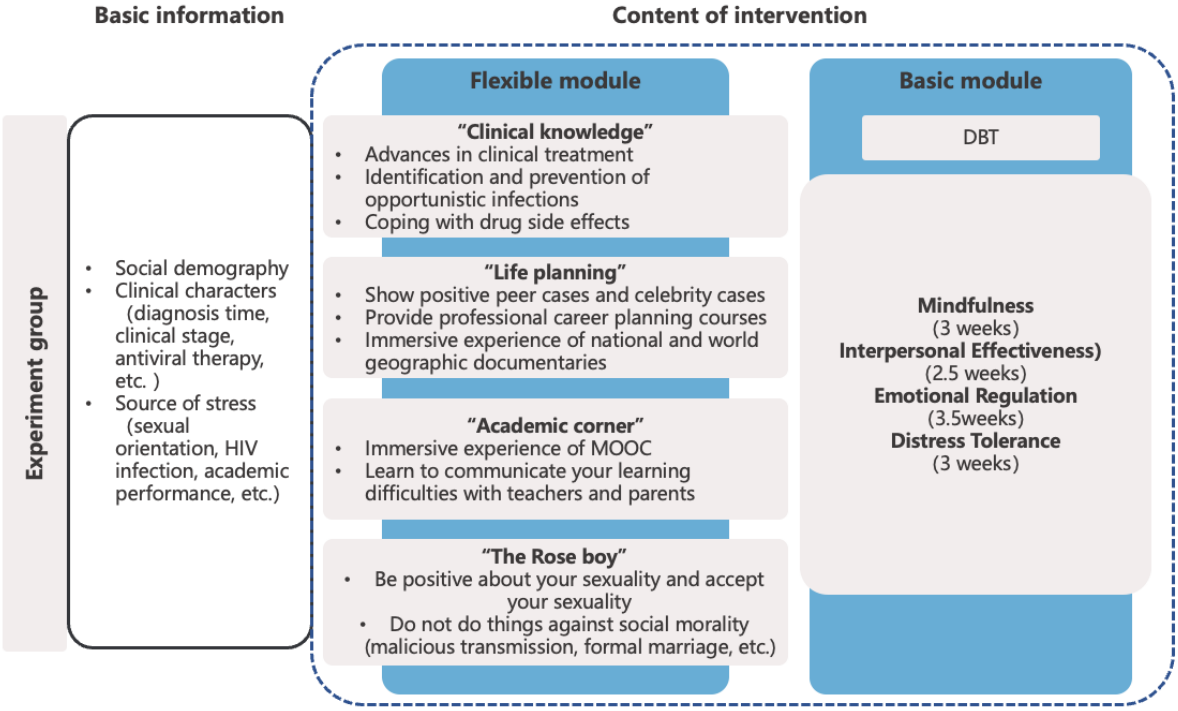
Content of the Intervention

The proposed study is guided by DBT and combined with the actual needs and unique characteristics of young people living with HIV to develop a specialized psychological intervention system suitable for the characteristics of this population.

The actual needs of mental health among young people living with HIV were collected based on literature and qualitative interviews with young people living with HIV. The outline of the qualitative interview mainly included (1) basic information and (2) The main source of stress (infection, drug side-effect, income, life expectancy).

Study subjects in the experimental group received 2 modules of psychological intervention. Module 1 was the basic intervention module, mainly the DBT treatment course, which covers 4 parts: mindfulness, distress tolerance, emotional regulation, and interpersonal effectiveness. The second module is a flexible intervention module applicable to the actual needs of young people living with HIV. As shown in Figure 1.

Figure 1. Psychological intervention content in the experimental group. MOOC: Massive Open Online Courses. DBT: dialectical behavior therapy.



Intervention Delivery

We set up a user management platform as the support for the intervention. The function of the platform included (1) information management: a complete record with a unique number is generated when each research object is enrolled. The researcher is the system administrator and can add and modify the relevant information of the patient, such as fixed number, basic personal information (deprivatized), clinical and therapeutic information, psychological assessment scale, etc. The system is associated with the VR intervention software, which can record and synchronize the completion of the intervention course of the research object, and the administrator can view and export the corresponding data through the number.

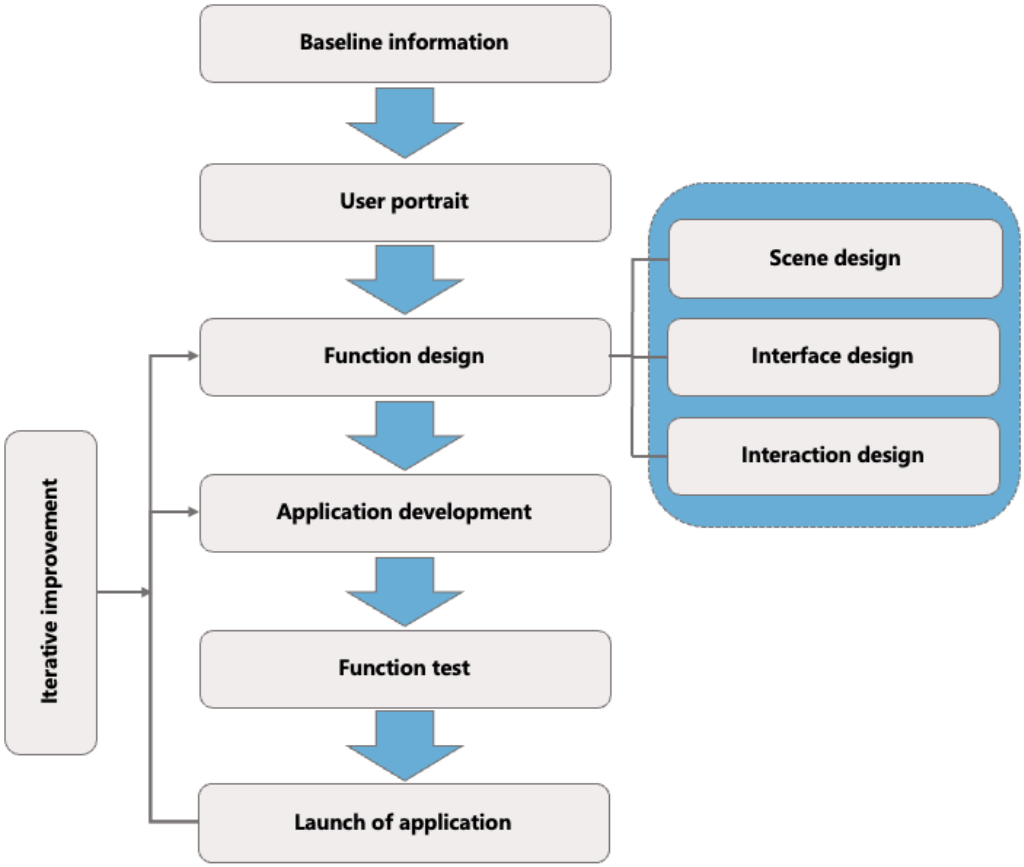
(2) Upload and update intervention resources: the intervention content involved in VR software forms a "resource library" in the management system, and the user portrait is generated when the subject is enrolled in the corresponding intervention content. The user portrait is the virtualization of real users and the category of research objects extracted; that is, the entire psychological intervention system is a big picture. Against this background, different types of subjects receive psychological intervention corresponding to their characteristics to achieve personalized customization. In the course of the experiment, the researchers continuously improved and updated the intervention resources.

(3) The intervention goal setting and process supervision: researchers use motivation type interview (motivational interviewing [MI]) to help subjects set up goals, regularly to supervise the completion of the intervention for subjects, and set a message to remind, intervention to ensure compliance.

VR Application Development

VR application development mainly includes 3 stages. First, Scene design is a virtual scene in which the participants experience psychological intervention therapy. This study mainly includes 2 scenes: natural landscape and indoor landscape. The natural landscape was used as the environment for participants to immerse in mindfulness and other skills training. The indoor landscape, including the home environment and the consultation environment, was used for the explanation and learning of psychological intervention courses. Second, regarding interface design, this study follows the principle of consistency of interface structure and style, choosing simple graphical design language and interface style with comfort and color sense. The icon uses a simple 2-dimensional graphic simulation to represent the functional form, which is convenient for the participant to identify and quickly associate the icon function, reducing the possibility of wrong selection. Third, interaction design refers to the use of VR hardware devices such as glasses and gamepads to realize the interaction of subjects in the scene. For example, when the participant enters the "family scene," he or she can move freely and roam in panorama; through the button control of indoor lighting and curtains, choose the bedroom, living room, consulting room, etc, to carry out the study of psychological courses. As shown in Figure 2.

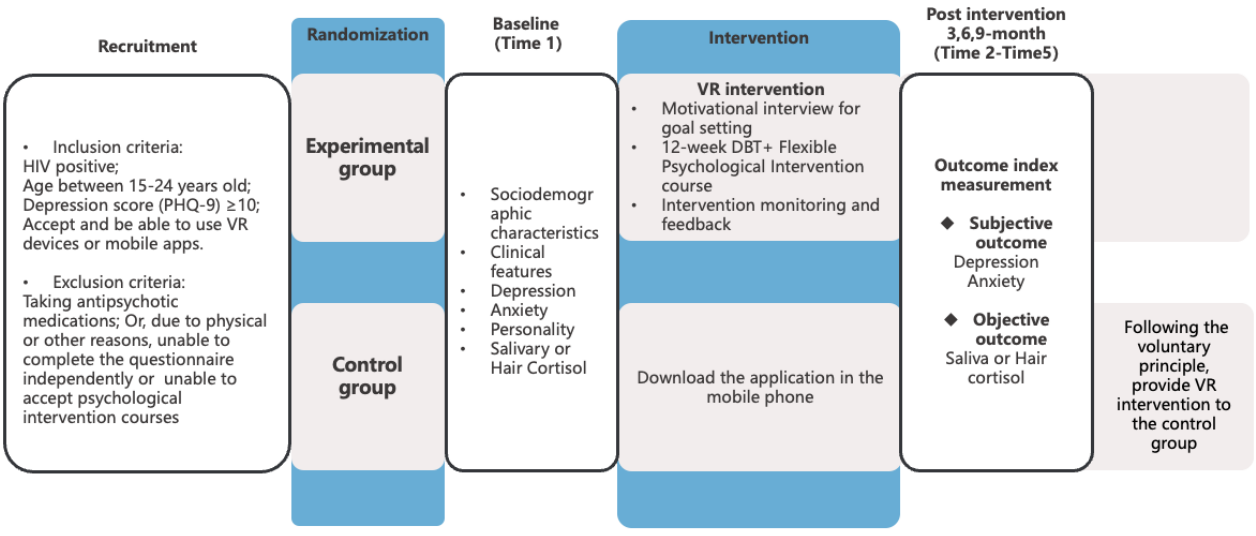
Figure 2. Virtual reality (VR) system development.



Verify the Effectiveness of VR Psychological Intervention

A 1:1 RCT will be conducted to verify the effectiveness of VR psychological intervention in reducing depression and anxiety in young people living with HIV. The RCT was not possible to blind the participants. The study lasted for 12 months. According to the inclusion and exclusion criteria, the participants are randomly divided into an experimental group and a control group. The experimental group received VR psychological intervention for 3 months, and the control group received non-VR mobile phone intervention for the same period. Data will be collected at 5 time points: baseline, postintervention, 3 months, 6 months, and 9 months after intervention, as shown in Figure 3.

Figure 3. The process of the intervention. PHQ-9: Patient Health Questionnaire-9. VR: virtual reality. DBT: dialectical behavior therapy.



Measurement

Depression score was measured by the Patient Health Questionnaire-9 (PHQ-9). PHQ-9 is shorter but has demonstrated both good reliability and validity in the Chinese populations [23,24]. The scale consists of 9 items, such as “Little interest or pleasure in doing things” and “Feeling down,

depressed, or hopeless," to measure the depressive status of the participants over the previous 2 weeks. Each item was rated on a 4-point Likert scale ranging from 0 (not at all) to 3 (nearly every day), providing a 0 to 27 total severity score, with higher scores indicating increased depressive symptoms [25].

Anxiety was measured by the Self-rating Anxiety Scale (SAS) that assesses anxiety in the last week with the Chinese version [26,27]. SAS has 20 items with responses of a 4-point Likert scale (1="never or rarely," 2="sometimes," 3="most of the time," 4="almost every day"). The total score ranges from 20-80, with 50 as a cutoff point, 50-59 being considered mild anxiety, 60-69 as moderate anxiety, and ≥70 as severe anxiety.

Study Participants

Inclusion criteria were a positive HIV test, age 15-24 years, depression score (PHQ-9)≥10 (with depressive symptoms), accepting and being able to use VR devices or mobile apps. Exclusion criteria were taking antipsychotic drugs or, for physical or other reasons, being unable to complete surveys or questionnaires independently, or being unable to accept psychological intervention courses.

Recruitment

The recruitment location is mainly based on Beijing Ditan Hospital Capital Medical University, which is treating 11,735 people in 2023. After clinic doctors have completed all the treatment procedures, researchers will distribute research leaflets to them to introduce the research project and invite them to participate. If the young people living with HIV agree to participate, the program's researchers will invite the participants to a separate room to be screened for enrollment conditions.

The staff will present the informed consent form of this study and inform the content of the informed consent form, including the introduction of the project, the benefits and possible risks of participating in this study, and the voluntary principle. The research subjects will be asked to sign the informed consent form after they have fully understood it.

Baseline Information Collection

The collection of baseline information in this study included 2 items: filling out questionnaires and retaining biological samples. A self-designed questionnaire was used to collect baseline information, including sociodemographic characteristics, medication and treatment information, clinical indicators, and mental health scale evaluation. The electronic questionnaire data can be downloaded directly, which is convenient to timely grasp or correct the information of infected people enrolled on the same day, and ensure the quality of data. To facilitate data collection, improve work efficiency, and improve data collection quality, electronic questionnaires were used at baseline and 3 follow-up visits.

Sample Size Calculation and Group Randomization

The sample size was calculated according to depression, the main outcome indicator of this study. Participants with PHQ-9 depression scale score ≥10 were classified as having depressive symptoms. It is expected that after intervention, the proportion of depression in the intervention group will be reduced by 20% compared with that in the control group. A bilateral test with a sample size ratio of the test group and control group as 1:1, test efficacy (1-β) as 0.9, and α as .05 was adopted, and a loss rate of 20% is expected. Through the calculation of PASS software (NCSS), 145 study subjects need to be included, and finally, 160 study subjects are rounded up, including 80 in the experimental group and 80 in the control group.

To ensure the balance between the experimental group and the control group, the block randomization method was adopted, code was written in R (R Foundation for Statistical Computing), random numbers were generated according to random seeds, and randomization was carried out to make the allocation of each treatment group more balanced and meet the research requirements. According to the order in which the subjects were enrolled, each participant was given a random number generated by the above random scheme. According to the group corresponding to the random number, the subjects were randomly assigned to the experimental group and the control group.

Quality Control

To improve the compliance of young people living with HIV, this study conducted regular telephone communication with the permission of the study subjects based on unified management through the user management platform to understand the intervention and treatment of the study subjects and give more humanistic care.

To ensure privacy and reduce reporting bias, this study was conducted anonymously, and the VR intervention was free during the study. The fixed and unique number assigned to each research subject when they were enrolled was used as the basis for information matching. After each collection of questionnaires, data was downloaded and backed up on the same day, and the questionnaire platform data was deleted in time. The downloaded questionnaires were formed into a special database and stored encrypted in an unconnected computer for safekeeping by the project leader. At the same time, the VR intervention software and the intervention program of the control group are regularly maintained, network security is regularly checked, user information is protected in many aspects, and security information is set in the application, such as adding mobile phone number association, email association, secret security issues, and the relevant computer professionals are supervised.

Statistical Analysis

Quantitative data were analyzed using SD or demographic characteristics of composition comparison baseline. The *t* test, ANOVA, or rank sum test were used for hypothesis testing of quantitative data. The chi-square test or Fisher exact probability method was used to test the hypothesis of qualitative data. The effect size would also be calculated. In this study, the intervention effect of the VR psychological intervention system was analyzed using generalized estimating equations (GEE). During the follow-up, the attrition diagram in each group would be plotted over time. In this study, binary classification PHQ-9 is used as the outcome variable, which belongs to longitudinal data, and there is a certain correlation between the data. When conducting statistical analysis of such data, the data correlation should be fully considered. Therefore, GEE was used to analyze

the intervention effect to correct for the correlation between data caused by repeated measurements at multiple time points.

Study Significance

The clinical cohort supported by this study is a long-term antiviral treatment cohort, which can ensure the sample size and representativeness of the enrolled participants. The research team includes experts and scholars from various disciplines, including epidemiology and health statistics, clinical medicine, psychology, computer science, technology, etc, to provide professional guidance for the design of a psychological intervention department and the implementation of mental health intervention. The case managers in the research team are from Beijing Red Ribbon Home and have rich experience in providing psychological support for people living with HIV. The Home of Red Ribbon was previously known as the Home of Red Ribbon of Beijing Ditan Hospital, which was established in 1999. On January 5, 2005, the Home of Red Ribbon was registered with the Beijing Municipal Civil Affairs Bureau as the first civil society organization in China specializing in comprehensive HIV/AIDS care. It has 6 independent branches focusing on medical support, self-help of HIV-positive people, volunteer service, social assistance, online publicity, and legal aid. Its purpose is to provide comprehensive support and services for people living with HIV by pooling strength from all social strata, carrying out a variety of HIV prevention and control measures, and health awareness campaigns for enhanced public understanding of HIV.

This study innovatively applied modern VR technology to psychological intervention for young people living with HIV, which provides a new idea for our country to carry out psychological treatment. As a special group, people living with HIV are in urgent need of effective psychological guidance and sensitivity for privacy. This study combines VR technology with psychological intervention, uses an immersive 3D virtual environment to overcome the disadvantages of 2D mobile phone intervention, and avoids the privacy exposure that may be caused by offline medical treatment. It can provide data support and a scientific basis for solving the mental health problems of young people living with HIV in the future.

Ethical Considerations

This study was part of a research project that had been approved by the ethics committee of Beijing Ditan Hospital of Capital Medical University (Approval number: 2024-012). All individual participants were provided oral informed consent at the time of enrolment.

Results

This study was funded by the Capital Medical University Research Development Fund (grant PYZ22138) in April 2023. The enrollment started in September 2023. The data analysis is expected to be finished in April 2025.

Discussion

This study innovatively transcends traditional intervention models to conduct a prospective randomized controlled trial of VR-based psychological intervention for young people living with HIV in China. The research results will provide the effectiveness of VR-based mental intervention among young people living with HIV.

This research might provide yields practical data that advocates for the integration of mental health services into the standardized treatment model for HIV, as well as the wider implementation of psychological intervention services within domestic HIV-designated medical institutions and other health care facilities lacking specialized psychological consultation clinics.

The limitation of the study was that the population involved in this study mainly were young people living with HIV, which might cause a selection bias. However, young HIV-positive people were a group with a high proportion of HIV prevalence in China, so the study results still were representative of the effectiveness of the VR intervention and had good prospects of the intervention expanding in China.

The study population needs to be expanded to include people with chronic diseases to achieve effective mental intervention based on VR technology in the future.

Acknowledgments

We thank the participants who were recruited in the research. We acknowledge the support provided by (1) the Beijing Municipal Administration of Hospitals' Ascent Plan (DFL20191802), (2) the Beijing Municipal Administration of Hospitals Clinical Medicine Development of Special Funding Support (ZYLX202126), (3) the High-level public health technical personnel construction project (2022-3-036), and (4) the Capital Medical University Research Development Fund (PYZ22138). AI was not used in any portion of the manuscript writing.

Data Availability

The datasets generated during and/or analyzed during this study are available from the corresponding author on reasonable request.

Authors' Contributions

HZ wrote the first draft of the manuscript. YS and JH conducted the field research management and collected field study data. HZ, Zhao H, and FZ critically reviewed and edited the manuscript. The author group was entirely responsible for study design, data collection, and data analysis. We declare that all authors have read and approved the final manuscript.

Conflicts of Interest

None declared.

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Abbreviations

CBT: cognitive behavioral therapy
DBT: dialectical behavior therapy
GEE: generalized estimating equations
MBP: mindfulness-based program
MI: motivational interviewing
PHQ-9: Patient Health Questionnaire-9
RCT: randomized controlled trial
SAS: Self-rating Anxiety Scale
UNAIDS: United Nations Program on HIV/AIDS
VR: virtual reality

Edited by A Mavragani; submitted 19.12.23; peer-reviewed by D Murphy, E Nsubuga; comments to author 20.02.24; revised version received 30.04.24; accepted 03.09.24; published 10.01.25.

Please cite as:
Zhang H, Han J, Su Y, Zhao H, Zhang F
Virtual Reality–Based Psychological Intervention for Young Adults Living With HIV: Protocol for a Randomized Controlled Trial
JMIR Res Protoc 2025;14:e55633
URL: https://www.researchprotocols.org/2025/1/e55633
doi:10.2196/55633
PMID:

Protocol

At-Home Immersive Virtual Reality Exergames to Reduce Cardiometabolic Risk Among Office Workers: Protocol for a Randomized Controlled Trial

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Abstract

Background: The worldwide rise in the prevalence of noncommunicable diseases has increased the recognition of the need to identify modifiable risk factors for preventing and managing these diseases. The office worker, as a representative group of physically inactive workers, is exposed to risk factors for metabolic syndrome, which is a primary driver of noncommunicable diseases. The use of virtual reality (VR) exergames may offer a potential solution to the problem of increasing noncommunicable disease prevalence, as it can help individuals increase their physical activity levels while providing a more immersive experience.

Objective: This exploratory study aims to examine the interventional efficacy of at-home immersive VR exergames on metabolic syndrome biomarkers among office workers. Additionally, it seeks to investigate the impacts of at-home immersive VR exergames on the active and sedentary behaviors of office workers.

Methods: A 3-arm, single-blinded pilot randomized controlled trial will be conducted to examine the therapeutic effects of at-home immersive VR exergames. A total of 120 Chinese office workers, engaging in less than 150 minutes per week of moderate to vigorous intensity physical activity, will be recruited via a convenience sampling method. The participants, who will be tested over a 12-week period, will be randomly assigned to one of three groups: (1) the VR exergame intervention group, (2) the regular physical activity control group, and (3) the nonexercise control group. Throughout the 12-week trial, three categories of variables will be collected across the three groups: clinical risk factors associated with metabolic syndrome, active and sedentary behaviors, and demographics. To analyze variance among the groups, a mixed linear model will be applied to assess the efficacy of each group. Differences in metabolic syndrome clinical risk factors among all groups will be used to evaluate the effects of at-home

immersive VR exergames. Changes in active and sedentary behaviors will also be used to determine the impacts of VR exergames on metabolic syndrome.

Results: The ethics committee of Guangzhou University, China, approved this study on September 25, 2024. Participant recruitment will begin in early 2025 and continue for approximately 3 months. Data will be analyzed after the 12-week trial is completed, with full results expected to be presented in early 2026.

Conclusions: This study explores an emerging topic by applying an at-home immersive VR exergame intervention, potentially contributing to understanding the effects of an exergame program on metabolic syndrome risk among office workers.

Trial Registration: ClinicalTrials.gov NCT06556784; https://clinicaltrials.gov/study/NCT06556784

International Registered Report Identifier (IRRID): PRR1-10.2196/64560

(JMIR Res Protoc 2025;14:e64560) doi:10.2196/64560

KEYWORDS

metabolic syndrome; noncommunicable diseases; active video game; interactive virtual reality environment; physical activity; workplace health; at-home intervention

Introduction

Noncommunicable diseases, such as cancer, cardiovascular diseases, diabetes, and heart disease, constitute the foremost cause of death internationally [1]. Noncommunicable diseases accounted for 63% or 36 million global deaths in 2008, which increased to 74% in 2019 [2,3]. The increasing prevalence of noncommunicable disease deaths worldwide has increased the need to identify modifiable risks in preventing and managing these diseases.

Metabolic syndrome is a common chronic disease characterized by the co-occurrence of several major biomarkers, including high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), impaired fasting glucose, insulin, triglycerides, blood pressure, waist circumference, and BMI [4,5]. Moreover, as a route to many noncommunicable diseases, such as cancer, cardiovascular diseases, and type 2 diabetes [6-8], metabolic syndrome plays a pivotal role in health status. For example, several systematic reviews have shown that individuals with metabolic syndrome are approximately two to five times more susceptible to developing cardiovascular disease and type 2 diabetes [9-11]. Although metabolic syndrome is one of the threats to a healthy life [12], its prevalence is increasing globally [13]. For example, a study conducted in the United States reported an increase of more than 35% in the prevalence of metabolic syndrome among US adults from 1988-1994 to 2007-2012 [14]. A systematic review reported that approximately 20% of the adult population in most Asian Pacific countries is struggling with a metabolic syndrome epidemic [15]. However, as an effective approach to mitigate the risk and treatment of metabolic syndrome, physical activity is facing a worrisome status across all countries [16,17].

Employed adults, the largest population in the world, spend a large portion of their waking time in the workplace [18,19]. Especially in desk-based workplaces, most of this time is spent sitting [20-22]. For example, in desk-based workplaces, Japanese workers spend approximately 70% of their time sitting with a low level of physical activity [23]. With the ongoing advancement of technology, the worldwide phenomenon of physical inactivity among employed adults has been occurring increasingly in recent decades [24]. An example study conducted in China revealed that the energy expenditure of occupational activity decreased by more than 22% and that the energy expenditure of domestic activity decreased by more than 51% over 9 years [25]. Other studies in the United States reported a steadily increasing trend of low-activity occupations of 76% from 1950 to 2000 [26] and a decreasing occupation-related caloric expenditure of more than 124 calories per day from 1960 to 2008 [27]. Prolonged sitting time adversely affects cardiometabolic health among office workers, an already at-risk population for metabolic syndrome [28]. For example, a study conducted in Central Iran reported that approximately 36% of office workers had metabolic syndrome [29]. Other studies have revealed that approximately one in ten office workers are at risk of metabolic syndrome in Korea [30] and Great Britain [31]. Physical activity promotion interventions have a strong positive impact on people with metabolic syndrome [32]. Nevertheless, several factors, such as the nature of the job and lack of motivation and time [33-35] for exercise, remain key barriers for office workers to adhere to an active lifestyle. Consequently, gym attendance rates are low even among people paying for membership [36], and more than 75% of people fail to keep their health target for more than 3 years [37].

Exergames are defined as video games that require players to be physically engaged in them to play [38,39]. Several systematic and narrative reviews have provided preliminary evidence for the correlations between playing exergames and users' physical activities [40,41]. For example, the contribution of exergames to increasing older adults' health and wellness through physical activity has been validated [41]. Previous studies have demonstrated that exergames can be used as interventions to increase physical activity, particularly among obese individuals [42]. With the ongoing advancement of virtual reality (VR) technology, exergames have become more immersive for users. The concept of immersion is defined as "users' engagement with a VR system that results in being in a flow state" [43]. Owing to the technology limitations of conventional VR, several shortages have been presented to users, such as difficulty in producing dynamic natural environments and interaction deficiencies in human-environment simulations. In contrast, with the development of visualizations and interactions with virtual environments, new immersive VR methods can address these limitations and lead to more accurate

and efficient virtual environment assessments [44]. Additionally, its new application in exergame areas has already shown potential for promoting the health and well-being of some disabled youth [45]. Nevertheless, research on the health impact of immersive exergames remains rare. A search of the terms "immersive exergame" or "video game," "physical activity" or "exercise," "cardiometabolic" or "metabolic syndrome," and "office worker" produced 0 results in the Scopus database as of May 6, 2024 [46]. Thus, using immersive exergames to promote physical activity in relation to cardiometabolic health is still in its infancy among office workers, with a need for increased knowledge about this topic. Therefore, as the first randomized controlled trial (RCT), to the best of our knowledge, the purpose of this study is to examine the effects of at-home immersive VR exergames on clinical risk factors among office workers, an already at-risk population for metabolic syndrome.

Methods

Study Design

RCTs, a top-level research methodology in the area of evidence-based medicine [47], have played a significant role in evaluating the effects of lifestyle changes on metabolic syndrome [48-50]. This protocol is a longitudinal pilot study that uses a 3-arm parallel-group RCT to examine the interventional efficacy of an at-home immersive VR exergame on several clinical risk factors of metabolic syndrome among office workers. On the basis of prior research on exercise and physical activity interventions [48,51], a 12-week duration was selected for this trial, as it is a commonly used period for evaluating the efficacy of interventions targeting metabolic syndrome. Several clinical risk factors for metabolic syndrome, as well as active and sedentary behavior, will be monitored in three stages during this 12-week trial. Stage 1 will be at the start of the trial, Stage 2 at week 6, and Stage 3 at the end of the trial. The therapeutic effects of the at-home immersive VR exergame intervention for metabolic syndrome will be evaluated by comparing these risk factors among three groups: the VR exergame intervention group, the regular physical activity control group, and the nonexercise control group. The study follows two checklists: the CONSORT-EHEALTH (Consolidated Standards of Reporting Trials Statement for Randomized Controlled Trials of Electronic and Mobile Health Applications and Online TeleHealth) [52] and the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials; Multimedia Appendices 1 and 2) [53,54].

Participant Recruitment

For this exploratory study, a convenience sampling method will be used to recruit 120 office workers from six office-oriented information technology companies in Guangzhou City, Guangdong Province, located in Southern China. This group represents a high proportion of physically inactive individuals [55,56] and is at greater risk of developing metabolic syndrome [56-58]. Recruitment emails will be sent to participants via the Tencent Enterprise Mailbox [59], a platform that allows companies to create email accounts with their corporate domain. This platform serves as a communication and office tool to support enterprises in providing unified notifications to office workers and to support office workers in providing timely and efficient feedback. The inclusion criteria for participants are office workers who are 16-60 years old (based on the standard age of the Labor Law of the People's Republic of China), capable of standing and exercising, and have no history of heart disease, cancer, or dementia. Additionally, participants should be interested in playing with the exergames and willing to adhere to a 12-week intervention exergame treatment because of the nature of the trial.

This research aims to examine the effects of at-home immersive VR exergames on the clinical risk factors for metabolic syndrome. Hence, individuals who are already engaged in more than 150 minutes per week of moderate to vigorous intensity physical activity will be excluded [60]. Additionally, pharmacological treatments, such as metabolic syndrome–related medicines (insulin sensitizers and biguanides, orlistat, sibutramine, etc), some surgeries (bariatric surgery), and traditional Chinese medicine (herbal medicine of ginseng, berberine, bitter melon, etc), are the other exclusion criteria because of their potential to influence cardiometabolic outcomes [61,62].

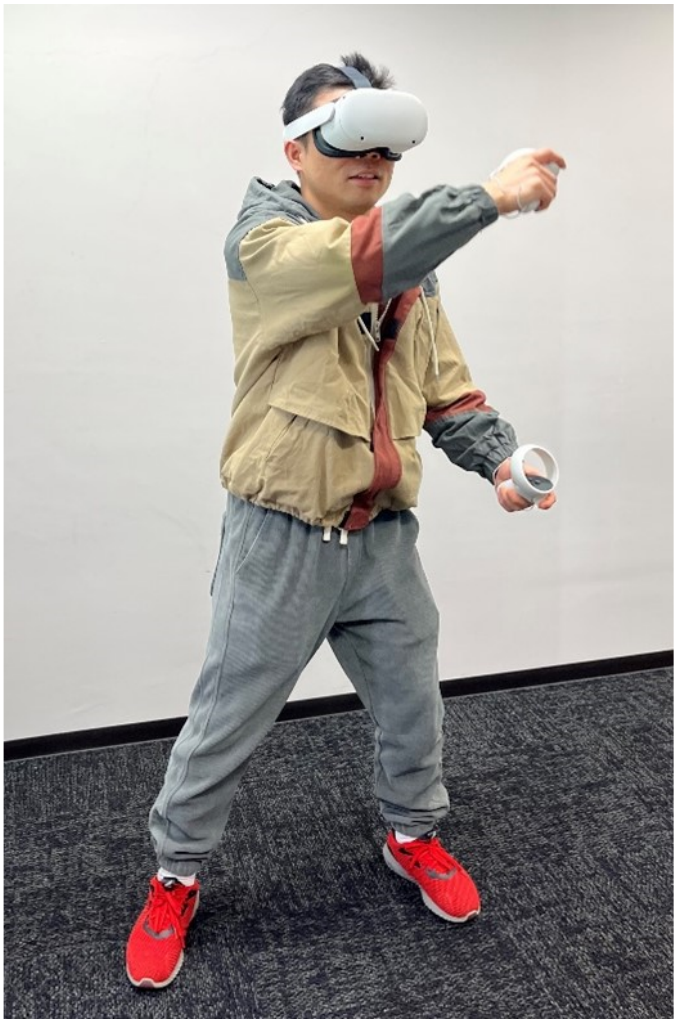
First, to encourage participation, some basic information related to exercise for health and immersive VR exergames will be introduced to potential participants. After a detailed explanation of what is needed during the trial, a precheck of the inclusion and exclusion criteria will be asked to identify eligible participants. Then, participants who meet the criteria will be instructed to review the information and provide informed consent and assent for this study. Given the nature of the clinical risk factors to be collected, a data collection center will be arranged at a cooperative clinic, and its address will be shared with all the participants for data collection and allocation of experimental equipment and material at the start of the trial.

Intervention and Control Groups

Following RCT guidelines [63,64], participants will be randomized into three equal groups: (1) the at-home immersive VR exergame intervention group, (2) the regular physical activity control group, and (3) the nonexercise control group. Including both the regular physical activity and nonexercise control groups will help determine whether VR exergame intervention offers unique benefits beyond those achieved through traditional exercise or no intervention. This design allows us to isolate the specific effects of immersive VR exergames. The at-home immersive VR exergame intervention includes a 12-week trial of exercise using Meta Quest 2, as shown in Figure 1. The Meta Quest 2 device is a valid tool that has been used in previous studies to support physical activity [65-68]. A VR headset and 2 handheld controllers are contained in the Meta Quest 2 set. Several active aerobic game apps will be installed on headset devices. These apps include the following [69]: Beat Saber (exercise: full-body, aerobic), Synth Riders (exercise: dance, aerobic), OhShape (exercise: dance, aerobic), Ragnarock (exercise: arms, shoulders, aerobic), Dance Central (exercise: dance, aerobic), Until You Fall (exercise: back, shoulders, arms, aerobic), In Death: Unchained (exercise: arms and shoulders, endurance/aerobic), and Space Pirate Trainer (exercise: full-body, aerobic). In these immersive games, the

users can present their body movements in the game world from a first-person perspective. Moreover, they are all designed to motivate users to participate in physical movements with various categories of motivational affordances. For example, Beat Saber is a rhythm game in which users need to move their bodies to slice blocks at an exact angle. Physical activities such as arm waving, moving, and squatting with an accelerating speed are motivated in the game with affordances of rank, point, and record. The participants in the VR exergame intervention group will be instructed to play one or more of these exergames for at least 150 minutes per week, which is in line with the World Health Organization's physical activity guidelines [60]. They will be requested to record the frequency and duration of their exergaming sessions. Participants in the regular physical activity control group will engage in a physical activity routine similar in duration and intensity to the VR exergame intervention. Participants in the nonexercise control group will not receive any specific exercise instructions. All groups will be advised to maintain regular eating and working habits without making significant changes throughout the 12-week trial. After completing the trial, participants in both control groups will be offered the same procedures as the intervention group, but their data will not be collected.

Figure 1. An example of exercising with aerobic immersive VR exergame using Meta Quest 2 (source: the authors). VR: virtual reality.



Measures

This exploratory pilot study aims to test the intervention of at-home immersive VR exergame on metabolic syndrome. Two variables, including clinical risk factors for metabolic syndrome and active and sedentary behaviors, will be measured throughout the three stages of the trial. Demographic information will be collected only at stage 1. Major clinical risk factors are objectively measured from participants' blood tests and a sphygmomanometer. The Global Physical Activity Questionnaire (GPAQ) will be used to measure participants' active and sedentary behaviors. A summary of the stages, measures, and indicators is shown in Table 1.

Table 1. Summary of stages, measures, and indicators.

Measures and indicators	Timeline		
	Stage 1	Stage 2	Stage 3
Demographics			
Age, gender	✓		
Clinical risk factors			
HDL-C[a]	✓	✓	✓
LDL-C[b]	✓	✓	✓
Impaired fasting glucose	✓	✓	✓
Insulin	✓	✓	✓
Triglycerides	✓	✓	✓
Blood pressure	✓	✓	✓
Waist circumference	✓	✓	✓
BMI	✓	✓	✓
Active and sedentary behaviors			
Exercise time (including exergaming time)	✓	✓	✓
Sedentary time	✓	✓	✓

[a]HDL-C: high-density lipoprotein cholesterol.

[b]LDL-C: low-density lipoprotein cholesterol.

To test the therapeutic effect of this intervention, primary clinical risk factors for metabolic syndrome, including blood tests for HDL-C, LDL-C, impaired fasting glucose, insulin, and triglycerides, along with sphygmomanometry of blood pressure, waist circumference, and BMI, will be measured [4,70,71]. Owing to several merits of immersive VR exergames, such as physical engagement [38,39], the nature of immersion, and attractiveness [43], the use of VR exergames may have a significant effect on behaviors, such as exercise and sitting time [72]. Therefore, we use the GPAQ to observe the changes in active and sedentary behaviors produced by immersive VR exergames. Moreover, the validity of the GPAQ has been proven for monitoring physical activity in health promotion research [73]. The whole questionnaire includes 16 items for 3 intensities (light, moderate, and vigorous intensity) of physical activity and sedentary behavior during work, transport, and leisure time [74]. The paper form will be printed and passed to participants to assess the changes in active and sedentary behaviors during the trial.

Study Procedure

Each group in this study will consist of 40 randomly allocated participants (using a simple computer-generated random number sequence managed by JZ), and the trial will be conducted in a single-blinded structure. In this three-arm study, participants will receive the VR exergame intervention, regular physical activity, or no exercise at all. The participants will inherently be aware of their assigned activity. However, they will be blinded to the specific study hypotheses and the detailed objectives regarding comparing the 3 groups. To reduce perceived differences, participants in both control groups will receive VR exergame devices after completing the trial, but no data will be collected from this phase. Additionally, outcome assessors and data analysts will remain blinded to group assignments to prevent bias in data collection and analysis. This single-blind design helps reduce bias in the interpretation of the study results, even though participants are aware of their assigned activity.

The comprehensive framework for this protocol consists of 3 stages over 12 weeks and the allocation of items for each stage is shown in Table 2. In stage 1, when participants arrive at the data collection center, experiment coordinators will distribute and explain the manual booklet to all participants, which includes a description of the procedures, requirements, and address for inquiries. After participants have confirmed the contents and requirements of the manual, the experiment coordinators and clinic nurses will collect demographics, clinical risk factors, and GPAQ from all participants as the baseline data. A Meta Quest 2 set of equipment (entire trial), GPAQ questionnaire (0 to 6 weeks), and a recording sheet of exergaming time (0 to 6 weeks) will be additionally assigned to the VR exergame intervention group. In stage 2, the GPAQ questionnaire (7 to 12 weeks) will be assigned to all 3 groups and a recording sheet of exergaming time (7 to 12 weeks) will be additionally assigned to the VR exergame intervention group. In stage 3, only the Meta Quest 2 set of equipment will be assigned to both control groups. The necessary items for each stage will be passed to participants when they arrive at the data collection center.

Table 2. Timeline and allocation of items.

	Stage 1[a]	Stage 2[b]	Stage 3[c]
VR[d] exergame intervention group	• Manual booklet • Demographic questionnaire • GPAQ[e] • Meta Quest 2 set • Recording sheet of exergaming time	• GPAQ • Recording sheet of exergaming time	—[f]
Regular physical activity control group	• Manual booklet • Demographic questionnaire • GPAQ	• GPAQ	• Meta Quest 2 set
Nonexercise control group	• Manual booklet • Demographic questionnaire • GPAQ	• GPAQ	• Meta Quest 2 set

[a]Start of the trial.

[b]Week 6 of the trial.

[c]End of the trial.

[d]VR: virtual reality.

[e]GPAQ: Global Physical Activity Questionnaire.

[f]Not applicable.

All participants will be asked to visit the data collection center in three stages for data collection and experimental material allocation. The self-reported GPAQ questionnaire will be completed by all participants at home, as it is a convenient at-home format for exploring impacts on active and sedentary behavior. The VR exergame intervention group will record the frequency and duration of their exergaming sessions, the regular physical activity control group will track their daily exercise routines, and the nonexercise control group will report any physical activities they perform beyond their baseline. Participants will be asked to bring all self-report sheets to the data collection center at stages 2 and 3. Coordinators will collect and summarize all the completed questionnaires and recording sheets for data processing. Major clinical risk factors are objectively measured from participants' metabolic syndrome biomarkers, which are operated by professional nurses at the data collection center (cooperative clinic). Since there is a fasting biomarker for testing metabolic syndrome, all participants are required not to consume any food or drink 12 hours before blood sample collection in the morning. After the major clinical risk factor data from all the participants for the entire trial are collected, the experiment coordinators will visit and obtain the data from the data collection center.

Analyses

After 12 weeks of the trial, 3 categories of data, including demographic, clinical risk factor, and active and sedentary behavior data, will have been collected. Regarding descriptive statistics for each indicator, the changes in clinical risk factors during the first 6 weeks, the last 6 weeks, and the entire 12-week trial will be calculated and presented as the means, SDs, and quartiles to show differences. Active and sedentary behavior will be presented as minutes of weekly light, moderate, and vigorous-intensity physical activity, and sedentary time will be obtained from the self-reported GPAQ items. Demographic variables will be presented as sum values or percentages. Additionally, the diagnosis of metabolic syndrome for all groups of participants will be summarized into sums and percentages at each stage according to the definition from a World Health Organization consultation report (high levels of insulin and impaired fasting glucose, together with at least two of the following items: HDL-C concentration less than 35 mg/dL for men [39 mg/dL for women], triglyceride concentration greater than 150 mg/dL, a waist circumference greater than 37 inches, BMI greater than 30 kg/m^2, systolic blood pressure greater than 140 mm Hg and diastolic blood pressure greater than 90 mm Hg) [4,70].

As it will be adjusted for demographic variables, the linear mixed model, which is recommended in the literature for individually assigned RCTs [75], will be used as an analysis method for determining the effects of the intervention. In cases where participants drop out or are nonadherent, missing data will be handled via multiple imputation techniques. The primary outcome assessed is the change in clinical risk factors for metabolic syndrome, including HDL-C, LDL-C, triglycerides, blood pressure, waist circumference, BMI, impaired fasting glucose, and insulin. The linear mixed model will compare these clinical risk factors across the 3 groups—VR exergame intervention, regular physical activity control, and nonexercise control groups—over three stages. The model will also assess the interaction between groups and time to determine whether the VR exergame intervention has different or additional effects compared with regular physical activity and no physical activity. Adherence to the intervention will be assessed through daily self-report logs for all participants and included as a covariate to account for variations in engagement with the interventions. Additionally, sensitivity analyses will be conducted to examine the potential impact of varying adherence levels on metabolic outcomes. This approach ensures that adherence variations are properly considered when the study's results are interpreted. In this study, the intervention or control groups are fixed factors,

and demographic factors would be considered as random factors for accommodating variabilities within or between participants. All available data will be imported into Stata (version SE 15.1; Stata Corp) for analysis, and the significance level will be set at $P<.05$. As this is an exploratory pilot study, the primary objective is to assess feasibility and gather preliminary data. Given the lack of prior studies using immersive VR exergames in this context, conducting a power analysis would be speculative. The focus of this pilot is to generate effect size estimates and assess practical considerations, which will inform the design of a future, fully powered RCT. In the larger RCT, a formal power analysis will be conducted using the data generated from this pilot study.

Ethical Considerations

This study was approved by the Institutional Ethics Committee of Guangzhou University, China (2024-112; September 25, 2024). Initially, potential participants will be provided with basic information regarding the benefits of exercise for health and immersive VR exergames. Subsequently, interested individuals will receive a detailed explanation of the study process, and they will be asked to sign the informed consent and assent forms. In addition, some personal information is required during this trial, including name, age, gender, email address, home address, and phone number for the purpose of marking data, sending the results of blood tests and diagnosis of metabolic syndrome, or analyses (eg, as covariates). All participant information will be collected directly by the experiment coordinator (JZ) to ensure the privacy of their personal information. Strict measures will be implemented to manage and store all the collected data. To compensate for participation, participants will be rewarded with RMB 150 (approximately US $21) for completing each stage, whereas participants who complete all the processes of the trial will be rewarded with RMB 500 (approximately US $71). All incentives will be sent via a registered postal cash envelope. For visiting the data collection center at each stage, transportation fees will also be reimbursed.

Results

This study was approved by the ethics committee of Guangzhou University, China, as of September 25, 2024. The completion of participant recruitment and the initiation of the intervention or control trial are anticipated by the middle of 2025. The full processes of this trial, including data analysis and paper writing, are expected to be completed in early 2026.

Discussion

Principal Findings

Our findings will reveal whether the clinical risk factors for metabolic syndrome within the intervention group significantly improved after a 12-week exergaming intervention compared with those in the two control groups. The increase in the time engaged in physical activity (all types of light, moderate, and vigorous intensity) and the decrease in the time spent in sedentary behavior will also be evaluated.

The phenomenon of physical inactivity among employed adults has been occurring increasingly worldwide because of the development of society and technology in recent decades [16,17]. Consequently, the population of employed adults at risk for metabolic syndrome is growing across the globe [14,15]. Several primary factors, such as a lack of motivation, weather restrictions, and busy schedules for work, social lives, and family, have been reported as key barriers to physical activity [34]. Notably, at-home immersive VR exergames can provide several advantages to address these barriers to physical inactivity for employed adults. However, to our knowledge, few studies have explored the health effects of immersive exergames. This study is the first RCT and aims to examine the effectiveness of at-home immersive VR exergame interventions for improving metabolic syndrome. Our hypotheses were based on several advantages of at-home immersive VR exergames. The first benefit to exergames is engagement and enjoyment, as various types of motivational affordances (eg, points, leaderboard, and badges) were found within the gaming process along with several positive psychological effects (eg, joyfulness) [76]. The second advantage is the convenience of at-home exercise, which can mitigate weather restrictions and fit into a flexible schedule. In addition, exergames also have positive impacts on both physical health and cognition [77], which may offer pathways to improve rehabilitation and wellness [41]. Although these positive results have been reported, there is also some evidence that these positive impacts from exergames may be temporary [78].

Strengths and Limitations

This study has several limitations. First, the possibility of VR sickness resulting from individual differences [79] may result in variable exercise time, which can indirectly influence the primary clinical risk factors for metabolic syndrome and bias the efficacy of the intervention. Second, the unsupervised process of self-recorded exercise time and self-reported GPAQ items may produce inexact data about trial results. Third, according to trial length within exercise or physical activity studies, 12 weeks to 1 year is the range for determining interventional efficacy for comprehensive metabolic syndrome risk factors [48,51]. The 12-week trial for this study is consistent with the minimum length threshold, but a longer treatment period may produce more robust and efficacious results. Additionally, our participants will be recruited from Guangzhou, China, where particular life habits and social conventions, such as long work hours [80] and food habits [81], may produce results with limited generalizability. Although these limitations exist, the strengths of this study include its RCT design, the use of clinical measures of risk factors for metabolic syndrome, the novel examination of the impacts of exergames on promoting physical activity and metabolic syndrome, and the improvement of health conditions within the at-risk population of office workers.

Conclusions

The use of at-home immersive VR exergames for improving metabolic syndrome is an emerging topic for promoting physical activity related to cardiometabolic health. The primary aim of this proposed study is to assess the feasibility and preliminary

effects of an at-home immersive VR exergame intervention on the clinical risk factors for metabolic syndrome. The results of using at-home immersive VR exergames may contribute to promoting office workers' health conditions and help reduce the burden of metabolic syndrome risk among a large and increasingly sedentary population. These results will inform the design and implementation of a larger-scale, fully powered RCT. This exploratory pilot RCT will provide data regarding the intervention's practicality and initial effectiveness, which will guide future research efforts.

Acknowledgments

MJK is supported by the JSPS KAKENHI (grant 23K09701). KO is supported by the JSPS Grants-in-Aid for Scientific Research program (grant 20H04113).

Conflicts of Interest

None declared.

Multimedia Appendix 1
CONSORT-eHEALTH checklist (V 1.6.1).
[PDF File (Adobe PDF File), 1013 KB - resprot_v14i1e64560_app1.pdf]

Multimedia Appendix 2
SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) checklist.
[PDF File (Adobe PDF File), 99 KB - resprot_v14i1e64560_app2.pdf]

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Abbreviations

CONSORT-EHEALTH: Consolidated Standards of Reporting Trials Statement for Randomized Controlled Trials of Electronic and Mobile Health Applications and Online TeleHealth
GPAQ: Global Physical Activity Questionnaire
HDL-C: high-density lipoprotein cholesterol
LDL-C: low-density lipoprotein cholesterol
RCT: randomized controlled trial
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials
VR: virtual reality

Edited by A Schwartz; submitted 20.07.24; peer-reviewed by A Tillander; comments to author 23.09.24; revised version received 11.10.24; accepted 26.11.24; published 20.01.25.

Please cite as:
Zhao J, Yasunaga A, Kaczynski AT, Park H, Luo Y, Li J, Shibata A, Ishii K, Yano S, Oka K, Koohsari MJ
At-Home Immersive Virtual Reality Exergames to Reduce Cardiometabolic Risk Among Office Workers: Protocol for a Randomized Controlled Trial
JMIR Res Protoc 2025;14:e64560
URL: https://www.researchprotocols.org/2025/1/e64560
doi:10.2196/64560
PMID:

Protocol

Tablet- and Group-Based Multicomponent Cognitive Stimulation for Older Adults With Mild Cognitive Impairment: Single-Group Pilot Study and Protocol for Randomized Controlled Trial

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Abstract

Background: Cognitive stimulation therapy is a group-based psychological treatment for people with dementia as well as those with mild cognitive impairment (MCI) and is shown to improve both cognition and quality of life. Previous studies have indicated the potential to benefit from the use of technological devices in group interventions.

Objective: The pilot study aimed to assess the effectiveness of a tablet- and group-based multicomponent cognitive stimulation therapy (MCST) for enhancing cognitive functions among older adults with MCI. The following study aims to report the protocol for a trial evaluating whether the MCST program is affecting individuals with MCI.

Methods: In the first study, 30 individuals with MCI participated in 10 sessions of the tablet- and group-based MCST group. A subsequent protocol study will compare tablet-based MCST, tablet-based cognitive stimulation therapy, and control groups among 93 individuals with MCI. All participants will be recruited from older adults living in semiurban communities. Intervention groups will be facilitated by trained therapists, nurses, or psychologists. The study will be assessed by a pre- and posttest evaluation, including computer-based neuropsychological tests and electroencephalography assessment. The effects of several indicators, such as cognitive functions, behavioral, and emotional, will be analyzed as being indexed by their neurophysiological data.

Results: The pilot study showed significant cognitive improvement (P<.001), reduced depression (P=.002), and decreased state anxiety (P=.001) post intervention. Quality of life remained unchanged (P=.18). The randomized controlled trial study was funded in March 2023. Enrolling began in August 2023 and was completed in December 2023. The data analysis was started, and the results are expected to be published by mid- to late-2025.

Conclusions: The study is the first tablet-group–based MCST for older adults with MCI in middle-income countries. It will provide deeper insight into participants' neuropsychological data, thus identifying specific processes underlying physiologically measured positive outcomes. Furthermore, the project will deliver solid and integrative results to mental health professionals in terms of knowledge and guidance for implementing the tablet- and group-based MCST in people with MCI.

Trial Registration: Thai Clinical Trials Registry TCTR20230829004; https://tinyurl.com/3wuaue3e

International Registered Report Identifier (IRRID): DERR1-10.2196/64465

(JMIR Res Protoc 2025;14:e64465) doi:10.2196/64465

KEYWORDS

computerized cognitive stimulation; multisensory integration; cognitive decline; aging; electroencephalography; randomized controlled trial; RCT; protocol; cognitive stimulation; mild cognitive impairment; cognitive; cognition; cognitive simulation therapy; CST; MCI; tablet; effectiveness; pilot study; neuropsychological tests; behavioral; emotional

Introduction

Mild cognitive impairment (MCI) is the stage between normal aging and dementia, including probable Alzheimer disease, characterized by noticeable cognitive deficits that do not impair daily functioning significantly [1-3]. The cognitive domains affected by MCI include learning and memory, language, visuospatial abilities, executive functions, and psychomotor skills. Notably, evident impairment in any of these domains is sufficient for an MCI diagnosis [4]. Furthermore, particular deficits in emotions such as anger, sadness, and fear have been observed in individuals with MCI, with anxiety being more prevalent in clinical samples than in community-based ones [5,6]. In addition, subjective cognitive decline has been linked to anxiety symptoms, independently increasing the risk of MCI or dementia [7]. Depression is also associated with early cognitive impairment, but patients with depression typically do not exhibit the memory deficits observed in MCI or dementia [8,9].

Group-based cognitive stimulation therapy (CST) has been shown to improve both cognitive functions and quality of life in older adults with dementia or MCI [10,11]. The guiding principles of CST were adapted to create 15 fundamental principles of individual-centered CST, including mental stimulation, reminiscence, learning and communication stimulation, and a person-centered approach. The program includes various activity sessions encompassing different areas such as life history, current affairs, creative tasks, games, and cognitive challenges [12,13]. The belief that continuous participation in various mental activities improves cognitive and social functioning underpins cognitive stimulation treatments [14]. Furthermore, Silva and colleagues [15] discovered that in MCI or mild dementia, a cognitive stimulation program could account for the improved cognition response observed. These data reveal that the lower the cognitive damage, the better the neuroplastic capacity and ability to learn, and the greater the potential to induce neurogenesis. Therefore, cognitive interventions should be implemented at the earliest stages of cognitive impairment [15].

Recent studies on tablet-based intervention with cognitive stimulation have focused on the feasibility, acceptability, and cognitive and psychosocial effects of the computerized cognitive stimulation (CCS) and computerized cognitive engagement programs. Both treatments were efficient and acceptable, allowing patients with MCI to improve in several aspects of their cognitive and psychosocial functioning. Still, the effect sizes on cognition, such as free recall and the Trail Making Test part A, were moderate, favoring the CCS group [16]. A further study explored whether CCS induced differential effects in older adults with MCI according to the degree of white matter hyperintensities, were separated into no-to-little and moderate-to-severe groups. Following the session, both groups improved on numerous cognitive tests but not in mood and psychosocial features except for motivation [17]. Previous research suggested that the effectiveness of tablet-based CST on cognition, emotion, or psychosocial outcomes should be investigated [17]. Furthermore, the increased computerization of intervention programs is a step toward treatment uniformity. Computer-based intervention methods are cost-effective, noninvasive, and simple to execute, requiring little human and financial resources [18]. In particular, tablet-based CST should also be further examined in middle-income or developing countries since the expected findings will close the gaps and expand the generalizability of the theories and therapeutic technologies.

In addition, extant research shows that CST is effective in enhancing cognitive functions in people with mild dementia investigated by using the resting-state functional magnetic resonance imaging technique [19] that provided solid evidence of enhancement in the neuronal networks in terms of structures and functionalities by using a group CST. Nonetheless, the previous research came with methodology limitations regarding the small sample sizes and comparison between groups. Furthermore, there is a lack of studies to show the effect of changes in neurobiological features in older adults with MCI. Thus, this study aims to monitor the effectiveness of tablet-based CST using neuroimaging techniques in people with MCI.

The underlying neurobiological factors contributing to MCI involve changes in neurotransmitters, including the noradrenergic, serotonergic, and dopaminergic systems [20]. Notably, the cholinergic system, particularly acetylcholine, plays a crucial role in cognitive function, with its decline correlating with cognitive impairment. Electroencephalography (EEG) measures have revealed alterations in brain activity patterns among individuals with MCI, including increased beta-two power and notable changes in the theta, alpha, and delta frequencies [21]. Atrophy of the hippocampus and the medial temporal lobe regions, along with hypometabolism in specific brain areas, are indicative of MCI [22]. Specifically, electrophysiological recordings and event-related potentials (ERPs) provide valuable insights into cognitive functioning. P300 latency delays have been observed in people living with MCI, and abnormalities in N400 and P600 components are associated with a higher risk of developing Alzheimer disease [23-26]. These EEG and ERP components could potentially serve as biomarkers for monitoring brain change in people with MCI.

Accordingly, the first study aims to evaluate the effects of the tablet- and group-based multicomponent cognitive stimulation therapy (MCST) program on cognition and emotions in older adults with MCI. The program draws on CST principles and multisensory stimulation techniques to create tailored activity

sessions that target cognitive function and emotions. This study hypothesizes that the intervention positively affects cognition and emotions in older adults with MCI after the intervention.

The following study aims to assess how a tablet-based MCST program, with or without multisensory integration (MSI), affects cognitive functions, emotions, and quality of life in older adults with MCI, comparing experimental and control groups designed as parallel groups. Changes in EEG and ERPs will be examined before and after the intervention. The cognitive domains targeted as primary outcomes for improvement include learning and memory, language, visuospatial abilities, executive functions, and psychomotor skills as well as emotions. Specific brain locations are associated with these domains, and the study aims to enhance the functioning of these regions to counteract the cognitive decline observed in MCI. The protocol study hypothesizes that the intervention will improve cognitive functions, emotions, and behaviors in older adults with MCI, outperforming an active comparator and control group. Expected EEG and ERP changes may reveal brain activity patterns tied to cognitive improvements, focusing on frequency bands and ERPs.

Methods

Overview

The pilot and protocol for a randomized controlled trial (RCT) intervention study have been approved by the Burapha University institutional review board (IRB4-191/2566). The study was conducted according to the Guideline for Good Clinical Practice and the Declaration of Helsinki [27]. Following the gold standard in research on intervention effectiveness—the CONSORT (Consolidated Standards of Reporting Trials; checklist provided in Multimedia Appendix 1), the RCT study design, including the proximal and distal outcomes, has been preregistered in the Thai Clinical Trials Registry (reference TCTR20230829004).

This project consisted of 2 studies. The first study involved a pilot of the MCST intervention and effective assessment of cognitive functions in older adults, which began in August 2023. The next study is the RCT, with recruitment starting in September 2023. The intervention and data collection were done over 14 weeks.

Study 1: Pilot Study

Study Design

This study investigates the efficacy of the tablet- and group-based MCST program, using a 1-group pretest-posttest design. Participants were randomly assigned to 3 subgroups, and dependent variables were measured both before and after the implementation of the program.

Participants

In total, 30 older adults participated as volunteers in the experiment. Participants ranged from 60 to 75 (mean 66.14, SD 4.72 years) years of age with normal or corrected normal vision, no color blindness or weakness, and no history of mental illness or neuropathy. Thai native speakers were capable of reading and comprehending writing. All participants were assessed using the Thai version of the Montreal Cognitive Assessment (MoCA-T) to assess cognitive impairment [28], the subjective memory complaint scale to assess complaints of defective memory [29], the Chula Index Scale and Activities of Daily Living to assess normal activities of daily living [30], and the Clinical Dementia Rating Scale to assess the absence of dementia [31]. These assessments are established screening tools as criteria for detecting MCI [32].

Participant characteristics show that among them, MCI was presented (MoCA-T scores between 17 and 24), 20% (6/30) were male and 80% (24/30) were female. Participants' occupations varied as 43% (13/30) were farmers, 10% (3/30) were freelancers, 10% (3/30) were sellers, 13% (4/30) were retired government officers, and 23% (7/30) were unemployed. Regarding health conditions, 23% (7/30) of participants had diabetes, while 40% (12/30) reported having hypertension. An additional 20% (6/30) reported other diseases. In terms of vision, 57% (17/30) of participants wore glasses and 43% (13/30) did not wear glasses.

Intervention

The MCST interventional program was adapted from group CST for MCI with 10 sessions and once a week over a period of 10 weeks [10]. The intervention is presented in the RCT study and shown in Table 1.

Table 1. Cognitive stimulation therapy sessions adapted to Thai culture.

Session	Theme	Activities
1	Physical activity	Finger exercise and using a touch screen and learning to navigate the tablet
2	Music and sound	Stimulating auditory and visual senses using old music and sounds from daily life
3	Childhood	Pictures of singers, actors, or celebrities from the past
4	Food and cooking	Different kinds of foods, recipes, and methods of cooking; being creative
5	Travel	Current affairs, places and sounds, well-known destinations and talking about the hometown
6	Occupations	People's jobs, using word games and word association
7	Sports	Sporting events, matching the picture to the word, senses, and sounds
8	Shopping	Using money, prices, and calculation
9	Household	Categorizing objects
10	Team games	Number games

Assessments

The results of the effectiveness of the tablet-based group intervention were evaluated. At the pre-and postintervention assessment, participants were asked to examine the MoCA-T, Thai geriatric depression scale (TGDS), State-Trait Anxiety Inventory (STAI)–state, and Older People's Quality of Life Questionnaire (OPQoL)-Brief (refer to Outcome Measures section for further details).

Data Analysis

Because the sample size in this study was not large enough to permit the assumption of normality on the study variables, the nonparametric test was used. The Wilcoxon signed-rank test was used to examine the effects of the tablet- and group-based MCST on cognition, emotions, and quality of life. The rank-biserial correlation coefficient (r_B) was considered as effect size and is interpreted the same as the r coefficient, such as trivial (<0.10), small (0.10), moderate (0.30), and large (0.50) [33]. The JASP (Jeffreys's Amazing Statistics Program; Version 0.16.2.0; University of Amsterdam), an open-source statistics program, was used for paired samples and effect size analysis [34].

Study 2: RCT

Overview

The RCT aims to assess the effects of the tablet-group–based MCST program on cognitive functions and emotions and quality of life based on the differences between experimental groups with and without MSI compared with a control group, and the changes observed in EEG and ERPs during the pre- and posttest interventions. The study hypothesizes that the intervention affects cognitive functions positively in older adults with MCI after the intervention compared with an active comparator and a control group. Furthermore, it is hypothesized that the intervention improves emotion and behavior in older adults with MCI after the intervention compared with an active comparator and control group. Changes in brain waves are also expected to reveal brain activity patterns associated with cognitive improvement, focusing on frequency bands and ERPs.

Trial Design

This research uses an RCT design with an experimental group, an active comparator group, and a control group. Participants are randomly assigned to 1 of the 3 study conditions. Each participant is randomly allocated 1:1:1 to an intervention or control condition. The study is designed as a randomized, controlled trial with 3 parallel groups. Randomization will be performed by Random Allocation Software (Isfahan University of Medical Sciences) [35].

Participants

Inclusion Criteria

Participants eligible for inclusion must meet the following criteria: (1) language proficiency: participants must be native speakers of the Thai language [32]; (2) age range: the study focuses on individuals aged 60 years or older; (3) objective memory performance: inclusion is based on objective memory impairment assessments [32] using well-established evaluation tools, including the MoCA-T and clinical dementia rating [36]; (4) subjective memory complaints [32]; (5) handedness: participants must be right-handed, as confirmed by the Edinburgh Handedness Inventory; (6) color vision: normal color vision is a requirement, evaluated using the Ishihara Plate Test; (7) health status: individuals with no chronic illnesses, deafness, blindness, or an diagnosed neurological disorder are eligible to participate; (8) cognitive status: eligible participants should not exhibit signs of dementia [32]; (9) reading ability: prospective participants are expected to be capable of reading and comprehending written material; and (10) computer proficiency: participants should be able to use computer devices effectively for the study activities.

Exclusion Criteria

The following criteria will lead to exclusion from participation: (1) a diagnosis of dementia: individuals diagnosed with dementia after participating in the study, irrespective of severity, will not be included in the study; (2) systemic illness: participants with concurrent systemic illnesses that could potentially confound the study outcomes will be excluded; and (3) refusal to participate: individuals who decline to participate or express

their unwillingness to engage in the study will not be considered for inclusion.

Sample Size

The sample size in the study was estimated using the G*Power program [37]. The required sample size considering an α=.05, a Cohen *d*=0.50 (medium magnitude for the effect size) [17,38], and power=0.95, is 26 or 27 participants in each condition, that is, a total of around 80 participants. Assuming a loss of 15% [17,38,39], in the event, the final sample consists of 93 participants, approximately 31 participants in each condition.

Recruitment

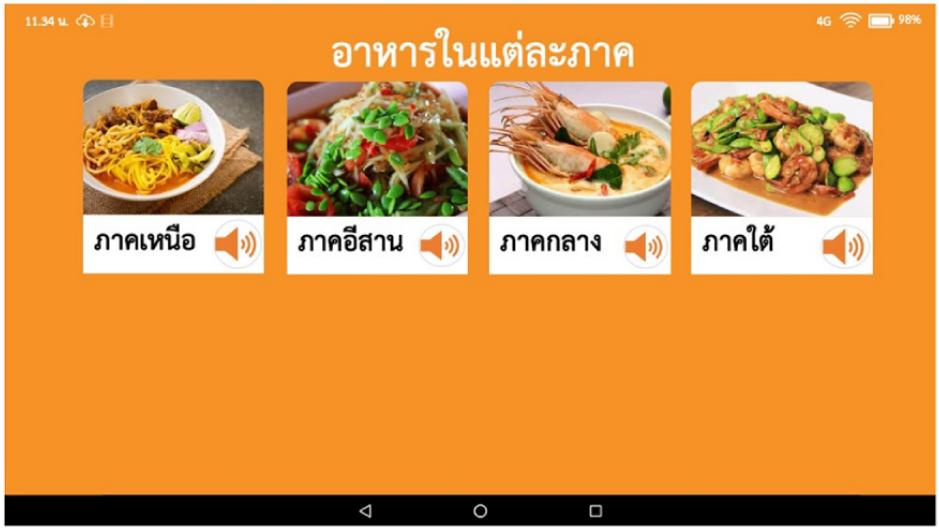
Older adults with MCI will be recruited via communities such as clubs for older adults and elderly schools in the semiurban area of Chonburi province, Thailand. Announcements regarding the study will be disseminated through radio and social media platforms (Line Messenger [Line Corporation], Facebook [Meta], and so on). Individuals who express interest will receive information and undergo a screening test. If they meet the inclusion criteria, they will be enrolled in this study.

Interventions and Control Group

Experiment Intervention

The interventional program was adapted from group CST for MCI with 10 sessions [10], the group CST principle [11,13,40], and adapting CST to other cultures [12,38]. Specifically, the program also adopted audiovisual temporal discrimination training to improve MSI [41], which was included in sessions as shown in Table 1 and Figure 1. Participants will be asked to use a 10-inch tablet with an Android operating system (Google) that has the computerized multicomponent cognitive stimulation app for each session installed so that they can participate in all activities. Intervention groups will be facilitated by trained therapists, nurses, or psychologists. Further details of the MCST intervention and the manual can be found on the website [42].

Figure 1. Screenshots of the computerized multicomponent cognitive stimulation app (screenshots present kinds of foods in different regions of Thailand).



Active Comparator

The comparator group is similar to the MCST intervention group but excludes MSI training, receiving only tablet-group–based CST. Each session will be like a structured session in the MCST intervention group.

Control Group

The participants in this group will not receive the treatment. They will be measured once at the start and then a second time 2 months later.

Data Collection

The study will take place at the Center of Excellence in Cognitive Science, which is part of the College of Research Methodology and Cognitive Science at Burapha University. Demographic and clinical information about age, gender, education, marital status, occupation, diseases, and physical issues will be self-reported at baseline. The results of the effectiveness of the tablet-based group intervention will be evaluated. The outcomes will be evaluated using measures of cognitive functions and brain waves, including EEG and ERP techniques that are recorded while participants perform the tasks.

At the beginning of the EEG and ERP assessment, participants will be asked to wear the neuro handset to correct the EEG resting-state data which will be measured during eyes-closed and eyes-open sessions at 5 minutes. Afterward, the EEG will be recorded while participants are performing the computerized neuropsychological tasks.

Cognitive functions and MSI tasks will use computer-based tasks to access neuropsychological data using PsychoPy software (Open Science Tools Ltd). Individuals will participate in a different sequence when dealing with order effects and time-related factors, changing the order by using counterbalancing. Furthermore, for each task, participants will rest for around 2 minutes before beginning the next task.

Electroencephalogram recordings on the Emotiv EPOC Flex saline and 10-20 layout 32-channel system will be recorded. The reference electrodes are located at the common-mode sensor (left side) and driven-right-leg (right side) sensor. All signals will be filtered automatically with a high-pass filter of 0.2 Hz and a low-pass filter of 45 Hz using a digital fifth-order sync filter and a sampling rate of 128 Hz, and the electrode impedance will be kept to at least 80% using EMOTIV PRO software to monitor EEG quality before recording and to collect the data [43].

Furthermore, after enrollment, the participants will be informed about the experimentation schedule, and the preconditions of the experiment such as proper sleep, and avoiding drinks like coffee and alcohol. Participants are required to shampoo their hair but avoid applying gel or lotion. Before starting the experiment, the researcher will confirm the participant's preparation before the experiment [44].

Outcomes Measures

Primary Outcomes

Learning, Memory, EEG, and ERP Components

The first running requires participants to learn and recall word pairs. The examination contains a variety of 12 pairs of words, such as related words, unrelated words, and name-word pairings. Participants are told to memorize unrelated word pairings (eg, hospital and lawyer). To test later, they are asked to recall those pairs of words. The total time for the test is approximately 10 minutes. A significant change in the recall numbers, EEG and ERP parameters (P<.05) is expected.

Executive Function Scores, EEG, and ERP Components

A standardized form of the Wisconsin Card Sorting Test, Berg Card Sorting Test will be used with the card sorting task using a 64-card deck. Participants are told to press the 1, 2, 3, or 4 keys that they believe match the card at the bottom of the screen. The cards' figures differ in color, number, and shape. The classification rule changes every 5 cards. Participants can complete the Wisconsin Card Sorting Test-64 within 10-15 minutes. The scoring includes percentage errors (%), perseverative responses (%), perseverative errors (%), nonperseverative errors (%), conceptual level responses (%), categories completed, trials to complete the first category, failure to maintain set, and learning to learn [45]. A statistically significant change in the EEG and ERP parameters (P<.05) is expected.

Language Scores, EEG, and ERP Components

The verbal fluency test is a short test of verbal functioning. It typically consists of 2 tasks, that is, category and letter fluency. Participants are given 1 minute to produce as many unique words as possible that are within a semantic category (category fluency: animal and fruit) and start with a given letter (letter fluency: words beginning with the letter Koh and letter Aoh in Thai). The participant's score in each task is the number of unique correct words [46]. For example, participants answered for animals such as dogs, cats, and monkeys, scoring 3 points for the category. The total time for the test is approximately 5 minutes. A statistically significant increase in fluency scores and EEG and ERP parameters (P<.05) is expected.

Visuospatial, EEG, and ERP Components

In the Corsi block-tapping task, participants were instructed to tap the blocks in the same serial order as presented (2 trials per sequence length ranging from 2 to 9 blocks). Participants receive 2 trials per level, starting from 2 to 9 lengths. Measures are the span (number in the longest correct sequence with the possible number from 2 to 9), the score (number of correctly reproduced sequences with the potential number from 2 to 9), and the product (span×score) [47]. The total time for the test is approximately 2-5 minutes. On the mental rotation task, participants are asked whether 2 objects rotated relative to one another (geometrical forms) are identical or mirror images [48,49]. The task consists of 69 stimuli, and each correct answer is worth 1 point, making a total of 69 points. Participants can complete the test within 5-10 minutes. A statistically significant

increase in all scores, EEG, and ERP parameters (P<.05) is expected.

Psychomotor, EEG, and ERP Components

In total, 2 reaction time tasks will be used, namely, the Deary-Liewald reaction time task and the number's reaction time box. In the simple reaction time test participants had to press a button or key in response to a single stimulus. The choice reaction time has 4 stimuli, and participants are asked to press the button corresponding to the correct response. The interstimulus interval ranged between 1 and 3 seconds and will be randomized within these boundaries. The task will record each trial's response time and the interstimulus interval for measuring [50]. The total time for the test is approximately 3-5 minutes. A statistically significant decrease in response time and total error, EEG, and ERP parameters (P<.05) is expected.

MSI, EEG, and ERP Components

The audiovisual task consisted of three conditions—2 control conditions (1 beep and 1 flash; 2 beeps and 2 flashes) and the illusion condition (2 beeps and 1 flash; 1 beep and 2 flashes). The auditory and visual stimuli will be presented simultaneously in the control conditions. The visual flash will be delivered simultaneously with the first auditory beep in the illusion condition. In each condition, the stimulus onset asynchronies used are between 150 and 300 milliseconds [51]. For a total of 80 stimuli, participants take approximately 2-3 minutes. Response time and the total error will be assessed. A statistically significant decrease in response time and total error and EEG and ERP parameters (P<.05) is expected.

The MoCA-T

The MoCA-T version 8 is the most frequently used screening test, and it was produced as a quick screening tool for MCI and dementia in its early phases. The visuospatial (5 points), naming (3 points), attention (6 points), language (3 points), abstract (2 points), memory (5 points), and orientation (6 points) abilities are assessed on this examination. When an assessment was completed, all scores were totaled out of a possible overall of 30. Higher scores indicated more significant cognitive function. The internal consistency of the MoCA-T was excellent (Cronbach α=0.91) [28]. It is expected to see a statistically significant increase (P<.05) in global cognition.

The TGDS-15

The TGDS-15 is a structured self-report scale that assesses depression symptoms over the previous week. The scale contains 15 items, with responses chosen as agreeing or disagreeing. The scale has a cutoff point for depression, which is 0-5 for no depression, 6-10 for suggestive of depression, and 11-15 for depression [52,53]. The Cronbach α coefficient of The TGDS-15 was 0.83, which showed high internal consistency [53]. It is expected to see a statistically significant decrease (P<.05) in depressive symptoms.

The STAI

On the State Anxiety Inventory Form Y-I scale, the STAI-state has the 20-item Thai version and has been validated by Thapinta [54]. Participants are asked how often, during the last 2 weeks, they have been bothered by each of the 30 questions of generalized anxiety disorder. Response options are "not at all," "for several days," "more than half the time," and "nearly every day," scored as 0, 1, 2, and 3, respectively. Therefore, the scores range from 0 to 80, with scores of ≥20, ≥40, and ≥60 representing mild, moderate, and severe anxiety symptom levels, respectively. The Cronbach α coefficient of the Thai STAI-state was 0.90, which showed high internal consistency [54]. A statistically significant decrease (P<.05) in the state anxiety symptom is expected.

Secondary Outcomes

The OPQoL-Brief in the Thai version [55] consists of 13 questions that are scored strongly agree=1, agree=2, disagree=4, and strongly disagree=5. The items are added together to get a total OPQoL-Brief score, and then positive items are reverse coded, such that higher scores imply better QoL. The entire sum score varies from 13 to 65. The Cronbach α coefficient of OPQoL-Brief was 0.94, showing that the first and the second questionnaire responses with a 2-week interval were highly stable [55]. A statistically significant increase (P<.05) in the OPQoL-Brief score is expected.

Data Analysis

As part of demographic and behavioral data, the means and SDs will be calculated to explain the general description such as age, gender, education, MoCA-T, TGDS-15, STAI-state, and OPQoL-Brief. Cognitive function scores of the 3 groups will be compared using 1-way analysis of covariance (ANCOVA) to examine differences in posttest scores of various neuropsychological tests controlling for pretest scores. The test involves computing an F-ratio large enough to indicate significant mean differences. Furthermore, ANCOVA is customary to measure the effect size with partial ω^2. In addition, post hoc analyses were performed using the Bonferroni Test.

In total, 4 EEG frequency bands' relative powers will be analyzed, and the latency and amplitude of ERP components will also be assessed. Furthermore, the EEG data collected will be cleaned and manipulated using the EEGLAB toolbox in the MATLAB environment. One-way ANCOVA will be applied to examine differences in the EEG and ERP posttest of various components among intervention groups (MCST, CST, and control) controlling for pretest scores.

Ethical Considerations

The study was approved by the Burapha University institutional review board (approval IRB4-191/2566; issue date: August 11, 2023; valid until date: August 11, 2024). It was also registered with the Thai Clinical Trials Registry (dated August 29, 2023; TCTR20230829004). All participants provided informed consent. All data will be anonymized. The participants were provided travel compensation (US $33 per participant).

Results

Pilot Study

The participants showed significantly improved global cognition as measured by the MoCA-T (P<.001), depression as measured by the TGDS (P=.002), and state anxiety as measured by the STAI-state (P<.001) but not in the quality of life as measured

by the OPQoL-Brief (*P*=.18). Furthermore, effect sizes among significant measures were large (r_B: 0.85-1.00; Table 2).

Table 2. Assessment results for older adults with mild cognitive impairment who completed both pre- and posttests.

Measure	Pretest (n=30), mean (SD)	Posttest (n=30), mean (SD)	Wilcoxon Signed Ranks Test		Effect sizes[a] (95% CI)
			Z value	*P* value	
MoCA-T[b]	19.50 (2.13)	23.13 (2.71)	4.70	<.001	1.00 (1.00 to 1.00)
TGDS[c]	3.53 (1.89)	2.40 (1.10)	2.99	.002	.85 (0.61 to 0.95)
STAI[d]-state	43.37 (5.40)	37.30 (5.87)	3.96	.001	.87 (0.73 to 0.94)
OPQoL[e]-Brief	52.47 (10.83)	56.00 (5.97)	1.33	.18	.28 (–0.13 to 0.61)

[a]The rank-biserial correlation coefficient (r_B).

[b]MoCA-T: Thai version of the Montreal Cognitive Assessment.

[c]TGDS: Thai geriatric depression scale.

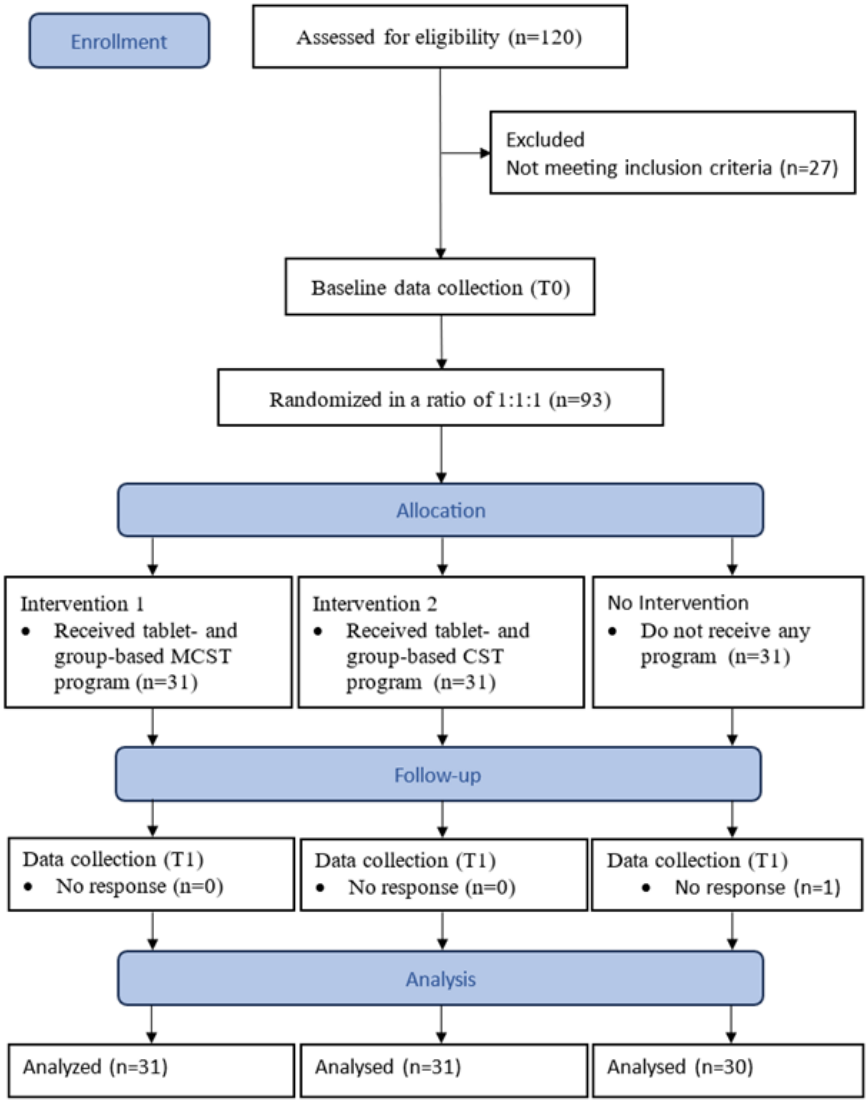
[d]STAI: State-Trait Anxiety Inventory.

[e]OPQoL: Older People's Quality of Life Questionnaire.

The RCT

In the RCT, the project secured funding in March 2023, started in April 2023, and received recommendations and approval from the Burapha University institutional review board in August 2023. Baseline data collection was conducted in September 2023, and the postintervention data collection started in December 2023. From baseline, we have data from 93 older adults with MCI. Results from the study will be available in mid- to late-2025 at the earliest and will be published in peer-reviewed international and national journals, as well as presented at relevant conferences. An overview of the trial flow is presented in Figure 2.

Figure 2. CONSORT (Consolidated Standards of Reporting Trials) flow diagram. CST: cognitive stimulation therapy; MCST: multicomponent cognitive stimulation therapy; T0: baseline for pretreatment assessment (ie, week 0); T1: the week immediately after the intervention (ie, week 10).



Discussion

Findings From the Pilot Study

The pilot study determined the cognitive function, emotions, and quality of life among older adults with MCI in Thailand. Such improvement was attributed to the tablet- and group-based MCST for 45 minutes per session and once a week over a period of 10 weeks aimed at improving their cognition, emotions, and quality of life. Findings showed that older people with MCI showed improvement in global cognitive function, as proven by scores on MoCA-T. Furthermore, this study also indicated a reduction in depression and anxiety, as demonstrated by scores on TGDS and STAI-state. However, the intervention cannot enhance the quality of life among participants. These findings support that the tablet- and group-based MCST program effectively improves global cognitive function and emotions in older adults with MCI.

The study findings align with previous research regarding CCS using tablet-PCs and social interactions among older adults with MCI [16,17]. A recent study employed the KODRO app (Altera-Group) on Android tablets, incorporating functions like cognitive games, communication tools, and entertainment features to engage various cognitive domains in participants with MCI. The investigation demonstrates that CCS using tablet-PCs enhances cognitive function [16], consistent with meta-analytical findings indicating cognitive training's positive impact on global cognitive function, memory, and working memory in older patients with MCI [56]. Further evaluation of specific cognitive domains will involve neuropsychological assessments and EEG in older adults with MCI.

In terms of emotion, depression and anxiety are common in people with MCI [57-59]. Fascinatingly, emotional symptoms, such as depression and anxiety, decreased following the session. Contrary to the previous study [16], there was unchanged postintervention. Nonetheless, other findings found that not only cognitive functions but also depression and anxiety were improved in people with MCI after they participated in the computerized cognitive training program [60]. The MCST program's social interaction through discussions and games may explain the findings, aligning with research showing that social engagement enhances cognitive interventions. This discovery aligns with previous research, indicating that social

interaction has the potential to modify the outcome of cognitive intervention programs [61].

In contrast to our hypotheses, this study had no significant effect on the participants' quality of life. Perhaps because all of our participants were aware of their diagnosis and expressed low satisfaction with their cognition and physical well-being, no change in their quality of life was seen after postintervention. It has been shown that patients with MCI who are aware of their diagnosis or have high memory complaints have a poorer quality of life than those who are oblivious to their diagnosis or have low memory complaints [62,63]. However, previous studies showed that reminiscence therapy improved cognitive performance and quality of life, supporting CST's use for cognitive decline [64]. Cognitive stimulation benefits daily activities in MCI [10], while another study reported enhanced social, physical, and mental health [65]. Londos et al [66] noted the quality of life gains from goal-oriented rehabilitation, though self and mood subscales showed no significant change. This suggests that enhancing the quality of life in patients with MCI who are aware of their diagnosis may require more targeted interventions.

Principal Results for the RCT Study

The protocol for the RCT study introduces a comprehensive cognitive intervention program designed to address cognitive functions in older adults with MCI. The proposed program is tailored to target both cognitive domains and MSI. The study hypothesizes that the intervention has a positive effect on cognitive performance in older adults with MCI compared with an active comparator and a control group. In addition, it is anticipated that changes in brainwaves, with a focus on frequency bands and ERPs, are also expected to reveal patterns of brain activity associated with cognitive improvement. This study's contribution lies in its novel approach to combining CST and MSI training to address those cognitive deficits associated with MCI. The inclusion of tablet-based interventions and interactive sessions adds a technological dimension to traditional cognitive interventions, thereby potentially enhancing engagement and outcomes.

The study draws upon established principles from CST and MSI techniques. The cognitive stimulation program is designed based on group-based CST and multisensory stimulation approaches. CST has been shown to improve cognitive function and quality of life in individuals with dementia or MCI [10,11]. Furthermore, the group-based cognitive stimulation program, which involves social support from friends and group activities, is critical for mental health and adherence to health-promoting behaviors. It can reduce feelings of loneliness and isolation, which are common in older adults with MCI. The guiding principles of CST were adapted to create 15 fundamental principles of individual CST, including mental stimulation, reminiscence, learning, and communication stimulation, using a person-centered approach [12,13].

The study uses an RCT design with experimental, active comparator, and control groups. The primary objectives are to evaluate the effects of the computerized multicomponent cognitive stimulation program on cognitive functions in older adults with MCI and to explore the changes in the EEG and ERP components following the interventions. The study's structured design, preregistration, and adherence to ethical standards ensure a robust methodology.

The cognitive domains targeted for improvement encompass learning and memory, language, visuospatial abilities, executive functions, psychomotor skills, and emotions. The study integrates various neuropsychological tasks to assess these domains, evaluating the intervention's impact comprehensively. The expected improvements in these domains align with the program's focus on CST principles and MSI, which have shown promise in enhancing both cognitive functions and quality of life. It is crucial to have a tablet-based intervention that boosts self-confidence and reduces depression and anxiety. This can involve personalized training, support groups, and skill-building activities to manage cognitive stimulation. For example, previous research has demonstrated that the feasibility and acceptability of the CCS program and computerized cognitive engagement programs were efficient and acceptable, allowing patients with MCI to improve in several aspects of cognitive and psychosocial functioning [16,17]. Computerized technology is cost-effective, and simple to execute, requiring little human and financial resources [18]. In addition, implementing this intervention in middle-income countries may face challenges like setup costs and limited digital infrastructure. However, these barriers can be mitigated through local adaptations and partnerships with community organizations that support technology access and training, making tablet-based programs more applicable across diverse socioeconomic settings [67]. Furthermore, CCS is being used more widely as a standard approach for delivering nonpharmacological interventions to older adults, but determining the effectiveness of nonpharmacological therapies can be challenging [68]. They lack an appraisal of brain activities and a neuropsychological evaluation that correlates with the specific cognitive functions in people with MCI.

The study's use of EEG and ERP measures to examine neurobiological correlations of MCI adds welcome depth to the investigation. The alterations in brain activity patterns and the ERP components associated with MCI and cognitive impairment contribute to understanding the underlying mechanisms of the condition and identifying potential biomarkers for assessing and monitoring the relevance of the study to treatment. For instance, previous research shows that the EEG of resting-state conditions and a simple cognitive task are important as likely biomarkers for discriminating between healthy, MCI, and Alzheimer groups [69]. It is consistent with Fauzan and Amran [21], finding that when the EEG resting-state measure of the MCI group was compared with typical healthy aging, the theta and alpha increases were more prevalent, showing symptoms of cognitive impairment in MCI, and a decrease in the delta is associated with cognitive decline. In patients with MCI, P300 latency was delayed significantly [26]. P300 latency was related significantly to disease severity in people with probable Alzheimer disease. P300 latency had the highest correlation coefficients with cognitive measurement [23,24]. Furthermore, the N400 component could be connected to verbal memory and learning. The N400 amplitude correlates negatively with semantic expectancy and is inversely proportional to the

semantic processing load. P600 has also been linked to memory encoding and retrieval processes [25].

As a result, EEG is a valuable technology for collecting biomedical data from participants pre- and posttest to compare the difference in brain waves after participating in the experiments. However, the limitations of this research are the research design and instrument. The planned follow-up does not take into account that the study may not provide information about the long-term benefits and hazards of medical interventions. Furthermore, EEG data will be collected using the Emotiv Flex which is not capable of native hardware event-marking that can lead to an effect on time-lock stimuli to EEG data [43].

Limitations and Future Implications

The limitations of this study include its short-term focus, which may capture primarily immediate outcomes while potentially overlooking long-term effectiveness. In addition, the results may have limited generalizability, as they are based on a general population sample and may not extend to specific MCI subtypes. The predominance of female or male participants further limits generalizability, highlighting the need for larger studies to explore potential sex-related variations in response.

Further implications will contribute to knowledge, including developing a novel tablet- and group-based MCST program that combines CST with MSI to improve cognitive functions in older adults with MCI. Using EEG and ERP markers to measure cognitive functions and MSI will provide an assessment of the intervention's effectiveness. The EEG-recorded results will give a greater understanding of participants' tablet- and group-based therapeutic data, allowing for the identification of particular mechanisms, such as changes in cognition and emotion, that were found to improve in the pilot study.

Conclusions

To summarize, the pilot study on older adults with MCI in Thailand revealed significant improvements in cognitive function and emotions following a tablet- and group-based MCST program. The intervention, conducted over 10 weeks for 45 minutes per session, notably enhanced global cognitive function while reducing depression and anxiety levels. These findings corroborate previous research on CCS among patients with MCI. However, contrary to expectations, the MCST program did not yield significant improvements in participants' quality of life, likely influenced by their awareness of diagnosis and dissatisfaction with cognition and physical well-being. Nonetheless, the study underscores the importance of cognitive interventions and highlights the need for further exploration into specific cognitive domains among older adults with MCI. Further research employing neuropsychological assessments and EEG may provide deeper insights into the mechanisms underlying cognitive performance enhancement in this population.

Acknowledgments

This research is funded by National Research Council of Thailand (Contract N41A660157), and it is part of the research project entitled "Development of Computerized Multicomponent Cognitive Stimulation for Improving Cognitive Functions in Older Adults with Mild Cognitive Impairment: A Multimodal Investigation Using Neuropsychological and EEG/ERP Assessment."

Data Availability

The datasets generated and analyzed during the current study are available from the corresponding author upon reasonable request.

Authors' Contributions

All authors contributed to conceptualization and methodology. Writing – original draft was contributed by KJ. Writing – review and editing was contributed by KJ, PM, PW, and AG. Supervision was handled by PM, PW, and AG. All authors have read and agreed to the published version of the manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
CONSORT-EHEALTH V1.6 checklist.
[PDF File (Adobe PDF File), 1231 KB - resprot_v14i1e64465_app1.pdf]

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Abbreviations

ANCOVA: one-way analysis of covariance
CCS: computerized cognitive stimulation
CONSORT: Consolidated Standards of Reporting Trials
CST: cognitive stimulation therapy
EEG: electroencephalography
ERP: an event-related potential
JASP: Jeffreys's Amazing Statistics Program

MCI: mild cognitive impairment
MCST: multicomponent cognitive stimulation therapy
MoCA-T: Thai version of the Montreal Cognitive Assessment
MSI: multisensory integration
OPQoL: Older People's Quality of Life Questionnaire
RCT: randomized controlled trial
STAI: State-Trait Anxiety Inventory
TGDS: Thai Geriatric Depression Scale

Edited by A Schwartz; submitted 18.07.24; peer-reviewed by B Najand; comments to author 22.10.24; revised version received 03.11.24; accepted 03.02.25; published 21.02.25.

Please cite as:
Jornkokgoud K, Makmee P, Wongupparaj P, Grecucci A
Tablet- and Group-Based Multicomponent Cognitive Stimulation for Older Adults With Mild Cognitive Impairment: Single-Group Pilot Study and Protocol for Randomized Controlled Trial
JMIR Res Protoc 2025;14:e64465
URL: https://www.researchprotocols.org/2025/1/e64465
doi:10.2196/64465
PMID:

Protocol

Enhancing Text Message Support With Media Literacy and Financial Incentives for Vaping Cessation in Young Adults: Protocol for a Pilot Randomized Controlled Trial

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Abstract

Background: The persistent high prevalence of e-cigarette use among young adults remains a significant public health concern, with limited evidence and guidance on effective vaping cessation programs targeting this population.

Objective: This study aims to outline the study design and protocol of a pilot randomized controlled trial aimed at investigating feasibility and assessing whether media literacy education or financial incentives enhance the effectiveness of evidence-based text message support in promoting vaping abstinence among young adult e-cigarette users.

Methods: The pilot study uses a 4-arm (1:1:1:1) randomized controlled trial design to assess the potential impact of different combinations of media literacy education, financial incentives, and text message support on vaping abstinence over a 3-month period. The first month serves as a preparatory phase for quitting, followed by 2 months focused on abstinence. A total of 80 individuals, aged 19-29 years, who have used e-cigarettes within the past 30 days, have internet access, and express interest in quitting vaping within the next 30 days, will be enrolled. Eligible individuals will be randomized into one of the four study groups: (1) Text Message, (2) Media Literacy, (3) Financial Incentive, and (4) Combined. All participants, regardless of group assignment, will receive text message support. Participants will be followed for 12 weeks, with abstinence status assessed at week 12, as well as during remote check-ins at weeks 6, 8, and 10. Feasibility measures include recruitment rate, reach, engagement, and retention. Other outcomes of interest include self-reported 7-day abstinence and changes in nicotine dependence and media literacy scores. Exit interviews will be conducted with those who complete the study to explore facilitators of and barriers to participation and engagement in vaping cessation, which will inform future program refinement and uptake.

Results: Recruitment for the study commenced in December 2023 and concluded in August 2024. A total of 40 participants were randomized into these groups: 9 for Text Message, 11 for Media Literacy, 10 for Financial Incentive, and 10 for the Combined group. The final assessment was completed in November 2024, and analyses are currently ongoing.

Conclusions: The findings from this trial could provide valuable insights into the design and uptake of vaping cessation strategies among the young adult population.

Trial Registration: ClinicalTrials.gov NCT05586308; https://clinicaltrials.gov/study/NCT05586308

International Registered Report Identifier (IRRID): DERR1-10.2196/60527

(JMIR Res Protoc 2025;14:e60527) doi:10.2196/60527

KEYWORDS

contingency management; e-cigarettes; social support; youth; electronic health record; opt-in; recruitment; tobacco marketing; cessation; peer support; young adult; feasibility; public health

Introduction

E-cigarettes have emerged as the most commonly used tobacco product among young individuals [1,2], rapidly becoming a public health concern in the United States, particularly among youth and young adults [3]. Data from the 2021 National Center for Health Statistics reported that e-cigarette use (ie, vaping) was highest among young adults aged 18-24 years, with 11% (approximately 3.4 million people) using e-cigarettes, compared with an overall adult rate of 4.5% [4]. The 2023 National Center for Health Statistics reported an increase in overall adult e-cigarette use to 6.5% [5]. Similarly, another study using the 2021 Behavioral Risk Factor Surveillance System Survey observed a high prevalence of e-cigarette use among US adults (6.9%, 95% CI 6.7%-7.1%), particularly among young adults aged 18-24 years (18%) [6]. The accessibility of vaping products has significantly increased, largely driven by marketing efforts featuring appealing flavors targeted at this population [7]. Moreover, the influence of social media and influencers has contributed to the widespread prevalence of vaping [8,9]. Given the persistently high rates of e-cigarette use, especially among young adults, it is critical to explore the feasibility and effectiveness of targeted cessation programs for this group.

Although marketed as a safer alternative to combustible cigarettes [1,7], evidence suggests that vaping still poses health risks [10,11]. Vaping has been associated with increases in both blood pressure and heart rates [12]. Nicotine, a toxic and highly addictive substance found in e-cigarettes, contributes to these risks, with concentrations varying widely depending on the type of devices, their power, and the brands and models. Notably, nicotine levels in e-cigarettes have increased from 1.7% in 2017 to 5.0% in 2022 [13]. However, critical questions regarding both the short-term and long-term health effects of e-cigarette use remain unanswered [14-16].

Vaping cessation efforts among young adults often yield poor results, with many experiencing failed attempts [17,18]. Data indicate that 53.4% of current young e-cigarette users express an intention to quit, and 67.4% report attempts to do so [19], yet successful cessation rates remain low [20]. Despite a strong desire to quit, many struggle to stop vaping. Evidence-based behavioral vaping cessation programs are scarce compared with pharmacological interventions, such as nicotine replacement therapies [21-23] or vape concentration tapering [24]. Moreover, the implementation and reach of these behavioral programs remain a challenge, particularly among youth and young adult populations [25].

Three recent studies have reported on the effectiveness of behavioral vaping cessation programs using text message support or financial incentives. For example, Raiff et al [26] conducted a pre-post intervention study with 8 college students, finding that all participants quit vaping during the 2-week intervention period, using a remotely delivered program with financial incentives to reinforce abstinence. However, in a feasibility trial involving 27 young adults, Palmer et al [27] found no significant difference in vaping abstinence between the contingency management and monitoring control groups, despite the positive feedback about the intervention program. Another study examined a vaping cessation text message program called This is Quitting [28], which provides social support for quitting. In a randomized clinical trial (RCT) involving 2588 young adults aged 18-24 years, participants in the This is Quitting group were 1.39 times more likely to quit vaping compared with those in the control group [29]. The urgent need for evidence-based behavioral vaping cessation initiatives among this population is critical to addressing this public health concern.

Vaping often appeals to younger populations through marketing campaigns that highlight various flavors and glamorize the practice [7]. Companies also use manipulative strategies like social media influencers and product placement, particularly targeting communities with lower levels of vaping-related media literacy, who tend to be more susceptible to vaping [30]. Although limited evidence exists on the direct impact of media literacy programs on vaping cessation, integrating such programs into vaping cessation initiatives may help promote abstinence by (1) promoting positive behavioral norms (educating people about the true risks of vaping can foster a social environment where quitting is seen as important and achievable [31]); (2) encouraging peer advocacy and mentoring (by understanding marketing tactics and gaining skills to debunk misinformation, individuals can become more effective in supporting their peer to quit vaping [32]); and (3) enhancing self-efficacy against vaping triggers (media literacy can help individuals recognize and avoid triggers that encourage vaping, such as targeted advertising or social media content that normalizes the behaviors [33]). In addition, although media literacy programs are primarily designed for youth for educational and prevention purposes, young adults may also benefit from the content due to the close age proximity between these groups.

Contingency management is a well-established behavioral intervention in which individuals receive reinforcement, such as financial incentives, contingent upon predetermined outcomes [25]. Financial incentives have been shown to be effective in

promoting healthy behaviors [34] and improving the reach and engagement of evidence-based programs as part of an implementation strategy [35]. Numerous studies have demonstrated the success of financial incentives in encouraging behavior changes [36,37]. Rooted in health promotion economic theory, financial incentives enhance the perceived benefits of abstaining from unhealthy behaviors, thereby bolstering motivation for change [36].

Peer influence plays an important role in vaping behaviors, with family and friend use cited as key reasons for vaping initiation [38]. In addition, vaping for "entertainment" purposes is prevalent among younger populations [39]. Peer support strategies have been shown to be effective [40,41], especially in promoting cigarette smoking cessation in youth and young adults [42,43]. Platforms like SMS text messaging and social media have shown promise as peer support tools [44-46]. Specifically, peer support delivered through text message (eg, This is Quitting) has demonstrated effectiveness in vaping cessation across multiple studies [29,47,48], capitalizing on the widespread use of these communication methods among young adults.

The objective of this paper is to outline the design and methodology of a pilot RCT investigating feasibility and assessing whether media literacy education or financial incentives enhance the effectiveness of evidence-based text message support in promoting vaping abstinence among young adult e-cigarette users.

Methods

Study Design

This pilot study uses a 4-arm RCT design to assess whether media literacy education or financial incentives can enhance vaping abstinence when combined with text message support over a 3-month trial period. The first month involves a preparatory phase for quitting, followed by 2 months focused on maintaining abstinence from vaping. Eligible participants will be randomly assigned to one of four groups in a 1:1:1:1 ratio: (1) Text Message (text message support), (2) Media Literacy (text message support and media literacy education), (3) Financial Incentive (text message support and financial incentives), and (4) Combined (text message support, media literacy education, and financial incentives).

All 4 groups will receive evidence-based text message support (ie, This is Quitting). In addition, to develop and assess the process of conducting biospecimen collection (ie, urine) and analysis, a subsample of 20 participants (5 participants from each study group) will be contacted in order of enrollment until the target is met at baseline. These participants will be asked to provide urine samples both at baseline and at the conclusion of the study. The samples will be shipped to the Division of Laboratory Sciences at the Centers for Disease Control and Prevention for biomarker analyses to evaluate exposures to tobacco-related toxicants from e-cigarette use.

The trial protocol has been reported in accordance with the SPIRIT (Standard Protocol Items Recommendations for Interventional Trials) 2013 checklist [49] (Multimedia Appendix 1).

Participants and Eligibility Criteria

Eligible participants are individuals who: (1) are aged 19-29 years (the minimum age is set at 19 to align with the legal age of majority in Nebraska); (2) have used e-cigarettes within the past 30 days, consistent with previous behavioral vaping cessation trials targeting youth and young adults [29,50]; (3) have access to the internet; and (4) are interested in quitting vaping within the next 30 days. Individuals who self-report as currently pregnant or planning to become pregnant within the next 3 months, or who are currently enrolled in other behavioral or medical vaping cessation programs, will be excluded.

Sample Size Justification

As this pilot RCT aims to assess the feasibility of a future large-scale study, a sample size of 80 (n=20 in each arm) is considered sufficient, following the flat rule of thumb for pilot trials with continuous outcomes of interest (eg, feasibility outcomes), which typically recommend group sizes ranging from 12 to 35 participants [51]. This sample size also takes into account available resources such as time and budget [52].

Recruitment and Sample Selection

We will recruit a total of 80 participants using a population health management approach [53,54], a comprehensive strategy that involves identifying subpopulations of individuals from an existing pool who would benefit from a given evidence-based intervention. This approach includes examining the characteristics of these populations using electronic health record (EHR) data. The potential participant pool will be limited to patients who have opted in to be contacted for research studies in the EHR system at Nebraska Medicine.

Specifically, we will collaborate with EHR Data Access Core at the University of Nebraska Medical Center to first generate a list of potentially eligible participants, filtering for age and using smart text data to determine the vaping or smoking status, as young adults are more likely to engage in multiple tobacco products at the same time [55]. A study invitation email, containing a link to an eligibility screening, will then be sent to individuals on this potential participant list by the study team. In this email, interested individuals will be directed to complete web-based screening questions via Research Electronic Data Capture (REDCap; Vanderbilt University) to assess their eligibility. Eligible participants will then be contacted by research staff members on days 1, 3, 7, 14, and 21 (if no response) after the completion of screening to schedule an in-person baseline visit.

If the recruitment goal of 80 participants is not met after exhausting the initial participant list, the research team will directly contact potential participants via phone calls. In addition, we will implement a social media recruitment strategy by posting study advertisements on platforms such as Facebook (Meta), Instagram (Meta), or X (formerly Twitter). We recognize that there may be differences between participants recruited from various sources (EHR vs social media) and will account

for these differences in the reporting of trial results and the planning of future large-scale studies.

Interventions

Text Message Support

Grounded in social cognitive theory and designed as a compassionate, nonjudgmental companion, the text message program "This is Quitting" is an evidence-based, cost-free, and personalized initiative by the Truth Initiative, aimed at helping young individuals quit vaping. Most of the support messages are contributed by other users, reinforcing perceived social norms and providing communal encouragement for quitting. A recent RCT involving 2588 young adults aged 18-24 years found that participants receiving text message support were significantly more likely to achieve vaping abstinence compared with the control group (odds ratio [OR] 1.39; 95% CI 1.15-1.68; *P*<.001) at the 7-month follow-up [29]. Participants will retain full access to the text message program even after completing the study.

Participants in this study will receive 1 message per day for the week leading up to their quit date and for 8 weeks following it.

Media Literacy

Media Education for Sensible Evaluation and Nurturing Substance-free Experiences (MediaSense) [56] is an evidence-informed antivaping media literacy education program designed to prevent and reduce vaping among adolescents and young adults. Developed by our research team, the program draws on the social influence framework and incorporates guidance from the Centers for Disease Control and Prevention and Food and Drug Administration tobacco and vaping prevention guides, as well as an extensive review of evidence-based prevention programs and identified vaping risk factors. The MediaSense program consists of 9 web-based modules covering a range of topics, including (1) understanding what e-cigarettes are and how they work; (2) exploring the health impact of e-cigarettes; (3) understanding the role of marketing and advertisement in promoting e-cigarettes; (4) dispelling myths and revealing facts about e-cigarette marketing; and (5) learning how to deconstruct vaping advertisements. These e-learning modules aim to transform participants' knowledge, attitudes, and beliefs regarding e-cigarette use while emphasizing vaping-related media literacy and developing skills to critically deconstruct e-cigarette advertisements.

In our previous study that examined the effect of MediaSense on vaping prevention among middle and high school students (n=384), we observed significant results. Specifically, vaping media literacy scores improved, with mean scores increasing from 2.3 (SD 2.3) to 3.4 (SD 2.4) (*P*<.001). In addition, there was a decrease in the perception of vaping harm (adjusted OR 1.6 95% CI 1.1-1.22) and a reduction in vaping susceptibility (adjusted OR 0.7, 95% CI 0.5-1.0; *P*=.04) [56], indicating a reduced likelihood of students considering vaping.

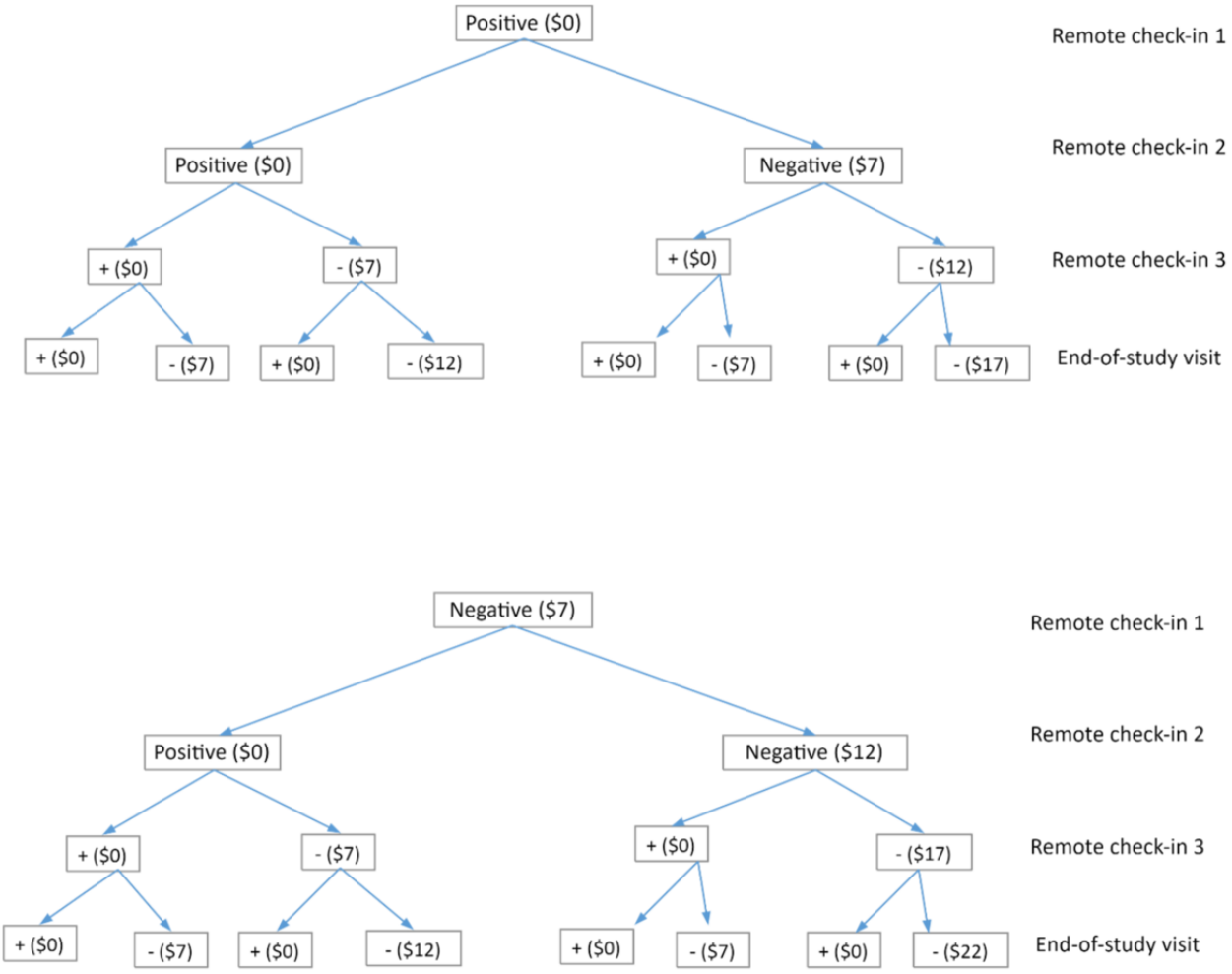
In this study, participants assigned to Media Literacy or Combined will complete these self-paced modules during the 1-month quitting preparatory phase and will be required to take a short quiz at the end of each module. These quizzes confirm module completion and assess participants' understanding of the education materials. Each module will take approximately 10 minutes to complete.

Financial Incentives

Participants will receive US $3 for each saliva sample submission, regardless of testing results, at week 6, week 8, week 10, and week 12 during the 2-month abstinence phase. In addition, they will earn escalating bonuses for each negative sample. The bonus will start at US $7 and increase by US $5 for each subsequent negative sample, that will be, US $7 for week 6, US $12 for week 8, US $17 for week 10, and US $22 for week 12. However, a reset contingency will be applied, meaning the bonus amount will revert to the initial US $7 if a sample is missing or tests positive for cotinine (refer to Figure 1).

Participants can earn up to $70 in total upon completing all 4 saliva sample submissions. They will be informed of their earnings after completing each scheduled task (ie, immediate reward) and will receive all payments as a 1-time disbursement at the conclusion of the study. The rationale behind the timing and amount of the incentives is to minimize the risk of inhibiting intrinsic motivation [57], as modest incentives (up to US $70) are less likely to undermine intrinsic motivation compared with the larger rewards typically offered in smoking cessation programs (eg, US $1185) [58].

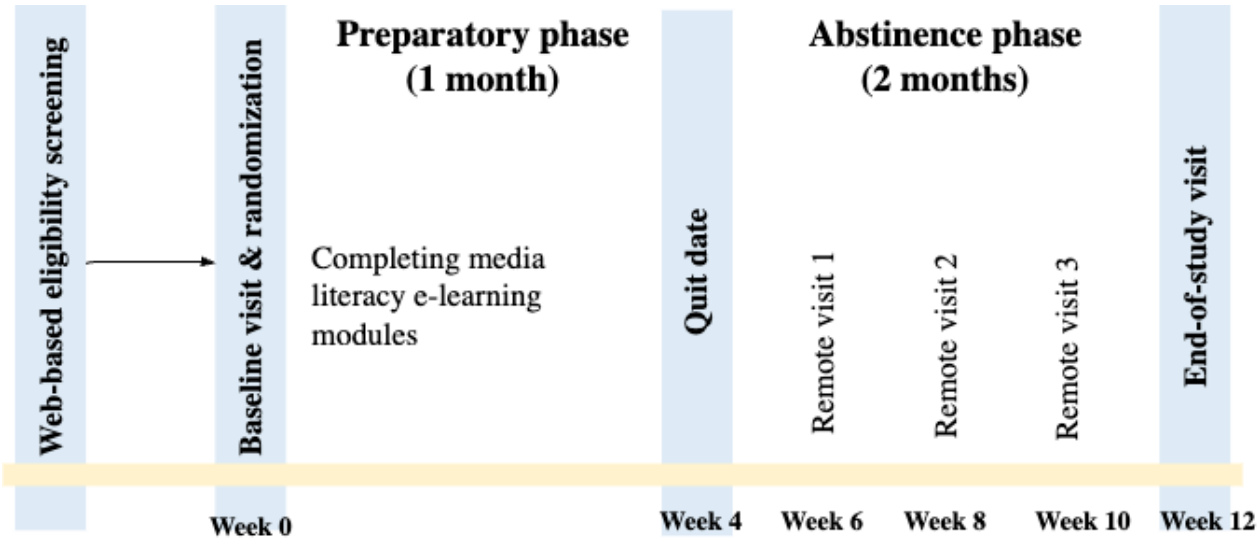
Figure 1. Financial reward decision flow. Values were negative (-) or positive (+).



Study Timeline and Data Collection

The study will span a duration of 3 months, consisting of a 1-month quitting preparatory phase (weeks 1-4) and a 2-month abstinence phase (weeks 5-12; Figure 2). Throughout the quitting preparatory phase, participants assigned to the Media Literacy or Combined groups will be directed to complete the web-based media literacy education modules by their quit date, Meanwhile, participants in the Text Message or Financial Incentive groups will be encouraged to prepare for quitting but not to quit before the specified quite date.

Figure 2. Study assessment timepoint.



Baseline Visit

This assessment will include a demonstration and facilitation of the saliva test, which participants will perform themselves at baseline and final study visits, as well as during remote check-ins. Participants will also sign a precommitment pledge (a psychological strategy to help individuals stick with their goals) and complete the baseline survey.

Following these activities, research staff members will conduct randomization using predetermined blocks of 4 and 8, with a computer-generated algorithm, to assign participants to one of the study groups. Participants will also be asked to specify a quit date (no later than 1 month after the baseline visit, which serves as the quitting preparatory phase), register for the text message program, and schedule the 3 remote check-ins for saliva testing.

Remote Check-Ins

During the abstinence phase, participants will engage in a total of 3 video calls, scheduled for week 6, week 8, and week 10. During each live video call, participants will receive instructions on how to complete the saliva sample collection on their own and submit the results. Specifically, they will be directed to open a new test kit and record their participant ID, visit number, date, and time on the kit. Participants will then perform the saliva test, allowing approximately 10 minutes for processing. In addition to verbally providing the test results (positive or negative) to the research staff members, participants will be required to take a picture of the results, including their participant ID, visit number, date, and time, and send it to the research staff members before concluding the call. Each video call will last no longer than 20 minutes. The primary purpose of these remote check-ins is to maintain participants' engagement and monitor their abstinence progress until the final study visit at week 12.

End-of-Study Visit

At the end-of-study visit (week 12), which may be conducted either remotely or in person, participants will provide the results of saliva testing and complete the end-of-study survey. Participants who provided a urine sample at the study baseline will be asked to attend the final visit in person for urine sample collection.

Exit Interview

For quality improvement and future modification and adoption of vaping cessation programs, we will conduct exit interviews with participants (n=8-12; 2-3 participants from each group) who have completed the study via video call. The interview guide will be developed based on the Pragmatic Robust Implementation and Sustainability Framework [59] to identify the barriers and facilitators of participating in a vaping cessation program and achieving abstinence goals.

Measures

Feasibility Outcome

As this is a pilot trial, our primary objective is to assess the feasibility of implementation. Specifically, we will use study records to measure the following: (1) recruitment rate, defined as the proportion of eligible individuals who consent to participate; (2) reach, assessed by the representativeness of sociodemographic characteristics among screened and enrolled individuals; (3) engagement, measured by the proportion of participants completing remote check-ins, and the proportion of participants in the Media Literacy or Combined groups who complete the media literacy e-learning modules; (4) retention, evaluated by the number of participants who withdraw from study, and the completeness of the end-of-study assessment; and (5) the number and proportion of participant providing a urine sample from each group at baseline and the end of study.

Cessation Outcome

The primary cessation outcome for this study is biochemically verified vaping abstinence, determined through the iScreen saliva cotinine test conducted at the end-of-study assessment. A negative cotinine result will be indicated by a cutoff of <30 ng/mL [60].

Additional Outcome

Additional outcomes of interest for this study include: (1) self-reported 7-day abstinence, determined by the question in the end-of-study survey: "Have you used any e-cigarettes, even a puff or pinch, in the last 7 days?" [61]; (2) changes in nicotine dependence, measured by the Penn State E-Cigarette Dependence Index at baseline and end-of-study; and (3) changes in media literacy, assessed using the Vaping Media Literacy Scale [30] at baseline and end-of-study.

Data Analysis Plan

Quantitative Analysis

Descriptive statistics will be used to summarize participants' sociodemographic characteristics, e-cigarette use history, exposure to tobacco marketing and its influence, social support, and self-efficacy at baseline. Bivariate analyses, using either the Chi-squared test for categorical variables or the ANOVA test for continuous variables, will be conducted to identify differences in sociodemographic characteristics and other vaping-related variables at baseline across the study groups.

We will provide a descriptive summary of feasibility outcomes, including the rate of recruitment, reach, engagement, and retention. In addition, we will assume that all covariate data are missing at random, and this assumption will be tested by comparing the missing data patterns with sociodemographic characteristics in the bivariate analyses.

Chi-squared tests will be used to determine differences in proportions of participants with negative saliva test results at the end of the study as well as each remote check-in. Missing end-of-study abstinence outcomes will be coded as vaping (not abstinent) [27]. Similarly, differences in the proportion of participants who self-reported 7-day abstinence across study groups will be evaluated using the Chi-squared test, while the ANOVA test will be used to assess changes in nicotine dependence index and media literacy scores.

Nonparametric methods (eg, Fisher exact test when the sample size is less than 5 in a category or the Kruskal-Wallis test) will be applied when appropriate. All quantitative analyses will be

conducted in SAS (version 9.4; SAS Institute Inc) with a 2-tailed significance level <.05 if applicable.

Qualitative Analysis

Using a hybrid deductive and inductive qualitative approach, we will analyze data obtained from semistructured interviews to explore the facilitators and barriers to participation and engagement in vaping cessation programs. All interviews will be recorded and transcribed verbatim. Subsequently, 2 trained research staff members will independently code the transcripts into reduced meaning units (sentences or phases with singular meaning). Intercoder reliability will be assessed using Cohen κ, with a threshold of ≥.80. All qualitative data analyses will be conducted using NVivo 14 (Lumivero) or Microsoft Excel.

Ethical Considerations

The study protocol was approved by the institutional review board (0596-22-EP) at the University of Nebraska Medical Center and was registered on ClinicalTrials.gov (NCT05586308).

Informed Consent

Approximately 10 days before the baseline visit, eligible individuals scheduled for the in-person visit will receive an email containing an initial packet with the informed consent form, a letter with instructions for their first visit, and contact information for any questions. During the baseline visit, trained research staff members or study investigators will verbally review the informed consent with participants, covering the data collection procedure and plans for protecting participants and their privacy (ie, data deidentification), address any questions, and obtain written informed consent before proceeding with the baseline assessment.

For participants who opt to provide a urine sample during the baseline visit, verbal consent will be obtained by the research staff members before the sample collection. Participants will be guided through the recommended procedures for urine sample collection according to best practices.

Compensation

All study participants will receive a US $25 gift card each for completing baseline and end-of-study visits. Participants who opt to provide a urine sample will receive an additional US $10 at both baseline and end-of-study visits. As a result, participants in the Text Message or Media Literacy groups can earn up to US $70 in total compensation, while those in the Financial Incentive or Combined groups may earn up to US $140, including additional financial rewards contingent on the submission of 4 saliva samples during remote check-ins or end-of-study visit.

Results

Recruitment for the study commenced in December 2023 and concluded in August 2024. A total of 40 participants were randomized into the following groups: 9 for Text Message, 11 for Media Literacy, 10 for Financial Incentive, and 10 for the Combined group. The final assessment was completed in November 2024, and analyses are currently ongoing.

Discussion

Principal Findings

This study is one of the few to assess the feasibility and potential effects of different vaping cessation program combinations in helping young adults quit vaping. We anticipate that the addition of either media literacy or financial incentives will lead to better preliminary abstinence outcomes (ie, more participants quit vaping) by the end of the study, compared with text message support alone.

Unlike other behavioral trials for vaping cessation, which often use a “doing nothing” approach (ie, assessment-only) for the control condition [28,50], we aim to enhance vaping abstinence outcomes by examining the potential additive effects of various interventions on top of an evidence-based program. This approach accounts for participants’ expectation of receiving some levels of interventions when taking part in research studies [28].

There are currently few published studies on behavioral interventions for young adult vaping cessation [26,27,29]. As of the time of writing, 9 other clinical trial protocols are actively recruiting participants to evaluate behavioral vaping cessation interventions among youth (n=3), young adults (n=4), or a mixed youth and young adult population (n=1). These trials have target sample sizes ranging from 30 to 1715 participants, as listed in their registration records on ClinicalTrials.gov. Given the persistently high prevalence of e-cigarette use among young adults, it is crucial to identify effective cessation programs and the supplementary components that may enhance their success. The study findings will be disseminated through peer-reviewed manuscript publications and presentations at national conferences, as well as shared with relevant stakeholders and communities.

Limitations

This study has several limitations that warrant acknowledgment. First, the exclusion of individuals without access to internet services may inadvertently overlook those most in need of cessation assistance, particularly those of low socioeconomic status or residing in remote areas. However, studies have indicated that approximately 95% of American adults have internet access and 90% own smartphones [62], suggesting that the benefits of using technology-assisted behavioral interventions likely outweigh the drawbacks of this exclusion criterion. Second, our use of a commercially available saliva cotinine test kit, which provides binary positive or negative results, to verify abstinence status may not fully capture the extent to which cotinine levels have fluctuated as a result of cessation efforts. Nonetheless, the saliva test offers cost-efficiency compared with urine testing and may serve as a useful monitoring tool for follow-up assessments during the intervention period. Third, although we apply a population health management approach to identify potential participants from an EHR database, it is likely that we are capturing only individuals who receive health care within a specific system rather than from a broader regional population. In addition, due to institutional policy, we are limited to including only those individuals who have opted in for research participation, which

may introduce selection bias, as these individuals may be less representative of the broader target population [63]. Furthermore, concerns exist regarding the reliability of using vaping or smoking status as a filter to identify potential participants from the EHR database. To address this, we have incorporated an additional step in the recruitment process, requiring potential participants to complete a screening survey to confirm their eligibility before scheduling the baseline assessment. Finally, while our study targets young adults aged 19-29 years, the text message program (This is Quitting) is tailored for individuals aged 18-24 years. We believe that individuals within the broader age range can still benefit from the support program. To accommodate this, participants aged 25-29 years in the trial will be instructed to adjust their age when registering for the text message program during the baseline visit.

Conclusion

In summary, the findings from this trial will aid in refining the study design, particularly regarding vaping program components, and in planning program implementation. In addition, the results may help identify or develop strategies to enhance participant reach and program uptake among young adult populations.

Acknowledgments

We would like to acknowledge Ms Hayley Jurek and Deb Meyer at the University of Nebraska Medical Center Office of the Vice Chancellor for Research, who have been instrumental in participant recruitment of the pilot trial.

The project described is supported by the National Institute of General Medical Sciences, U54 GM115458, which funds the Great Plains IDeA-CTR Network (gpctr@unmc.edu), and the National Institute on Drug Abuse R34CA287719 (principal investigator: Dr Daisy Dai). Dr Michaud was awarded funding from the Early Career Investigator Program for the Great Plains IDeA-CTR Network to conduct the proposed study. The content is solely the responsibility of the authors and does not necessarily represent the official views of the Great Plains IDeA-CTR Network or NIH.

Data Availability

Data sharing is not applicable to this article, as no datasets were generated or analyzed during this study due to the trial being ongoing.

Conflicts of Interest

None declared.

Multimedia Appendix 1
The SPIRIT checklist.
[DOCX File , 38 KB - resprot_v14i1e60527_app1.docx]

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Abbreviations

EHR: electronic health record
MediaSense: Media Education for Sensible Evaluation and Nurturing Substance-free Experiences
OR: odds ratio
RCT: randomized clinical trial
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials

Edited by A Schwartz; submitted 14.05.24; peer-reviewed by R Mermelstein; comments to author 05.09.24; revised version received 26.09.24; accepted 23.12.24; published 21.02.25.

Please cite as:
Michaud T, Puga T, Archer R, Theye E, Zagurski C, Estabrooks P, Dai HD
Enhancing Text Message Support With Media Literacy and Financial Incentives for Vaping Cessation in Young Adults: Protocol for a Pilot Randomized Controlled Trial
JMIR Res Protoc 2025;14:e60527
URL: https://www.researchprotocols.org/2025/1/e60527
doi:10.2196/60527
PMID:

Protocol

Examining a Telemedicine-Based Virtual Reality Clinic in Treating Adults With Specific Phobia: Protocol for a Feasibility Randomized Controlled Efficacy Trial

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Abstract

Background: Virtual reality (VR) has strong potential to enhance the effectiveness of telemental health care (TMH) by providing accessible, personalized treatment from home. While there is ample research supporting VR for in-person treatment, there is only preliminary data on the efficacy of telemedicine-based VR. Furthermore, the majority of VR apps used in therapy are not designed for mental health care. VR has the potential to enhance TMH through innovative technology solutions designed specifically for the enhancement of remotely delivered evidence-based practices. This feasibility randomized controlled efficacy trial aims to fill both of these gaps by piloting a novel telemedicine-based VR app (Doxy.me VR) equipped with animal phobia exposure stimuli.

Objective: This is a feasibility randomized controlled efficacy trial comparing exposure therapy via a telemedicine-based VR clinic versus standard TMH with adults with an intense fear of dogs, snakes, or spiders. The primary objective is to assess the feasibility of a fully powered trial. The secondary objective is to conduct a preliminary examination of clinical outcomes (eg, specific phobia symptoms).

Methods: This single-site trial will enroll a minimum of 30 and a maximum of 60 adults with self-reported fear of dogs, snakes, or spiders. Potential participants will be recruited through clinical trial and research recruitment websites and posting flyers. All self-report assessments and homework will be partially automated using REDCap (Research Electronic Data Capture; Vanderbilt University) forms and surveys, but the baseline assessment of phobia symptoms and exposure intervention will be administered by the study therapist.

Results: The feasibility of the proposed trial methodology will be assessed using enrollment, retention, assessment completion, and treatment protocol fidelity benchmarks. Between-group differences in specific phobia, anxiety, and depression symptoms while covarying for pretreatment scores, will be conducted using repeated measures ANOVA along with differences in therapeutic alliance and presence. Data obtained from these analyses will inform power analyses for a fully powered efficacy trial. In total, 54 participants were randomized between October 25, 2023, and July 26, 2024 (Doxy.me VR n=28 and TMH n=26). Data analysis will be completed and submitted by the end of the second quarter of 2025.

Conclusions: This feasibility randomized controlled trial comparing Doxy.me VR versus TMH aims to enhance the delivery of evidence-based treatments via telemedicine and reduce barriers to remotely delivered exposure therapy. This feasibility trial will be followed by a fully powered efficacy trial on telemedicine-based VR for animal phobias.

Trial Registration: ClinicalTrials.gov NCT06302868; https://clinicaltrials.gov/study/NCT06302868
International Registered Report Identifier (IRRID): DERR1-10.2196/65770

(JMIR Res Protoc 2025;14:e65770) doi:10.2196/65770

KEYWORDS

virtual reality; exposure therapy; phobias; telemedicine; telemental health; tele-VR; immersive simulations

Introduction

Background

Telemental health care (TMH) has revolutionized mental health services by providing accessible, personalized treatment from the comfort and privacy of home [1,2]. TMH is equally to more effective than in-person care, with patients generally reporting higher satisfaction and reduced costs [3-11]. Furthermore, TMH alleviates sociocultural (eg, stigma) and geographic (eg, transportation) barriers to mental health care [12-14]. TMH increased from 41.8% to 62.8% of all telehealth services during 2022, surpassing all other forms of digital clinical care [15]. This trend suggests that clients view TMH as an appropriate substitute for in-person care. As TMH services continue to evolve, there will be a growing need for innovative solutions to enhance the effectiveness of remote care [1,16,17].

Virtual reality (VR) is a promising avenue for advancing TMH. By leveraging immersive simulations, VR can recreate stressors—both physical and psychological—in a safe, controlled environment, which can enhance the effectiveness of remotely delivered evidence-based treatments [18-21]. VR improves treatment compliance and patient retention by offering engaging content for in- and between-session mental health exercises [22]. There is abundant support for on-site VR mental health therapy [23,24]; however, evidence for telemedicine-based VR mental health is limited to a few studies of preliminary efficacy [25-27]. VR has strong potential to drive innovations in TMH [28,29].

The customizable simulations of VR can create new opportunities to personalize TMH. For example, exposure therapy is a gold standard treatment for phobias and other anxiety-related mental health disorders that is efficient and produces durable effects [30,31]. By exposing an individual to fear-related stimuli (eg, a dog) in a controlled setting (eg, the therapist's office), anxiety reduces, and the fear response diminishes over prolonged and repeated exposure (eg, the individual is no longer fearful around dogs). One approach to conducting gradual exposure includes using multimedia stimuli (eg, screen-shared photos or videos), but it can be challenging to standardize exposure formats and assess client affect over conventional telemedicine [32,33]. Another approach is exposing patients to their fears using VR. VR-based exposure therapy (VRET) is a safe, accessible, and engaging alternative to in vivo exposure therapy that can be less stressful and more conducive to treatment success [34-37]. However, most VRET research to date has been conducted in-person, requiring that patients travel to and complete therapy in a clinician's office [38]. Delivering VRET over telemedicine may provide patients with highly engaging and immersive treatment with greater accessibility [39]. Telemedicine-based VR may also address lingering barriers to TMH by expanding the experience of therapeutic alliance and presence. Therapeutic alliance, or working alliance, refers to the extent to which a patient and therapist experience a collaborative and trusting relationship [40,41] and is among the strongest predictors of outcomes in mental health care [42,43]. Presence, also referred to as telepresence, is the extent to which places, activities, and other individuals feel real in a digital environment (eg, VR and videoconferencing) [44].

To explore the potential of telemedicine-based VR therapy, we conducted in-depth interviews with 18 practicing TMH therapists who had delivered exposure therapy via conventional telemedicine [45]. Therapists wanted VR features to build rapport with their patients and the ability to customize VR components for individual patient needs. Therapists needed clinical evidence supporting tele-VR, low costs to adopt VR into their TMH practice, and information on possible side effects for patients. We then surveyed 176 practicing TMH therapists about their perspectives on telemedicine-based VR. We asked therapists to rate the relative importance of tele-VR simulations, features, and implementation factors. Therapists strongly favored tele-VR simulations related to social anxiety, flying, driving, and animals. Therapists rated between-session VR exercises and immersive cooperative activities as some of their most valued tele-VR features. Therapists' highest-rated factors for implementing telemedicine-based VR were HIPAA (Health Insurance Portability and Accountability Act)-compliant, followed by affordability, insurance coverage, and accessibility [46].

Using insights obtained from these studies, we developed Doxy.me VR—an innovative app developed specifically to facilitate immersive TMH. We developed Doxy.me VR with the frequent and direct involvement of key stakeholders. Doxy.me VR is designed for a therapist to meet with a client remotely in a private, comfortable VR clinic that looks and feels like a therapist's office (refer to Figure 1 for screenshots of the clinic). To join the VR session, the therapist provides their unique, persistent 4-digit room code to their client, who enters the code to check in. Once the therapist admits the client, they can interact by speaking and gesturing with each other in immersive VR. Therapists can use a menu to spawn animals such as dogs, snakes, and spiders for use in treating specific phobias. Multiple exemplars are available for each type of animal in varying sizes. For example, there are small dogs (eg, Chihuahua, Corgi, and Jack Russell Terrier), medium dogs (eg, Golden Retriever, Shiba Inu, and Pit Bull), and large dogs (eg, German Shepherd, Doberman, and Husky). Each animal is animated with 4 behavior states, that is, idle (ie, no movement), calm (ie, small, slow movements in a relaxed posture), active

(ie, fast, frequent movements in a playful posture), and aggressive (ie, fast, attacking movements in a defensive posture). Each behavior state also includes corresponding audio such as a calm dog breathing lightly, an active dog panting and barking playfully, and an aggressive dog snarling and barking loudly. Therapists can select, rotate, and move these animals around the room before making them visible to clients. Once therapists make the animal visible, they can continue to move and rotate the animal or remove the animal entirely. Clients cannot directly manipulate objects; however, clients gain access to all the control features while engaging with Doxy.me VR's homework mode, which is used for between-session practice.

Figure 1. Screenshots from Doxy.me VR. Virtual reality clinic space (top left); client admission menu (top right); phobia stimulus menu (bottom left); and therapist and client interacting with phobic stimulus in virtual reality (lower right).

This Study

We present the protocol for a feasibility randomized controlled efficacy trial comparing exposure therapy delivered via Doxy.me VR versus standard TMH to adults with an intense fear of dogs, snakes, or spiders. The primary aim of this study is to assess the feasibility of and refine our study methodology in preparation for a large, fully powered randomized controlled efficacy trial. The secondary aim is to conduct a preliminary examination of clinical outcomes, including between-group differences in specific phobia symptoms, therapeutic alliance, and presence.

Methods

Enrollment and Randomization

This study will use a feasibility randomized controlled efficacy trial design. This single-site trial will enroll a maximum of 60 adults with self-reported fear of dogs, snakes, or spiders with the goal of completing treatment with 30 adults. Participants will be randomly assigned using the REDCap (Research Electronic Data Capture; Vanderbilt University) [47-49]. Randomization Module on a 1:1 allocation ratio to receive 12 weekly sessions of exposure therapy over the course of three months delivered via standard TMH (n=15) versus Doxy.me VR (n=15). Participants randomized to the Doxy.me group will be provided with Meta Quest 2 VR headsets preloaded with the Doxy.me VR app, to be returned to the study team following completion of the study. All therapy sessions will be conducted via remote videoconferencing, with the Doxy.me VR group transitioning to the Doxy.me VR clinic for the exposure exercise portion of the session, and the standard TMH group using multimedia (ie, photos and videos) shared by the study therapist during video calls. Participants randomized to Doxy.me VR received a Meta Quest 2 headset via mail with the VR clinic already downloaded and were provided a clinic code by their therapist at the beginning of each session.

Study Intervention

This study will follow the treatment protocol developed specifically for VRET by Bouchard et al [50], Côté and Bouchard [51], Michaliszyn et al [52], and St-Jacques et al [53]. Following the baseline assessment session, treatment consists of 12, ≤60-minute therapy sessions, including 1 psychoeducation and treatment planning session (session 1), 10 exposure sessions (sessions 2-11), and 1 relapse prevention session (session 12). During the first therapy session, patients learn about the principles of cognitive behavioral therapy, the etiology of anxiety and specific phobias, and procedures for exposure. They then complete a fear hierarchy (ie, a list of situations ranked from least to most anxiety-provoking) with therapist guidance. Fear hierarchies include a text-based list of various VR situations

or multimedia situations (ie, static and active states of different types of feared animals) and "in vivo" or live situations (eg, petting a dog and touching a snake at a pet store). Therapy sessions 2-11 begin with a review of homework assigned during the previous week's session, followed by an approximately 35-minute virtual exposure session. Patients report their anxiety level using a 1- to 100-point scale at a 5-minute interval throughout the exposure and remain in the exposure until their self-reported anxiety reaches a 50% reduction from their peak anxiety rating from baseline following the introduction of the stimulus or 35 minutes elapses. That is, participants will spend a maximum of 35 minutes in the exposure and if they have reached a 50% reduction or greater from their peak anxiety rating before the 35 minutes is over, they will move on to the next exposure. Following the exposure, the therapist and patient process thoughts and feelings related to the exposure, reframe appraisals of their feared stimuli through cognitive restructuring, and practice box breathing. The Doxy.me VR group will conduct their in-session exposures in the VR clinic and the TMH group will conduct their in-session exposures using multimedia on the Doxy.me platform by screen-sharing videos and photos. Once patients have progressed through all VR and multimedia situations in their hierarchy and are ready to complete their first in vivo exposure between therapy sessions for homework, weekly therapy sessions will be devoted to processing and planning between-session in vivo exposures.

Homework

All therapy sessions will include the assignment of homework, including reading an informational handout after the psychoeducation and treatment planning session (session 1) and exposure therapy assignments after therapy sessions 2-11. Daily exposure-based homework assignments will require participants to practice exposure exercises similar to those completed during that week's therapy session (ie, using VR or multimedia stimuli) for a minimum of 30 minutes. When the patient states that they are ready, these will include in vivo exposure exercises planned during the therapy session. Participants will receive text or email reminders with links to REDCap surveys with instructions for the homework assignment and the situation to be used in the exposure exercise. The survey will also ask participants to report the date and time of the exposure, their baseline anxiety rating, their peak anxiety level during the exposure, and their anxiety level following completion of the exposure exercise.

Recruitment Strategy

Potential participants will be recruited through Clinical Connection [54], Research Match (retrieved from researchmatch website [55]), Facebook (Meta [56]) advertisements, and flyers distributed on the University of South Florida campus and off-campus community centers. Potential participants will be provided with a URL or QR code directing them to an online prebaseline screening questionnaire administered via REDCap. Those meeting preliminary eligibility criteria will then schedule an initial consent and baseline assessment visit via Microsoft Bookings with text or email reminders 24 hours and 1 hour before the scheduled visit time.

Eligibility Criteria

Eligible participants will (1) be ≥18 years old; (2) have a self-reported fear of dogs, snakes, or spiders; (3) have subthreshold or present specific phobia symptoms as determined by the study therapist via administration of the Diagnostic Assessment Research Tool (DART) Specific Phobia Module [57]; (4) have access to the internet and a computer or smartphone with videoconferencing capabilities; and (5) plan to reside in the state of Florida for the duration of the study.

An individual who endorses any of the following criteria will be excluded from participation in the study: (1) participation in ongoing mental health therapy from a nonstudy therapist; (2) changes to psychotropic medication use within 6 weeks preceding enrollment in the trial; (3) active suicidal or homicidal intent or plan as determined by the study therapist via the DART Risk Assessment Module [57]; (4) active auditory, visual, or tactile hallucinations via the DART Psychosis Module screening question; or (5) a diagnosis of photosensitive epilepsy by a medical doctor or a history of experiencing seizures caused by photosensitivity.

Criteria for Withdrawing Participants

Anticipated circumstances under which participants will be withdrawn without their consent include (1) new participation in mental health therapy from a nonstudy therapist; (2) changes to psychotropic medication use; (3) active suicidal or homicidal intent or plan; (4) onset of auditory, visual, or tactile hallucinations; (5) onset of photosensitive epilepsy or seizures; and (6) moving out of the State of Florida during the study period.

If participants completely withdraw or are administratively withdrawn from the study, staff will attempt to provide them with a referral to a therapist in their area. If participants partially withdraw from the research, study staff will attempt to administer mid- and posttreatment assessments. Participants will be given the option to completely withdraw from the study, including withdrawing previously collected data.

Criteria for Wait-Listing Participants

If potential participants do not meet eligibility criteria due to participating in ongoing mental health therapy from a nonstudy therapist or recent changes to psychotropic medication use within 6 weeks preceding enrollment in the trial, they will be presented with a message on the prescreening survey inviting them to revisit the prescreening questionnaire at a later date if and when those conditions no longer apply.

Consent and Baseline Assessments

The consent and baseline assessment visit will be conducted via videoconferencing platform and will not be audio or video-recorded. During this visit, study staff will (1) confirm the potential participant's responses on the online prescreening questionnaire, (2) provide detailed information about the study and obtain informed consent, (3) assist participants in completing baseline questionnaires via REDCap survey, (4) administer the Specific Phobia and Risk Assessment modules of the DART, and (5) make a final determination on the participant's eligibility. Eligible participants will then be

randomized using the REDCap Randomization Module and scheduled for their first treatment visit. Neither participants nor study staff will be blinded to the comparator of interest or their group assignment.

Assessment Strategy and Measures

Overview

All assessments were chosen considering several factors including (1) sound psychometric properties, (2) ease of administration, (3) past use in similar clinical trials, and (4) brevity. All assessments will be facilitated remotely by the study therapist and will occur at baseline, each session, midtreatment (ie, after completion of 6 therapy sessions, up to 6 weeks post baseline), and 12 weeks post baseline. Self-report questionnaires will be completed by patients via REDCap survey with the study therapist present to answer any questions. Structured diagnostic interviews will be administered by study therapists and recorded in REDCap.

Specific Phobia Symptoms and Severity

The DART [57] is a modular semistructured interview corresponding with the *DSM-5* (*Diagnostic and Statistical Manual of Mental Disorders* [Fifth Edition]) [58]. Study therapists will administer the DART Specific Phobia Module, which provides designations of absent, subthreshold, and present. While the DART is a new tool, initial validation indicates excellent construct validity, discriminant validity, and convergent validity across modules [57,59].

The Severity Measure for Specific Phobias (SMSP) for adults [60] is a 10-item self-report questionnaire assessing the severity of specific phobia symptoms as they relate to the respondent's feared stimulus. Total scores range from 0 to 4 with higher scores indicating higher phobia severity. The SMSP has excellent internal consistency, criterion, and discriminant validity [61].

Other Mental Health Symptoms

Suicide and Homicide Risk

The DART-Risk Assessment Module [57] will be administered by study therapists to assess risk for suicidal and homicidal ideation, intention, and plans and guides the formation of safety plans where warranted.

Generalized Anxiety

The Generalized Anxiety Disorder-7 Scale (GAD-7) [62] is a 7-item self-report measure of anxiety symptom severity. Scores range from 0 to 15 with higher scores indicating higher anxiety severity. The GAD-7 is widely used and has demonstrated excellent internal consistency reliability and good convergent validity [63].

Depression

The Patient Health Questionnaire-8 (PHQ-8) [64] is an 8-item self-report measure of depression symptom severity. Scores range from 0 to 27 with higher scores indicating higher depression severity. The PHQ-8 has demonstrated excellent internal consistency reliability, good convergent validity, and specificity for depression diagnosis [65].

Treatment-Related Factors

Working Alliance

The Working Alliance Inventory [66] is a 10-item client-rated measure of therapeutic alliance. Total scores range from 1 to 5 with higher scores indicating a better therapeutic alliance. The WAI-SR has demonstrated excellent internal consistency, reliability, and good convergent validity [67].

Presence

The Single Item Presence Questionnaire (SIPQ) [68] is a 1-item self-reported measure of telepresence. Respondents are asked, "To what extent did you feel present in the environment, as if you were really there?" and provide ratings on a scale of 0 "not at all present" to 10 "totally present." The SIPQ has demonstrated good to excellent content, face validity, test-retest, convergent and divergent validity, and sensitivity [68].

Cybersickness

The Cybersickness in Virtual Reality Questionnaire (CSQ-VR) [69] is an 8-item measure of nausea, vestibular, and oculomotor cybersickness experienced in VR. Scores range from 6 to 27 with higher scores indicating higher levels of cybersickness. The CSQ-VR has demonstrated excellent internal consistency and convergent validity [70].

Client Satisfaction With Treatment

The Client Satisfaction Questionnaire-8 (CSQ-8) [71] is an 8-item client-rated measure satisfaction with treatment. Scores range from 8 to 32 with higher scores indicating higher satisfaction. The CSQ-8 has demonstrated good structural validity and internal reliability and is correlated with clinical outcomes and posttreatment functioning [72].

System Usability

The System Usability Scale (SUS) [73] is a 10-item self-report measure of the usability of a particular software system, platform, or app. Scores range from 0 to 100 with higher scores indicating better usability. The SUS has demonstrated good internal consistency reliability and is a useful tool for comparing system usability between 2 and more platforms.

Fidelity to the Treatment Protocol

All treatment sessions will be recorded and 20% (120/600) will be rated by the supervisor (principal investigator) using a treatment fidelity checklist based on the treatment manual. Refer to Table 1 for a summary of study assessments.

Table 1. Study assessments.

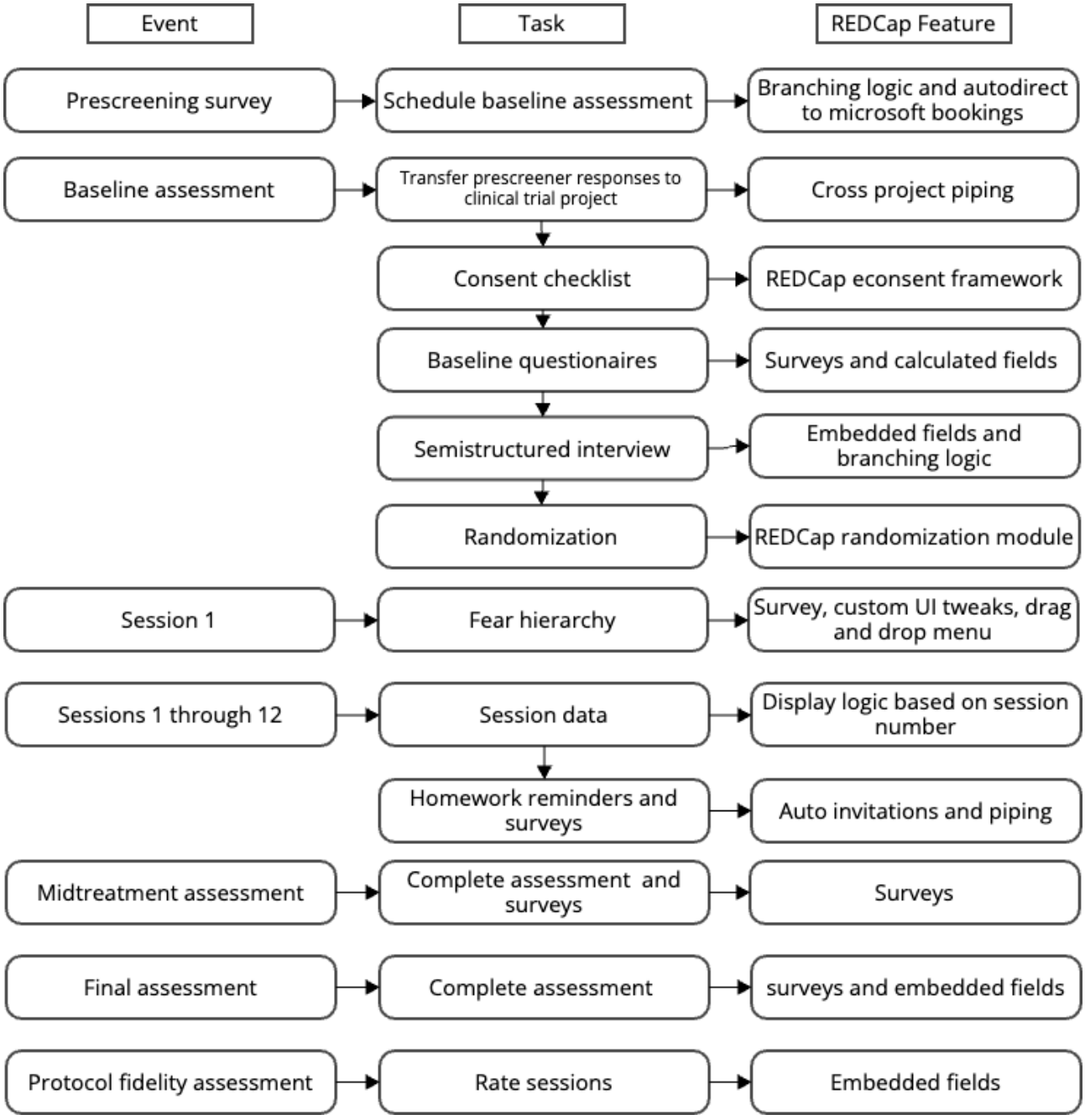
Domain	Measure	Time point				
		Pre	Baseline	Weekly	Mid	Post
Demographics	Demographics Questionnaire		✓			
Specific phobia diagnosis	Diagnostic Assessment Research Tool–Specific Phobia Module (DART-SP)		✓			✓
Specific phobia severity	Severity Measure for Specific Phobia-Adult (SMSP-A)	✓	✓		✓	✓
Risk	Diagnostic Assessment Research Tool–Risk Assessment (DART-RA)		✓			
Anxiety severity	General Anxiety Disorder-7 (GAD-7)		✓		✓	✓
Depression severity	Patient Health Questionnaire-9 (PHQ-9)		✓		✓	✓
Therapeutic alliance	Working Alliance Inventory- Short Revised (WAI-SR)				✓	✓
Presence	Single Item Presence Questionnaire (SIPQ)			✓		
Cybersickness	Cybersickness in Virtual Reality Questionnaire (CSQ-VR)			✓		
Treatment satisfaction	Client Satisfaction Questionnaire (CSQ-8)				✓	✓
Usability	System Usability Scale (SUS)				✓	✓

Partial Automation of Trial Data Collection Using REDCap

All feasibility trial data will be collected via 2 REDCap projects. The first REDCap project will include a survey to collect responses to the online prescreening questionnaire, which will include questions about basic eligibility criteria, the SMSP, and contact information. If potential participants meet the initial study eligibility criteria of the REDCap survey, they will be directed to a Microsoft Bookings page to schedule their baseline assessment, with automated reminders about the appointment 24 and 1 hours before the appointment.

The second, main REDCap project will facilitate all other data collection for the feasibility trial. Participants' online prebaseline screening questionnaire responses will be automatically transferred to the main clinical trial project using the REDCap piping function in preparation for the baseline assessment. After obtaining informed consent, supported by the REDCap e-Consent Framework feature, participants will be automatically directed to baseline questionnaire surveys, for which REDCap auto-calculates the scores. Following completion of the baseline assessment, the participant will be randomized to their respective treatment conduction using the Randomization Module. All therapy session data (ie, session number, date, time, and length), adherence checklist, clinical notes, and in-session exposure ratings will be entered into a REDCap form by the study therapist during each therapy session. Following the completion of each session, participants will receive automated survey invitations to complete homework assignments, which will be delivered on specific days during the following based on the session number, session date, and treatment condition. Weekly postsession questionnaires (ie, SIPQ and CSQ-VR) will be completed via REDCap surveys, displayed conditionally based on treatment condition (eg, the CSQ-VR will only be displayed to those in the Doxy.me VR condition). Specific REDCap automations and features used for each stage of the trial are included in Figure 2.

Figure 2. REDCap (Research Electronic Data Capture) automation and features. UI: user interface.



Ethical Considerations

The protocol was approved by the University of South Florida institutional review board (#006215). All participant data will be stored in the University of South Florida REDCap database and only study staff members have access to the REDCap project. All data exported for analysis from REDCap will be anonymized with only participant ID numbers. Participants will be compensated US $50 for completing the baseline, midtreatment assessment, and 3-month post baseline assessment at a total of US $150. Participants will be compensated using Tango e-gift cards.

Procedures to Ensure Participant Safety

Some questions asked during assessments and exposure exercises may cause participants distress, but this distress is expected to be similar to what participants would experience with routine care for specific fears or phobias. The study therapist will ensure that any questions causing distress are discussed with participants and provide them with techniques to reduce distress. A temporary increase in the severity of anxiety is expected at the beginning of exposure therapy, along with a gradual decline in severity over the course of treatment. If participants are distressed and unable to participate in the study following baseline assessments, or at the end of the study, participants feel that they need further treatment, the study therapist will provide a referral to therapists in the participants' local area. Referrals will be provided verbally to participants and the study therapist will follow up in 1 week via telephone to inquire as to the state of the referral and provide further assistance as necessary. If participants endorse suicidality or homicidality at any point during the study, we will follow the

standard operational procedures of the University of South Florida Department of Psychiatry and Behavioral Neurosciences requiring safety planning with the participant at risk and mandatory reporting responsibilities.

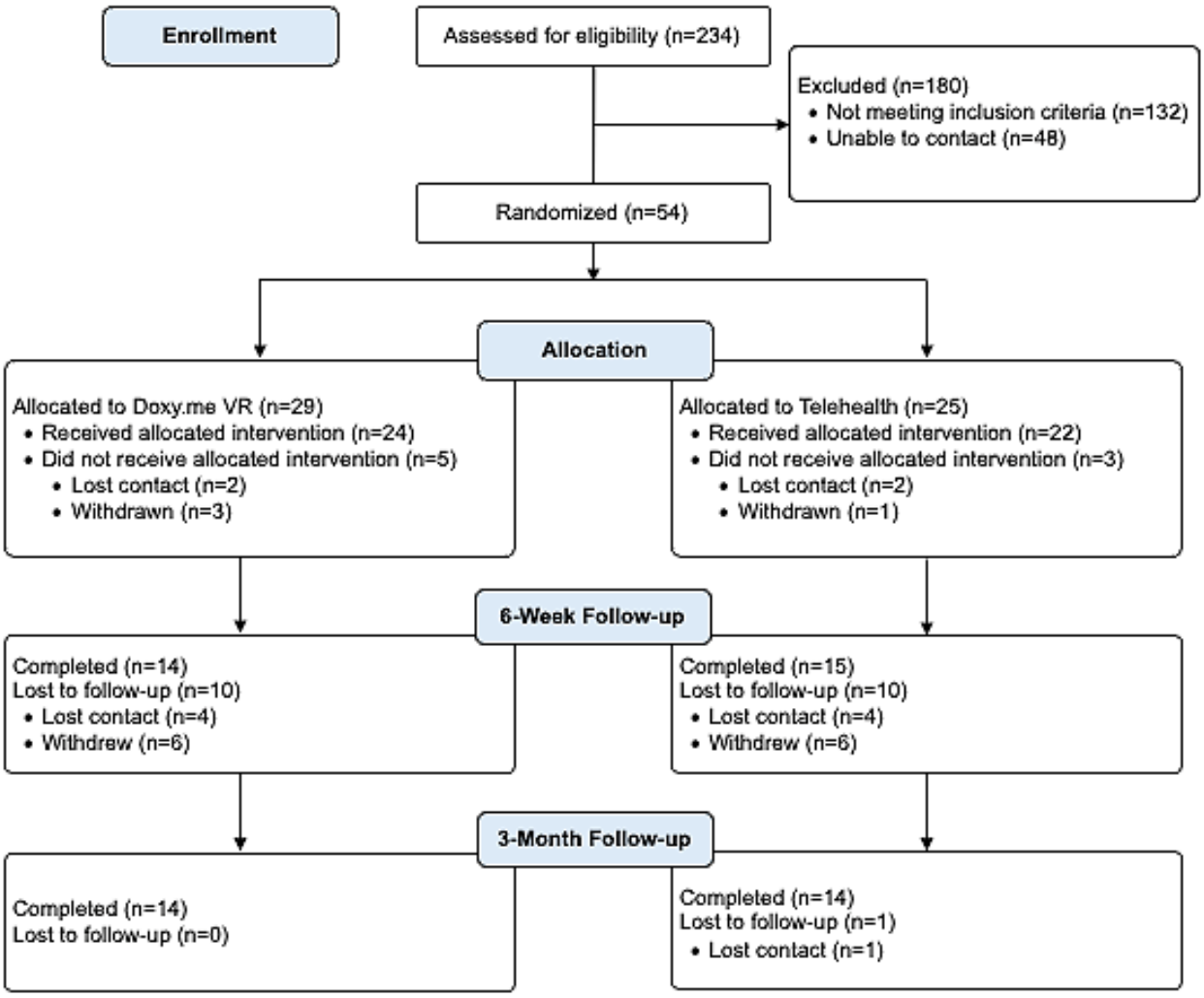
Data Analytic Plan

We will assess the feasibility of the proposed trial methodology using the following benchmarks: (1) 30 participants will be enrolled in months 1-9 of the trial, (2) ≥70% (21/30) of participants will be retained for 3-month follow-up assessments, (3) 70% (420/600) of weekly self-report assessments will be completed, and (4) treatment fidelity we will be ≥80%. The small sample size of this feasibility trial will prevent us from making conclusions about efficacy; however, a repeated measures ANOVA will be used to conduct a preliminary assessment of between-group differences in clinical outcomes while covarying for pretreatment scores. We will also conduct a preliminary examination of associations between study targets (ie, therapeutic alliance and presence) and homework adherence. Data obtained from these analyses will inform power analyses aimed at determining sample size requirements for a fully powered efficacy trial.

Results

The first participant was enrolled on October 25, 2023, and the last therapy session and 3-month post baseline assessment were completed on July 26, 2024. In total, 54 participants were randomized. Refer to Figure 3 for the CONSORT (Consolidated Standards of Reporting Trials) diagram and Multimedia Appendix 1 for the CONSORT-EHEALTH (Consolidated Standards of Reporting Trials of Electronic and Mobile Health Applications and Online Telehealth) checklist. Data analysis for the primary and secondary aims of the clinical trial will be completed and submitted by the end of the second quarter of 2025.

Figure 3. CONSORT diagram.



Discussion

Overview

There will be a growing need for innovative solutions to enhance the effectiveness of remote care as TMH services continue to evolve [1,16,17]. VR has tremendous potential to increase the efficacy of evidence-based practices that were originally designed for in-person treatment but are now delivered via TMH with increased regularity (eg, exposure therapy). This feasibility trial comparing exposure therapy via Doxy.me VR versus TMH for adults with an intense fear of dogs, snakes, or spiders fills an important gap in the nascent research on telemedicine-based VR exposure therapy. Using this protocol, we will assess the feasibility of our proposed study methodology in preparation for a fully powered efficacy trial. We anticipate meeting or exceeding these feasibility criteria, which will provide valuable insights into the feasibility of conducting a large-scale efficacy trial.

Principal Findings

As anticipated, we exceeded our recruitment goal of enrolling 30 or more participants in months 1-9 of the clinical trial by enrolling 54 participants during months 1-7. Data analysis will be completed and submitted by the second quarter of 2025 at which point we will report on the remaining feasibility results.

Comparison With Previous Work

Our study builds upon previous research demonstrating the efficacy of VR exposure to enhance treatment delivery. While there is significant support for in-clinic VR mental health therapy, evidence for telemedicine-based VR mental health is limited. Our study addresses this important gap by evaluating the feasibility and preliminary efficacy of exposure therapy via an innovative telemedicine-based VR clinic (ie, Doxy.me VR), thereby contributing to the nascent research on the use of VR in TMH.

Limitations

The small sample size proposed by this study limits the generalizability of our findings and prevents us from drawing conclusions about treatment efficacy. A large-scale efficacy trial will address this limitation.

Conclusions

This feasibility randomized controlled trial comparing Doxy.me VR versus TMH represents an important step toward leveraging VR technology to enhance the delivery of evidence-based treatments via telemedicine. By evaluating the feasibility and preliminary efficacy of exposure therapy via a telemedicine-based VR clinic, we will contribute a potential solution to common barriers to remotely delivered exposure therapy.

Future Directions

Future research will involve fully powered efficacy trials on telemedicine-based VR and the potential of this technology to improve treatment outcomes for mental health disorders.

Acknowledgments

Research reported in this publication was supported by the National Institute of Mental Health of the National Institutes of Health (award R43MH129065). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Data Availability

The datasets generated during and/or analyzed during this study are available from the corresponding author on reasonable request.

Conflicts of Interest

BEB, TO, and BMW are employees of Doxy.me Inc, a commercial telemedicine company. The authors declare no other conflicts of interest.

Multimedia Appendix 1
CONSORT-eHEALTH checklist (V 1.6.1).
[PDF File (Adobe PDF File), 1272 KB - resprot_v14i1e65770_app1.pdf]

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Abbreviations

CONSORT: Consolidated Standards of Reporting Trials
CONSORT-EHEALTH: Consolidated Standards of Reporting Trials of Electronic and Mobile Health Applications and Online Telehealth
CSQ-8: Client Satisfaction Questionnaire-8
CSQ-VR: Cybersickness Questionnaire for Virtual Reality
DART: Diagnostic Assessment Research Tool
DSM-5: Diagnostic and Statistical Manual-Fifth Edition
GAD-7: Generalized Anxiety Disorder-7
HIPAA: Health Insurance Portability and Accountability Act
PHQ-8: Patient Health Questionnaire-8
REDCap: Research Electronic Data Capture
SIPQ: Single Item Presence Questionnaire
SMSP: Severity Measure for Specific Phobias
SUS: System Usability Scale
TMH: Telemental health care
VR: virtual reality
VRET: virtual reality–based exposure therapy

Edited by A Schwartz, T Leung; submitted 25.08.24; peer-reviewed by D Tamayo, F Mesa; comments to author 27.12.24; revised version received 27.01.25; accepted 25.02.25; published 10.04.25.

Please cite as:
Schuler KR, Ong T, Welch BM, Craggs JG, Bunnell BE
Examining a Telemedicine-Based Virtual Reality Clinic in Treating Adults With Specific Phobia: Protocol for a Feasibility Randomized Controlled Efficacy Trial
JMIR Res Protoc 2025;14:e65770
URL: https://www.researchprotocols.org/2025/1/e65770
doi:10.2196/65770
PMID:

Protocol

Mobile App–Delivered Motivational Interviewing for Women on Eating Disorder Treatment Waitlists (MI-Coach: ED): Protocol for an App Development and Pilot Evaluation

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Abstract

Background: A significant increase in eating disorder (ED) service waitlists has been observed in the past several years, exacerbating existing barriers to care (eg, long waitlists, scarcity of treatment centers, and positive beliefs surrounding pathology). Given that treatment delays have important clinical correlates (eg, entrenchment of ED pathology), exploring new methods of mental health service delivery for this population is of critical concern. App-based motivational interviewing (MI) delivered prior to the start of treatment has the potential to improve accessibility by simultaneously addressing structural (eg, travel costs) and individual (eg, low motivation) barriers to care. Despite the potential benefits, there remains a lack of empirically validated, ED-specific MI-based mobile apps. Evaluating the feasibility and acceptability of such interventions is a crucial first step before progressing to full-scale efficacy trials.

Objective: This multiphasic mixed methods study aims to develop and assess the feasibility and acceptability of MI-Coach: ED, a novel app designed to increase motivation among women waitlisted for ED treatment. Specifically, this study seeks to determine participant engagement levels, user satisfaction, and perceived usability of the app, as well as to explore preliminary trends in motivation and ED-related symptoms following app use.

Methods: Phase I adapted the content and interface of an existing app based on evidence-based principles (MI-Coach) for an ED population. Phase II pilot tested the app through a pre-post evaluation. Participants (n=30) aged 18 years and older were recruited from ED treatment waitlists in British Columbia, Canada. After completing baseline assessments evaluating demographic and clinical variables (eg, motivation, eating pathology, depression, and anxiety symptoms), participants were provided access to MI-Coach: ED for 1 month. Participants completed postintervention assessments and provided both quantitative and qualitative feedback on the app. Feasibility will be evaluated through the total number of participants recruited, study dropout rates, and engagement indicators (eg, modules completed) within the app. Acceptability will be assessed through self-report measures and semistructured exit interviews, which will explore user experiences, perceived benefits, and barriers to app engagement. Additionally, exploratory analyses will examine changes in motivation and ED symptoms before and after the intervention.

Results: The MI-Coach: ED app has been developed, and recruitment was initiated in November 2022 and terminated in May 2024. Results are being analyzed and will be submitted for publication in May 2025.

Conclusions: This study has the potential to transform ED service delivery and mitigate the impacts of existing treatment barriers for this population. By leveraging a digital MI-based intervention, MI-Coach: ED could serve as a scalable and accessible pretreatment tool, helping to bridge the gap between initial help-seeking and formal ED treatment. Findings from this study will inform the refinement of the intervention and recruitment strategies for future large-scale efficacy trials.

International Registered Report Identifier (IRRID): DERR1-10.2196/66298

(JMIR Res Protoc 2025;14:e66298) doi:10.2196/66298

KEYWORDS

eating disorders; motivational interviewing; treatment barriers; digital interventions; pilot test; protocol; eating disorder; eating; woman; women; female; Canada; Canadian; mobile apps; mobile health; mHealth; app development; app-based; mental health; pilot evaluation; waitlists; mixed methods; feasibility; acceptability; service delivery

Introduction

Eating disorders (EDs) are serious, life-threatening psychological illnesses that involve disturbances surrounding body image, emotion regulation, and eating behaviors [1,2], resulting in a number of deleterious health consequences and high levels of psychiatric comorbidity [3-5]. Despite the severity of these disorders, ED populations are significantly less likely to access mental health services compared to those with other disorders [5,6]. For instance, wait times exceeding 12 months for ED-specific services have been reported in Ontario, Canada, and nonprofit organizations have observed a 2-fold increase in requests for peer-support services following the COVID-19 pandemic [7]. In this regard, several treatment barriers have been identified limiting access to ED treatments and services. As EDs require specialized forms of care, treatment centers are typically few in number, necessitating significant travel time and associated costs (eg, costs related to travel and childcare and loss of income due to sick leave), and often resulting in long waitlist durations [6]. Further, ambivalence regarding treatment is common among ED populations, with motivation for recovery often in conflict with other factors, such as engaging in ED behaviors to cope with difficult emotions or to provide a sense of control [8-10].

Unfortunately, treatment delays are associated with adverse outcomes, such as reductions in pretreatment levels of motivation and poorer long-term prognosis. Early intervention has been associated with improved treatment outcomes following discharge, longer durations between relapses, and improvements in related psychological symptoms such as depression and anxiety [11]. Recent efforts to bridge treatment barriers and improve outcomes for this population include the delivery of brief interventions such as motivational interviewing (MI) prior to the start of formal treatment. Initially developed by Miller and Rollnick [12] to address ambivalence within substance use treatment, MI is a person-centered approach that aims to strengthen the individual's intrinsic motivation to change [13]. A recent systematic review conducted by Denison-Day et al [8] found substantial support for the use of MI interventions for individuals with EDs, with a majority (74%) of the studies reviewed reporting significant and long-term improvements in motivation as a result of MI interventions compared to passive interventions, such as psychoeducation. Broadly, studies report that brief MI interventions lead to improvements in motivation, self-esteem, depressive symptoms, and positive treatment outcomes (eg, greater engagement in treatment), particularly when delivered prior to the start of formal treatment [14-16].

Despite the potential for pretreatment MI interventions to address individual treatment barriers, they are typically conducted through in-person, face-to-face sessions [8,14,16,17]. In-person interventions may not adequately address structural treatment barriers, such as costs and scarcity of treatment providers. In order to address this issue, internet and communications technology (ICT)–based interventions have been proposed as a low-cost and accessible form of delivering ED interventions [5,18-20]. Apps in particular show potential in the delivery of pretreatment MI interventions, as they are easy to use, require low effort, and become habitual over time. Further, unlike other ICT-based interventions, they have high hedonic motivation (ie, they are enjoyable to use), which increases their use and adoption [21,22]. In addition, the digital components embedded within apps (eg, modules, graphic design, and diverse multimedia content) have been shown to significantly improve adherence to interventions and reduce dropout rates [23].

Despite preliminary findings suggesting that apps may be an acceptable means of delivering ED services, there is a paucity of effective, evidence-based apps available for use [24-27]. Most publicly available app interventions are based on CBT and behavioral self-monitoring principles but demonstrate limited efficacy compared to traditional delivery methods [24,28]. However, considering the accessibility of apps and their wide adoption in various health and social contexts [29], they may be an effective mode of delivery for pretreatment MI contexts. Help-seeking individuals waiting for formal services likely do not have access to in-person treatment options, despite their urgent need for services. Further, as they have not yet started formal ED treatment, receiving a pretreatment MI intervention may significantly improve treatment outcomes. For example, such interventions may increase motivation to stay on the waitlist and adhere to treatment once services are received [30]. An app-based MI intervention thus has the potential to simultaneously address structural and individual treatment barriers. Despite the potential benefits, to date, no research has investigated the use of app-based MI pretreatment interventions for EDs.

The proposed study aims to adapt and pilot-test MI-Coach, a widely available app-based MI platform, for individuals on ED treatment waitlists. Created by Resiliens Inc, MI-Coach is an evidence-based self-help app developed in collaboration with a registered clinical psychologist. The app was adapted for use within an ED pretreatment context. Furthermore, this will be the first study to investigate whether an app-based MI pretreatment intervention improves clinical symptoms, motivation for treatment, and openness to change for individuals while they wait for ED treatment.

Methods

Hypotheses

This project is guided by the technology acceptance model (TAM), which theorizes that an ICT's acceptability is determined by its perceived ease of use and usefulness [31]. It is thus hypothesized that greater perceived usefulness and ease of use of the MI-Coach: ED app will lead to greater use and engagement with the app, and subsequently, improved treatment

outcomes. It is also hypothesized that participants will experience an improvement in their motivation to recover from an ED following use of the app. In addition, the app's acceptability and feasibility will be examined, as well as the possible impacts of other clinical variables (eg, depression, anxiety, BMI, and ED severity) on motivation to recover.

Ethical Considerations

Ethics approvals were granted by the University of British Columbia Okanagan Campus' Behavioral Research Ethics Board (H22-02046) on October 4, 2022, and by the Vancouver Coastal Health Research Institute (V22-02046) on October 10, 2023. All eligible participants provided informed consent electronically through the secure web-based platform Qualtrics prior to enrollment, after receiving detailed information about study procedures, potential risks and benefits, data confidentiality, and voluntary participation. Participants were informed of their right to withdraw from the study at any time without penalty. Participant privacy was maintained by storing data on password-protected university servers accessible only to research personnel. All identifying information was stored separately from the study data. Participants received compensation of up to CAD $40 (≈US $28.41) in the form of digital gift cards. Compensation was clearly outlined in the informed consent form and was structured to avoid influencing participation or app use.

Study Design

The current pilot test evaluation follows a naturalistic pre-post design. A pilot test framework was chosen to assess the initial feasibility and acceptability of the app and to identify any potential issues with the study design and delivery format prior to evaluating the app's efficacy at a larger scale [32]. The MI-Coach: ED app was designed to improve motivation in women-identifying people waiting for formal ED treatment and will be pilot-tested in the province of British Columbia, Canada. Qualitative and descriptive data were collected to determine the acceptability and feasibility of the MI-Coach: ED app.

Study Population

Sample Size Estimation

Given the focus of this study on the acceptability and feasibility, rather than the efficacy, of the MI-Coach: ED app, formal analytic methods were not used to estimate the prehoc sample size. In keeping with previous feasibility studies in the ED field [14,33,34] and pilot study guidelines, which suggest that modest sample sizes based on the pragmatics of recruitment are sufficient when evaluating the processes, feasibility, and preliminary acceptability of novel interventions [32,35], a sample size of 30 participants was selected, recruited while they wait for ED services and treatments in British Columbia, Canada. Additionally, it was determined that qualitative interviews would be conducted with interested participants on a rolling basis until thematic saturation is reached [36].

Participant Recruitment

ED treatment providers and clinicians located in British Columbia were contacted by email and asked to distribute study recruitment flyers providing an overview of the study, incentives, and instructions to contact the study team to indicate their interest to clients on their waitlists (Multimedia Appendix 1). To address existing barriers to ED treatment (eg, logistical challenges and clinician burnout [6,37]) and research [38], a multipronged approach to recruitment has been used in previous studies [15,39], whereby clinician-based referrals are supplemented by web-based recruitment and partnerships with peer support organizations. As such, clinician-based referrals were supplemented by web-based recruitment strategies, including postings on the National Eating Disorder Information Center website and social media, as well as partnerships with peer support organizations. Additionally, a research partnership was established with a local provincial health authority, the Vancouver Coastal Health Eating Disorders Program, which embedded the study flyer as part of an initial resource package provided to patients newly added to their waitlist. Given the findings that recruitment strategies influence sample characteristics and engagement [38], this multipronged approach aimed to maximize the accessibility of the study and diversity within the study sample.

Eligibility Criteria

Eligibility criteria were (1) being on a waitlist to receive services for an ED-specific concern and not for a separate mental disorder in British Columbia, (2) being at least 18 years of age, (3) self-identifying as a woman, (4) fluency in written and spoken English, (5) meeting the criteria for a diagnosis of a threshold or subthreshold ED (ie, BN, AN-R, AN-BP, BED, and OSFED), (6) absence of psychosis or diagnosis of a schizophrenia-spectrum disorder, and (7) absence of cognitive impairments or sensory deficits that may interfere with technology use (eg, hearing impairments and recent traumatic brain injury).

Intervention

MI-Coach is a self-help app created by Resiliens Inc [40] targeting motivation to engage in health behavior change (eg, exercising, smoking cessation, and sleep hygiene), and is widely available on both Apple and Android app stores. Developed in collaboration with a clinical psychologist and MI expert from the University of Queensland (Stan Steindl, PhD), the app features eight modules, consisting of over 35 lessons led by a registered clinical psychologist with accompanying exercises. In addition, the app includes short articles, mood and behavior assessments, mindfulness-based audio tracks, summary screens and analytics, community-based discussion groups, and the ability to communicate directly with a trained mental health professional.

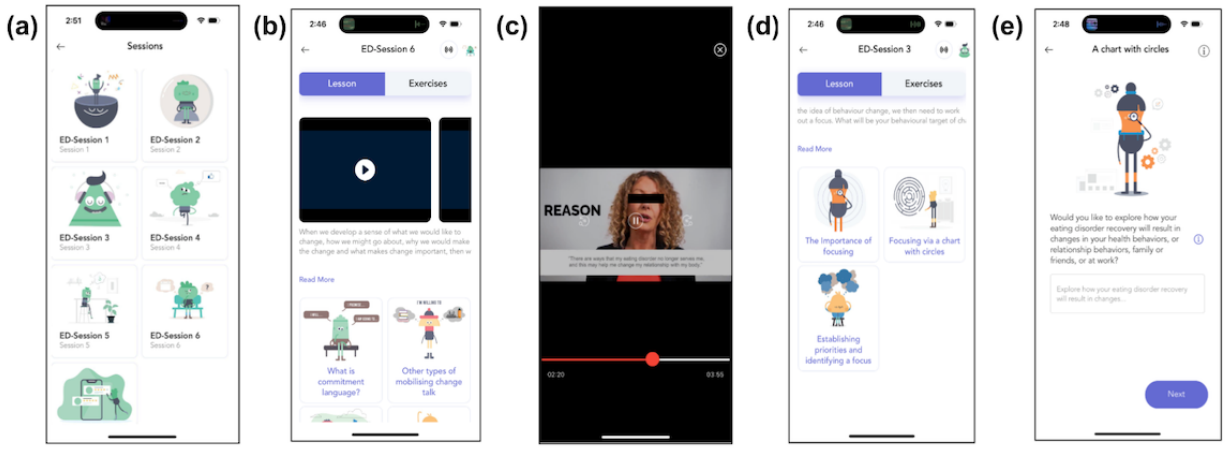
For the purposes of this study, the content of MI-Coach was tailored for an ED population. In line with best practices for developing ED-specific digital interventions [17,30,41], an in-depth review of potentially iatrogenic or triggering content in the existing app was identified. Specifically, content referring to weight loss or health-focused exercise goals was identified, which prior research suggests may inadvertently reinforce disordered eating behaviors [28,30,37,42]. Subsequently, a literature review was conducted to identify MI topics and ED behavior change goals used in previous interventions, such as exploring reasons for and against pursuing treatment, validating

the difficulties of addressing ED pathology, and identifying values and goals driving ED recovery efforts [11,17,30,41].

Following approaches outlined in previous research [15], the research team then performed iterative content analyses to remove or reframe any references misaligned with ED recovery principles (eg, shifting from weight-centric to motivation-centered goals that explore the individual's reasons for seeking treatment, and the inclusion of topics such as ambivalence and identification of goals and values relevant to recovery). The overall structure and MI principles used in the original app were retained given their demonstrated effectiveness within an ED context [8]. Throughout this process, informal stakeholder consultations were conducted with ED-specialized clinicians involved in the project, who verified the appropriateness of the revised app content. All video lessons were subsequently refilmed using the University of British Columbia Okanagan's recording studio and equipment. The new videos featured a clinical psychologist with ED treatment expertise to reduce discrepancies between the original and adapted app content (eg, clinical expertise and years of training). Examples of the MI-Coach: ED interface are provided in Figure 1.

Once the adaptation of app content was completed, a new section was built into the interface of the existing MI-Coach app by technological partners (Resiliens Inc) to house the adapted content. Several components of the base app (ie, assessments, audio tracks, analytics, discussion groups, and communication with the mental health professional) were removed to reduce the scope of the project and to protect participant confidentiality. The final adapted MI-Coach: ED app consisted of seven modules (Multimedia Appendix 2) targeting motivation to engage in ED recovery behaviors (eg, help-seeking, values exploration, and self-acceptance) covering the following topics sequentially: ambivalence and behavior change, self-acceptance and compassionate motivation, exploring possible behavior change goals, sustain and change talk, commitment language, and relapse prevention.

Figure 1. Screenshots of the MI-Coach: ED interface illustrating (a) the home screen with session modules, (b) example module content, (c) brief videos, (d) examples of exercises available per module, and (e) example exercise content. Each feature targets ED-specific barriers such as ambivalence or low treatment motivation. ED: eating disorder.



Outcomes and Measures

The primary outcomes that will be evaluated are the overall acceptability and feasibility of the MI-Coach: ED (Multimedia Appendix 3). Feasibility will be assessed through attrition rates throughout the study period, frequency of app use, and module completion. Acceptability will be assessed through qualitative and quantitative feedback from participants through semistructured interviews and self-reports. Additionally, exploratory analyses will be conducted regarding the impacts of the MI-Coach: ED app on motivation and associated clinical characteristics.

Self-reported demographic data, including gender identity, age, level of education, ethnicity, and socioeconomic status were collected using Qualtrics, a web-based and secure data collection platform. Additionally, clinical data (ie, weight and height, history of ED treatment, age of ED onset, presence of cognitive difficulties, sensory deficits, history of traumatic brain injury, other mental health comorbidities, and ED waitlist experiences) was collected. The Sick, Control, One, Fat, and Food questionnaire [43], a brief screener that identifies the presence of common ED symptoms, was used to determine eligibility prior to enrollment. Clinical characteristics (ie, eating pathology, recovery motivation, body dissatisfaction, depression, and anxiety symptoms) were evaluated through several self-report questionnaires administered at baseline and posttest, including the Eating Disorder Examination Questionnaire (EDE-Q) [44], the Readiness and Motivation for Change Questionnaire (RMQ) [45], the Body Shape Questionnaire (BSQ) [46], the Patient Health Questionnaire-9 (PHQ-9) [47], and the 7-item General Anxiety Disorder Scale (GAD-7) [48]. Additionally, technological literacy was evaluated at baseline using the Mobile Device Proficiency Questionnaire [49] and the eHealth Literacy Scale [50].

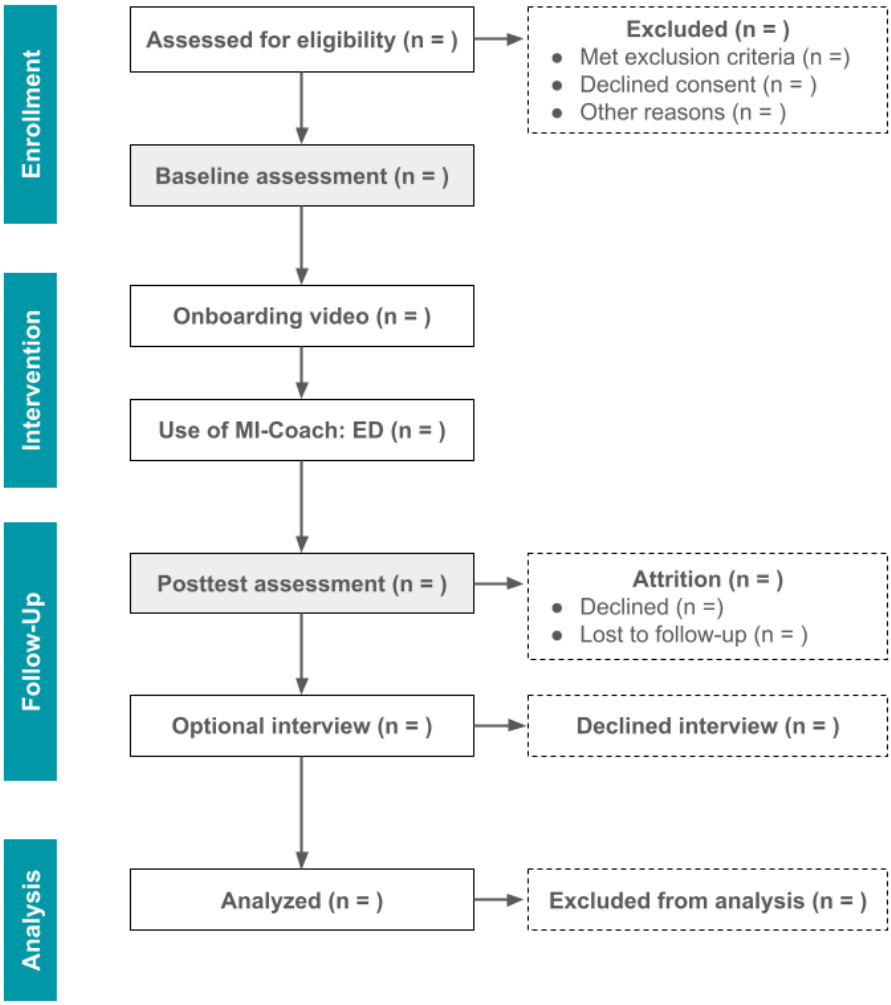
Quantitative measures of feasibility and acceptability of the MI-Coach: ED app were assessed using an adapted version of the TAM Questionnaire [31] and the user version of the Mobile App Rating Scale (uMARS) [51]. The adapted version of the TAM questionnaire includes changes to each item to better fit the research question and sample characteristics of this study (eg, "Using CHART-MASTER in my job would enable me to

accomplish tasks more quickly" was modified to "Using MI-Coach: ED allowed me to access mental health services more quickly"). An optional semistructured interview was conducted with interested participants to assess their experiences with the app and to further evaluate the feasibility and acceptability of MI-Coach: ED.

An overview of participant flow is provided in Figure 2. Participants were recruited between November 2022 and April 2024. Clinicians and administrators working in a range of ED treatment settings (eg, provincial health authorities, nonprofit charities, and private practice clinics) were contacted via email and asked to share the recruitment advertisement with clients on their waitlists. Interested participants were asked to communicate with the study team via email to enroll in the study. Once initial contact was established, a 15-minute telephone screener was conducted by the study team to assess participants' eligibility for the study and to provide additional details regarding the study. The Sick, Control, One, Fat, and Food questionnaire was used to evaluate the presence of ED symptoms. Once eligibility was established, consent (Multimedia Appendix 4) and baseline measures were collected through Qualtrics, including a demographics questionnaire, the EDE-Q, the RMQ, the PHQ-9, the GAD-7, and the BSQ. Following this, an onboarding session was conducted through a secure videoconferencing platform (ie, Zoom), during which participants were given a demonstration on downloading and using the app and provided their log-in information.

The subsequent pilot-test portion of the study consisted of a four-week period during which participants used the app in a naturalistic way. Following study completion, participants were compensated CAD $10 (≈US $7.10) for each study portion completed (ie, baseline questionnaire package, onboarding session, posttest questionnaire package, and exit interview), receiving up to CAD $40 (≈US $28.41) through the Tango Card rewards platform. To reduce the impact of possible confounds (eg, financial motivation), participants were informed that their compensation would not be impacted by their app use during the pilot test phase and that there are no minimum requirements for app use. Once the pilot test was completed, a second brief consent form (Multimedia Appendix 5) and posttest questionnaires assessing self-reported clinical features (ie, the EDE-Q, RMQ, PHQ-9, GAD-7, and BSQ) and feedback regarding the app (ie, the adapted TAM-Q and uMARS) were completed. Finally, participants were invited to participate in a videoconferencing-based exit interview to provide additional feedback on their experience with the study author. The semistructured interview guide (Multimedia Appendix 6) was used as an outline to standardize the interview process across participants [52].

Figure 2. Participant flow diagram.



Statistical Analysis

Prior to analysis, interview audio recordings will be transcribed verbatim by 2 trained research assistants and verified by the primary researcher (AH-A). Qualitative interview transcripts will be analyzed using the NVivo software package (version 12; QSR International), to assess in-depth feedback regarding MI-Coach: ED's feasibility and acceptability. A thematic content analysis will be conducted to analyze the qualitative responses from the open-ended uMARS questionnaire and semistructured interview data using Braun and Clarke's [36] framework. A bottom-up theoretical approach was used, in which the analysis was driven by the data generated through the semistructured interviews [36,53].

Additionally, quantitative analyses will be conducted using the R statistical package (version 4.2.0; R Core Team). Descriptive analyses of posttest feedback questionnaires, attrition data, and sessions completed will be used to determine the feasibility and acceptability of the MI-Coach: ED app. Means, SDs, ranges, and percentages will be calculated for all descriptive variables (ie, age, ethnicity, BMI, height, and weight), and total and mean scores will be calculated for app acceptability measures. Overall app use (ie, number of modules completed, days that the app was used, assessments and exercises completed, and logins) will be calculated using in-app data provided by Resiliens Inc.

Finally, tests of clinical significance [54] will be used to evaluate changes in clinical presentation across time points. The following categorizations will be used to identify whether change is clinically significant: reliably improved, in which there is reliable change and the clinical cutoff is no longer met; reliably deteriorated, in which there is a reliable change in the disordered direction and the individual's score falls within the clinical range; and unchanged, in which neither criteria of the Jacobson-Truax method are met [54,55]. Finally, exploratory growth curve analyses will be used to model individual participants' change trajectories across the 4-week pilot test period [56].

Results

The MI-Coach: ED app has been developed and is available for download and use. Recruitment was initiated in November 2022 and terminated in May 2024. Data analysis is currently underway, and we anticipate reporting results through peer-reviewed academic publications in May 2025.

Discussion

Anticipated Results

This study aimed to evaluate the feasibility and acceptability of MI-Coach: ED, an app designed to support motivation for ED recovery among individuals on treatment waitlists. It is anticipated that the intervention will be feasible to implement, with a high rate of participant engagement with the app, and that MI-Coach: ED would be perceived as an acceptable and useful tool for supporting motivation during the waitlist period. Prior research suggests that digital mental health interventions targeting ED populations are generally acceptable and feasible to users, particularly when they incorporate evidence-based therapeutic principles such as MI [15,28]. Additionally, app-based self-help interventions have demonstrated high engagement rates, which MI-Coach: ED was designed to include [23,27]. Furthermore, we anticipate that exploratory analyses will demonstrate preliminary improvements in motivation and ED-related symptoms following app use, given findings that brief MI-based interventions can enhance motivation for change, improve treatment engagement, and reduce ambivalence in ED populations [8,14,16,17]. As motivation is a key predictor of ED treatment outcomes [11], even small gains during the waitlist period could have meaningful clinical implications.

Conclusions

Individuals with EDs face substantial barriers to accessing appropriate care, despite their urgent need for treatment [37,57,58]. Though both MI and app-based interventions have been suggested as ways to support treatment-seeking ED patients, in isolation, these interventions may not adequately address treatment barriers. For example, in-person MI interventions may be inaccessible to individuals in rural and remote locations, and interventions currently delivered through apps have limited evidence to support their efficacy [24]. As such, this study aims to simultaneously address individual and structural treatment barriers by developing and pilot-testing an MI-based app intervention for women on waitlists for ED treatment.

Providing app-based interventions to individuals who are waiting for ED treatment has the potential to improve treatment outcomes and represents a largely barrier-free, positive-approach method of addressing the growing problem of wait times for mental health care. Although this pilot study focuses on a modest sample, existing intervention frameworks and ED-focused digital interventions demonstrate how pilot studies can be used to guide the adaptation and evaluation of novel interventions through large-scale clinical trials [15,20,28]. For example, collecting and implementing end user feedback prior to formal efficacy testing has been suggested to ensure that the final intervention is used by the targeted population [28]. Furthermore, exploratory analyses on motivation and ED-related symptoms will help identify meaningful clinical outcome measures and establish preliminary effect size estimates to guide the design and power calculations for a full-scale randomized controlled trial. Additionally, by collecting demographic and digital literacy data, this study will provide insights into the app's accessibility across diverse populations and inform potential adaptations to increase inclusivity. Future evaluations will also aim to follow participants into formal psychological treatment to assess the long-term clinical impact of pretreatment MI interventions.

Given that prior research has demonstrated that multimodal recruitment modalities can enhance sample diversity, improve engagement, and ensure the inclusion of individuals with varying levels of symptom severity in digital intervention studies [38], data collected through this pilot study will be particularly valuable in refining future participant engagement strategies. In this regard, feasibility data collected from this study (including recruitment and retention rates, participant engagement with the app, and qualitative user feedback) will directly inform refinements to MI-Coach: ED and recruitment

methods for subsequent large-scale efficacy evaluations, ensuring that the intervention is optimally structured for broader implementation. For example, future studies may continue to use a multipronged approach, such as the use of social media campaigns to supplement clinician referrals [38], and partnerships with provincial authorities may be expanded to integrate study recruitment directly into clinical workflows given their success in prior research [59]. As such, this pilot study serves as a crucial step in optimizing MI-Coach: ED for large-scale implementation and has the potential to provide tangible psychological support to its participants while contributing to the reconceptualization of ED service delivery.

Acknowledgments

This research stream is funded by both the Canadian Institutes of Health Research and the Social Sciences and Humanities Research Council as part of the Canadian Triagency funding program. Additionally, we would like to extend our gratitude toward Resiliens Inc for providing access to their app and offering technological support during the development of MI-Coach: ED. However, it is important to note that they did not directly fund or provide monetary incentives to the research team for this line of research.

Authors' Contributions

AH-A and ML are the primary authors responsible for the development of the underlying research, and all named authors contributed to the drafting of the manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Study recruitment flyer.
[DOCX File , 428 KB - resprot_v14i1e66298_app1.docx]

Multimedia Appendix 2
Overview of MI-Coach: ED Modules.
[DOCX File , 21 KB - resprot_v14i1e66298_app2.docx]

Multimedia Appendix 3
Study measures and outcome variables.
[DOCX File , 57 KB - resprot_v14i1e66298_app3.docx]

Multimedia Appendix 4
Consent form.
[DOCX File , 327 KB - resprot_v14i1e66298_app4.docx]

Multimedia Appendix 5
Brief consent form.
[DOCX File , 311 KB - resprot_v14i1e66298_app5.docx]

Multimedia Appendix 6
Qualitative interview guide.
[DOCX File , 17 KB - resprot_v14i1e66298_app6.docx]

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Abbreviations

BSQ: Body Shape Questionnaire
ED: eating disorder
EDE-Q: Eating Disorder Examination Questionnaire
GAD-7: 7-item General Anxiety Disorder Scale
ICT: internet and communications technology
MI: motivational interviewing
PHQ-9: Patient Health Questionnaire-9
RMQ: Readiness and Motivation for Change Questionnaire
TAM: Technology Acceptance Model
uMARS: user version of the Mobile App Rating Scale

Edited by A Schwartz, J Sarvestan; submitted 11.09.24; peer-reviewed by Z Wang, YY Kristian; comments to author 31.01.25; revised version received 20.02.25; accepted 10.03.25; published 10.04.25.

Please cite as:
Halicki-Asakawa A, Mocci J, Libben M
Mobile App–Delivered Motivational Interviewing for Women on Eating Disorder Treatment Waitlists (MI-Coach: ED): Protocol for an App Development and Pilot Evaluation
JMIR Res Protoc 2025;14:e66298
URL: https://www.researchprotocols.org/2025/1/e66298
doi:10.2196/66298
PMID:

Protocol

Efficacy of a Personalized Mobile Health Intervention (BedTime) to Increase Sleep Duration Among Short-Sleeping Patients With Type 2 Diabetes: Protocol for a Pilot Randomized Controlled Trial

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Abstract

Background: A strong association exists between sleep duration and glycemic control in patients with type 2 diabetes (T2D), yet convincing evidence of a causal link remains lacking. Improving sleep is increasingly emphasized in clinical T2D treatment guidance, highlighting the need for effective, scalable sleep interventions that can affordably serve large populations through mobile health (mHealth).

Objective: This study aims to pilot an intervention that extends sleep duration by modifying bedtime behavior, assessing its efficacy among short-sleeping (≤6 hours per night) patients with T2D, and establishing robust evidence that extending sleep improves glycemic control.

Methods: This randomized, single-blinded, multicenter study targets 70 patients with T2D from 9 institutions in Japan over a 12-week intervention period. The sleep extension intervention, BedTime, is developed using the Theory of Planned Behavior (TPB) and focuses on TPB's constructs of perceived and actual behavioral control (ABC). The pilot intervention combines wearable actigraphy devices with SMS text messaging managed by human operators. Both the intervention and control groups will use an actigraphy device to record bedtime, sleep duration, and step count, while time in bed (TIB) will be assessed via sleep

diaries. In addition, the intervention group will receive weekly bedtime goals, daily feedback on their bedtime performance relative to those goals, identify personal barriers to an earlier bedtime, and select strategies to overcome these barriers. The 12-week intervention period will be followed by a 12-week observational period to assess the sustainability of the intervention's effects. The primary outcome is the between-group difference in the change in hemoglobin A_{1c} (HbA_{1c}) at 12 weeks. Secondary outcomes include other health measures, sleep metrics (bedtime, TIB, sleep duration, total sleep time, and sleep quality), behavioral changes, and assessments of the intervention's usability. The trial commenced on February 8, 2024, and is expected to conclude in February 2025.

Results: Patient recruitment ended on August 29, 2024, with 70 participants enrolled. The intervention period concluded on December 6, 2024, and the observation period ended on February 26, 2025, with 70 participants completing the observation period. The data analysis is currently underway, and results are expected to be published in July 2025.

Conclusions: This trial will provide important evidence on the causal link between increased sleep duration and improved glycemic control in short-sleeping patients with T2D. It will also evaluate the efficacy of our bedtime behavior change intervention in extending sleep duration, initially piloted with human operators, with the goal of future implementation via an mHealth smartphone app. If proven effective, this intervention could be a key step toward integrating sleep-focused mHealth into the standard treatment for patients with T2D in Japan.

Trial Registration: Japan Registry of Clinical Trials jRCT1030230650; https://jrct.niph.go.jp/latest-detail/jRCT1030230650

International Registered Report Identifier (IRRID): DERR1-10.2196/64023

(JMIR Res Protoc 2025;14:e64023) doi:10.2196/64023

KEYWORDS

digital therapeutics; behavior change; Theory of Planned Behavior; sleep duration; type 2 diabetes; randomized controlled trial

Introduction

Worldwide, approximately 537 million people aged 20-79 years have diabetes [1]. Diabetes is a serious public health concern, significantly impacting health care expenditures and human life, causing 4.2 million deaths annually [2,3]. Type 2 diabetes (T2D) is difficult to cure once it develops and, if left untreated, can lead to complications such as cardiovascular disease and microvascular damage [4].

T2D treatment guidelines include both pharmacological and lifestyle modification elements. Traditionally, lifestyle modifications have focused on diet and exercise, but recently, improving sleep in patients with T2D has gained prominence [5,6]. Some patients with T2D suffer from sleep disorders, including obstructive sleep apnea, restless leg syndrome, and insomnia, for which treating the underlying disorder is the appropriate approach [7]. Sleep quality is associated with T2D risk [8], and interventions to improve sleep quality have shown effectiveness [9]. Many patients with T2D do not get sufficient sleep, experiencing what is termed *short sleep*. Definitions of short sleep vary across studies, ranging from 6 or fewer hours per night to less than 4.5 hours per night [10]. This issue is widespread, with data indicating that 39.4% of patients with T2D in Japan sleep fewer than 6.4 hours per night [11].

There is strong evidence that short sleep is associated with an increased risk of T2D and poorer glycemic control. In Japanese patients with T2D, short sleep is linked to higher hemoglobin A_{1c} (HbA_{1c}) levels [11], with a meta-analysis indicating a 0.23% difference in HbA_{1c} due to short sleep [12]. Prospective studies have also shown an increased risk of T2D associated with short sleep [8]. Plausible biological mechanisms support these findings, as sleep extension has been shown to reduce energy intake [13], while sleep restriction worsens insulin sensitivity [14].

Surprisingly, there is a lack of strong evidence for causality—specifically, increasing sleep duration in short-sleeping patients with T2D without sleep disorders leads to improvements in HbA_{1c} levels. Recent meta-analyses [15,16] found limited and conflicting evidence on the effect of sleep interventions on glycemic control. Some studies have investigated interventions for patients with T2D with insomnia [17,18]. One study examined an educational intervention for patients with T2D, including those with short sleep, but results from a published abstract [19] are unclear, and no full paper has been published. Two related studies used cognitive behavioral therapy to improve HbA_{1c} by enhancing sleep quality rather than duration [20,21]. Overall, strong evidence is lacking to support the idea that increasing sleep duration in short-sleeping patients with T2D without sleep disorders leads to improved HbA_{1c} levels.

Numerous studies have successfully increased sleep duration in various populations. A recent meta-analysis of 42 studies found that extending time in bed (TIB) has the greatest potential to modify sleep, with direct interventions (ie, scheduling a longer period in bed) resulting in an average increase of 1 hour and 23 minutes in sleep duration [22].

Mobile health (mHealth) interventions, such as mobile phone apps supporting self-management, have been shown to be effective in increasing physical activity, reducing body weight [23,24], and improving glycemic control [25,26]. However, to our knowledge, no mHealth apps have been designed specifically to improve sleep duration in short-sleeping patients with T2D without sleep disorders. Personalization of intervention components has been shown to enhance patient motivation and engagement with the app [27]. Several studies

have found that tailored interventions are more effective at changing health behaviors than nontailored ones [28,29]. Moreover, interventions based on behavior change theory have been shown to be more effective than those lacking a theoretical foundation [30], with those based on the Theory of Planned Behavior (TPB) being particularly effective [31]. TPB emphasizes intention and ABC as key determinants of behavior, with perceived behavioral control (PBC)—similar or identical to Bandura's self-efficacy—playing a central role in shaping intention [32,33].

To address the lack of evidence on whether improvements in sleep duration lead to better glycemic control, we developed a pilot study of a personalized mHealth intervention, BedTime, designed to increase sleep duration and assess its impact on glycemic control in short-sleeping patients with T2D. The intervention is based on the TPB framework to promote behavior change toward earlier bedtimes. This trial aims to evaluate the efficacy of the BedTime approach in a 12-week, single-blind, randomized controlled pilot trial. The specific research objectives and hypotheses are as follows:

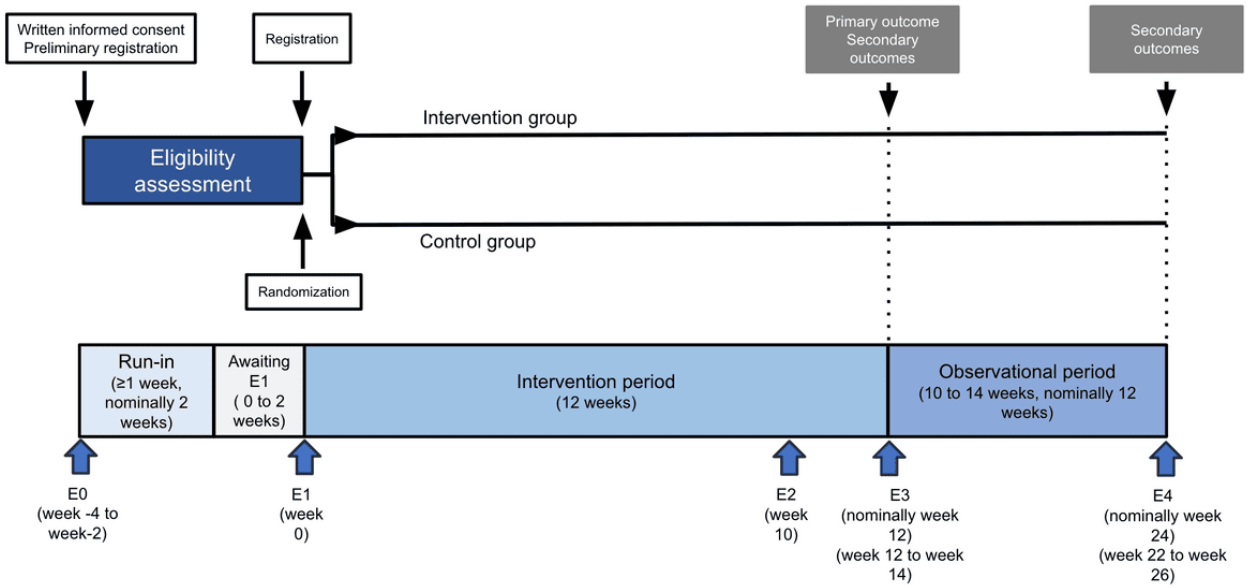
- Objective 1: To evaluate the efficacy of the BedTime approach in shifting patients to an earlier bedtime, as measured by daily bedtime reporting, and increasing sleep duration, as measured by daily actigraphy.
- We hypothesize that, by the end of the intervention, the intervention group will show statistically significant changes in bedtime and sleep duration compared with the control group.
- Objective 2: To evaluate the efficacy of the BedTime approach in reducing HbA_{1c} levels.
- We hypothesize that, by the end of the intervention, the intervention group will show a statistically significant reduction in HbA_{1c} levels compared with the control group.

Methods

Study Overview

This single-blinded, multicenter pilot study is a 2-arm randomized controlled trial designed to evaluate the efficacy of the BedTime mHealth intervention in promoting earlier bedtime behavior and increasing sleep duration among short-sleeping patients with T2D. The trial will be conducted and reported in accordance with CONSORT (Consolidated Standards of Reporting Trails) guidelines. As outlined in Figure 1, the study begins with recruitment (E0), followed by a baseline measurement period (nominally 2 weeks, but at least 7 days), and then randomized assignment to intervention and control groups (E1). Patients in the intervention group will record their daily bedtime, sleep duration, and step count using an actigraphy device, with TIB assessed via sleep diaries. They will receive weekly bedtime goals, daily feedback on their bedtime performance relative to these goals, and guidance to identify personal barriers to an earlier bedtime along with strategies to overcome them. The control group will also record daily bedtime, sleep duration, and step count using an actigraphy device, with TIB assessed via sleep diaries, but they will receive no feedback and will not be assigned goals. During week 10 of the intervention period (E2), the intervention group will complete a TPB questionnaire. The intervention will last for 12 weeks, followed by end-of-intervention assessments of the primary and secondary outcomes (E3). After the intervention period, there will be an observation phase, nominally 12 weeks in length, but its duration will depend on the date of the final visit (E4), which may occur between 10 and 14 weeks after the intervention ends. The study will be conducted over 1 year, from February 8, 2024, to January 22, 2025.

Figure 1. Overview of the study timeline.



Intervention Design

Some features of the intervention are shared by both the control and intervention groups, while others are unique to the intervention group (Table 1). This mHealth intervention incorporates a physical activity monitoring system (iAide2; Tokai) and a researcher-designed paper diary for patients in both groups. The iAide2 measures activity intensity levels, skin

temperature, and pulse rate [34,35] to assess step count and sleep, providing minute-by-minute wake/sleep assessments [36,37]. Additionally, the iAide2 enables timely behavioral feedback via a wirelessly connected Event button and near-real-time data access for researchers through an administrative screen. During the 12-week intervention period, patients in both the control and intervention groups wear the iAide2 device at all times except when bathing and press its Event button at bedtime each day. Patients record their bedtime and risetime daily in the paper diary. For the intervention group, the diary includes additional pages implementing specific aspects of the intervention. Bedtime is defined as the time when a patient begins trying to sleep, and risetime as the time when they stop trying to sleep. Diary entries are used to calculate TIB, the duration between bedtime and risetime. The intervention is designed to encourage an earlier bedtime, with the expectation that this will extend TIB and thereby increase sleep duration (ie, the portion of the TIB interval during which the patient is asleep).

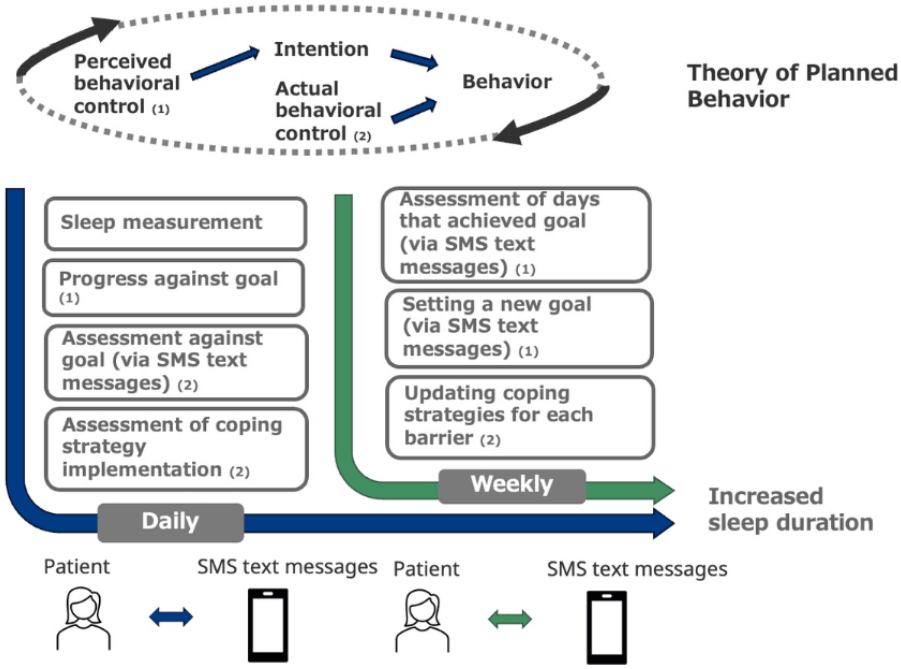
Table 1. Intervention features for the intervention and control groups.

Features	Intervention group	Control group
iAide2		
Press the Event button to send bedtime	Yes	Yes
Measure daily sleep and steps (without providing this information to patients)	Yes	Yes
Diary		
Enter bedtime and risetime	Yes	Yes
Define barriers and coping strategies and report the number of coping strategies implemented	Yes	No
TPB[a] questionnaire at E2	Yes	No
SMS text message		
Diary reminder	Yes	Yes
Low battery message	Yes	Yes
Daily feedback and target bedtime	Yes	No
Request for a reply message when patients forget to press the Event button	Yes	No
Surveys and questionnaires		
Screening at E0	Yes	Yes
Sleep and Transtheoretical Model Questionnaire at E0, E3, and E4	Yes	Yes
Feedback survey	Yes	No
TPB questionnaires at E1	Yes	No
Ask if taking any medication that may affect one's sleep at E0, E1, E3, and E4	Yes	Yes
Obtain information about medications, including type 2 diabetes treatments and other drugs, either by asking the patients or by checking their medical records at E0, E1, E3, and E4	Yes	Yes
Measure height at E0, and measure weight and blood pressure at E0, E1, E3, and E4	Yes	Yes
Ask about any adverse events or malfunction in iAide2 at E1, E3, and E4	Yes	Yes
TPB questionnaires at E3 and E4	Yes	Yes

[a]TPB: Theory of Planned Behavior.

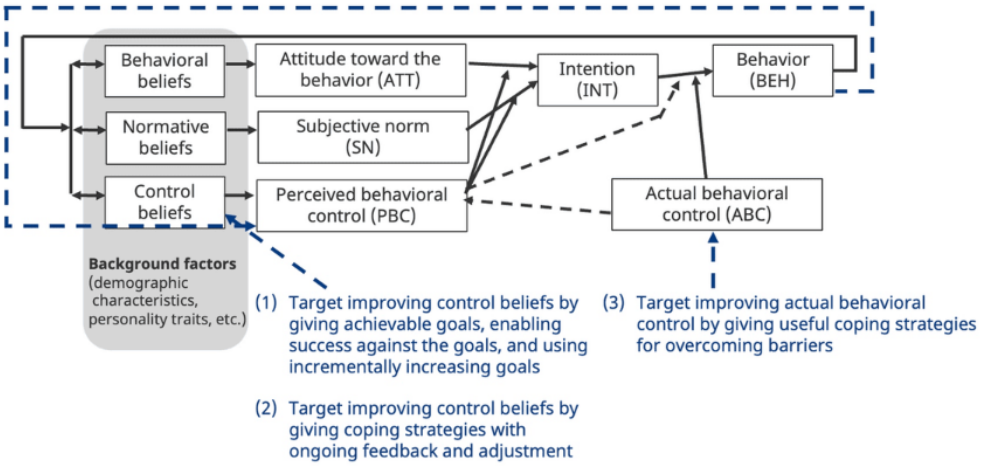
For the intervention group, daily and weekly messaging will deliver a TPB-based intervention targeting PBC and ABC (Figure 2). A researcher or clinical research coordinator (CRC), under the supervision of the researcher, will establish a baseline bedtime and set an initial goal for an earlier bedtime. They will also assist patients in identifying barriers to an earlier bedtime and developing coping strategies. Intervention group patients will receive a daily SMS text message assessment of their performance relative to their target bedtime and will record whether they implemented their coping strategies each day. They will also receive weekly assessments of their progress toward the goal, along with an updated target bedtime, via weekly SMS text messages. Additionally, they will determine coping strategies for the upcoming week.

Figure 2. BedTime's process for implementing Theory of Planned Behavior–based personalization.



The intervention is based on the TPB framework (Figure 3) [32,33]. According to TPB, behavior is driven by an individual's intention to perform the behavior and their ABC, or ability to do so. A behavior is more likely to occur when both intention and actual ability are high. Intention itself is influenced by 3 factors: personal attitude toward the behavior, subjective norms or the perceived expectations of important others, and PBC, which reflects one's confidence in their ability to perform the behavior. Each of these 3 drivers of intention (attitude toward the behavior, subjective norms, and PBC) is, in turn, influenced by the person's beliefs about them. The stronger the positive behavioral, normative, and control beliefs, the more likely an individual is to intend to perform the behavior. Actually carrying out the behavior depends on both intention and ABC. As ABC is difficult to measure, researchers generally use PBC as a proxy for ABC in predicting behavior [32,38].

Figure 3. Theory of Planned Behavior applied to the BedTime intervention.



The BedTime intervention is designed to influence PBC by modifying control beliefs. The primary strategy for improving control beliefs—and thus PBC—is to set achievable goals, enabling patients to experience success and build positive self-mastery. We implement progressively challenging but attainable goals using a simple algorithm based on our prior work [39]. This algorithm adjusts the suggested target bedtime each week based on the number of days the user met their goal in the previous week. Adjustments include increases of 5, 10, or 15 minutes and decreases of 5 or 10 minutes, depending on past target bedtime achievement levels.

The secondary mechanism for improving control beliefs involves daily self-reflection on barriers and coping strategies, reinforcing patients' sense of control over their behavior. These mechanisms align with those used to enhance self-efficacy in social cognitive theory [32]. Beyond influencing PBC, the barrier and coping strategy intervention may also improve ABC by providing useful coping strategies. However, its impact on ABC is expected to

be minor, as the suggested strategies may not be entirely novel or groundbreaking for patients. Each week, participants select or write down 1-3 barriers to achieving their target bedtime and propose a coping strategy for each (Table 2). Participants can select coping strategies from a literature-based list of solutions to common barriers to early bedtime [40-60] or describe their own. At the end of each day, they use the diary to report the number of coping strategies they implemented.

Table 2. Example of personalized coping planning strategy (with English translation).

Japanese		English translation	
Barriers	Coping strategies	Barriers	Coping strategies
遅い時間に夕食を食べて、まだやるべきことがある	就寝時刻の少なくとも2時間前に夕食を終える	I eat dinner late and still have things to do.	Finish dinner at least 2 hours before bedtime.
遅い時間にお風呂に入って、まだやるべきことがある	寝る1～2時間前にぬるめのお風呂に入る	I take a bath late and still have things to do.	Take a lukewarm bath 1-2 hours before going to bed.
就寝前にやるべき仕事がある	もっと睡眠をとるようにという医師の指示を上司に伝え、終業時間を早めるよう交渉する	I have work to do before bed	Tell your boss about your doctor's orders to get more sleep and negotiate an earlier finish time.
仕事から帰ってくるのが遅いため、まだやるべきことがある	もっと睡眠をとるようにという医師の指示を上司に伝え、終業時間を早めるよう交渉する	I'm late coming home from work, so I still have things to do.	Tell your boss about your doctor's orders to get more sleep and negotiate an earlier finish time.
家事など、まだ手をつけていないことがある	就寝1時間前を空けるようにスケジュールを組み立てる	There are things I haven't gotten around to yet, such as housework.	Plan your schedule so that you leave an hour before bedtime.
N/A[a]	やることのリストを作成し、就寝時ではなく翌日にそれをすることに専念する	N/A	Make a to-do list and commit to doing it the next day instead of at bedtime.
N/A	より多くの睡眠をとるようにという医師の指示に基づいて、他の人の助けを借りて家事をする	N/A	Do housework with the help of others based on your doctor's instructions to get more sleep
就寝時に高血糖または低血糖を管理する必要がある	必要な食事療法や投薬治療が就寝時刻までに完了するように、就寝時刻の 30 分～60 分前に血糖値を測定する	I need to manage hyperglycemia or hypoglycemia at bedtime	Measure your blood sugar 30-60 minutes before bedtime to ensure that any necessary dietary or medication therapy is completed by bedtime.
もう少し「自分」の時間が必要だ	「自分」の時間として、日中に10分間の休憩をいくつか取り入れる	I need a little more "me" time.	Incorporate several 10-minute breaks during the day for "me" time.

[a]N/A: not applicable.

The intervention provides daily individualized feedback via an SMS text message (Table 3). These messages, typically sent between 12 PM and 6 PM, inform the patient whether they went to bed earlier or later than their target bedtime the previous night, using an encouraging tone. This timing ensures that participants receive feedback well before their usual bedtime, allowing them sufficient time to adjust their nightly activities accordingly. The exact delivery time of the SMS text messages varies slightly due to the manual nature of the sending process.

At the end of each week, the intervention provides feedback via an SMS text message reporting the number of days the goal was achieved.

Table 3. Example of daily feedback (with English translation).

Situation	SMS text message	English translation
Last night, bedtime was earlier than the target bedtime which is 10 minutes earlier than the baseline bedtime.	昨夜は、「少なくとも10分早く就寝する」という目標を達成できました。よく頑張りました! 健康を改善するための行動ができています！	Last night you achieved your goal of going to bed at least 10 minutes earlier. Great job! You're taking action to improve your health!
Last night, bedtime was 15 minutes later than the goal bedtime of 30 minutes earlier than the baseline bedtime.	昨夜は15分遅く就寝しましたね。「30分早く就寝する」という目標には達しませんでしたが、今夜は目標就寝時刻の達成に向けてがんばりましょう。 あなたならできます！ お選びになった対処方法を確認して、今夜の就寝時刻を考えてください。 早く寝ると健康増進につながります！	You went to bed 15 minutes later than your goal last night. You didn't reach your goal of going to bed 30 minutes earlier than your baseline bedtime. Try your best to reach your target bedtime tonight. You can do it! Review your chosen coping strategy and think about your bedtime tonight. Sleeping early will improve your health!

Patient Recruitment

Patients will be recruited from 9 medical institutions in Japan (Textbox 1). Attending physicians will conduct recruitment during patients' regular outpatient consultations. The recruitment period will run from February 8, 2024, to July 30, 2024.

Textbox 1. Participating institutions: 11 medical centers in Japan.

- The University of Tokyo Hospital
- Mitsui Memorial Hospital
- Meiji Yasuda Life Insurance Company Tokyo Hospital
- Kobe University Hospital
- Akita University Hospital
- Tokai University Hospital
- Okayama Saiseikai General Hospital
- Sawaki Internal Medicine and Diabetes Clinic
- Yokota Medical Clinic
- Aikawa Comprehensive Internal Medicine Clinic
- Yokohama Rosai Hospital

To detect a 0.3% difference in the primary outcome (change in HbA_{1c}), assuming an SD of 0.41% (the average observed in 2 prior studies [17,61]), and to achieve a 2-sided significance level of .05 with 80% statistical power, the minimum required sample size is 31 patients per group. Considering an estimated dropout rate of approximately 10%, we aim to recruit a total of 70 patients (35 in the intervention group and 35 in the control group).

All participants will receive a comprehensive written and verbal explanation before providing written informed consent. Eligibility screening will be conducted only after consent is obtained. If any findings related to efficacy or safety arise during the trial that may impact patient consent, we will promptly disclose this information to participants and obtain renewed consent.

We will use survey instruments as part of the inclusion and exclusion criteria (Textbox 2). To recruit patients who are both likely to benefit and capable of participating, we will include only those meeting all inclusion criteria (Textbox 3) while ensuring they do not meet any exclusion criteria (Textbox 4), following the methods of a prior study [62]. We anticipate a roughly equal sex distribution and an average participant age in the late 50s. Women undergoing menopausal transition will be included if they meet the study's criteria.

We will use a Transtheoretical Model (TTM) questionnaire to categorize participants into the contemplation stage (willing to change health behavior within the next 6 months), preparation stage (willing to change health behavior within the next month), or action stage (has already made modifications to health behavior) [63]. In our previous study, patients in the contemplation and preparation stages were more likely to prefer smartphone-based self-management tools than those in the precontemplation stage [64]. Therefore, we will target patients in the contemplation, preparation, or action stage of increasing their sleep duration by 1 hour per day.

Textbox 2. Screening surveys.

- STOP-J (Snoring, Tiredness, Observed Apnea, High Blood Pressure Screen, Japanese version): screening for obstructive sleep apnea [65]
- ISI-J (Insomnia Severity Index, Japanese version): screening for insomnia [66]
- IRLSQ-J version 2.2 (International Restless Legs Syndrome Study Group Rating Scale, Japanese version): screening for restless legs syndrome [67]
- AUDIT-C-J (Alcohol Use Disorders Identification Test—Consumption, Japanese version): screening for alcohol use disorder [68,69]
- PHQ-8-J (Patient Health Questionnaire-8, Japanese version): screening for major depression [70,71]
- TTM (Transtheoretical Model) Sleep Questionnaire: assess the TTM stage [63] relative to sleeping 7 or more hours nightly

Textbox 3. Study inclusion criteria (selecting patients who are likely to benefit from the intervention and are likely to be capable of participating).

At the time of consent acquisition (E0)

- Diagnosed with type 2 diabetes and attending the hospital/clinic
- Hemoglobin A_{1c} (HbA_{1c}) is 7.5% or higher at the time of obtaining consent
- A patient with short sleep (self-reports an average sleep duration in the prior month of 6 or fewer hours)
- In the contemplation, preparation, or action stage of the Transtheoretical Model (TTM) for the action of sleeping 7 hours or more per day
- Willing and able to wear a wristband-type measuring device on the nondominant wrist during the research period
- Has and uses a mobile phone capable of sending and receiving SMS text messages
- Able to attend consultations at designated times during the research period
- 18 years or older
- Fluent in spoken and written Japanese
- Does not have impaired cognitive function as determined by the investigator or subinvestigator
- Can undergo sleep treatment, as determined by the investigator or subinvestigator
- Fully informed about participation in this study, and has given free and voluntary written consent based on a thorough understanding of the study

Textbox 4. Exclusion criteria, focusing on patients who may not be able to participate safely or whose participation may interfere with the effectiveness of the study.

1. Exclusion criteria at the time of consent acquisition (E0)
    - BMI is greater than 35.0 kg/m^2
    - Age is 76 years or older
    - A shift worker or someone who occasionally deviates from a single main sleep period at night
    - A caregiver (of a child or adult) who needs to wake up during the night
    - At high risk of obstructive sleep apnea (STOP-J [Snoring, Tiredness, Observed Apnea, High Blood Pressure Screen, Japanese version] score of 3 or higher)
    - At high risk of insomnia (ISI [Insomnia Severity Index, Japanese version] score of 15 or higher)
    - Possibility of restless legs syndrome (IRLSQ-J [International Restless Legs Syndrome Study Group Rating Scale, Japanese version] score of 1 or higher)
    - High possibility of depression (PHQ-8 [8-item Patient Health Questionnaire] score of 10 or higher)
    - Taking medications that affect sleep
    - Changed type 2 diabetes medication within the past 8 weeks
    - Currently participating in another clinical research program
    - A heavy user of alcohol (AUDIT-C-J [Alcohol Use Disorders Identification Test—Consumption, Japanese version] score of 4 or higher for females, and 6 or higher for males)
    - Has severe chronic pain (due to cancer, etc)
    - Has a diagnosed clinical sleep disorder
    - Has an uncontrolled psychiatric disorder
    - Pregnant at the time of consent acquisition
    - Any other reason why the patient is classified as unfit for participation by the investigator or subinvestigator
2. Exclusion criteria before allocation (E1)
    - Recorded both bedtime and risetime in a diary for fewer than 7 days during the trial period
    - Recorded the Event button of the iAide2 fewer than 7 days during the trial period
    - Recorded fewer than 7 days of valid iAide2 data showing sleep duration, as judged by the investigator or subinvestigator

We will provisionally register patients who meet the eligibility criteria at E0. At this stage, each participant will receive an actigraph (iAide2) and will be instructed to wear it 24 hours a day, except when bathing, to press the Event button at bedtime, and to record their bedtimes and risetimes in the diary. Patients who fail to press the Event button for 7 or more days or fail to complete the diary for 7 or more days during the run-in period will be excluded to ensure adequate participation. Data collected during the run-in period will be used to confirm eligibility and establish baseline sleep and step counts. We will randomize eligible participants in a 1:1 ratio to either the intervention or control group using covariate-adaptive randomization by minimization to ensure balance across age (<65 and ≥65 years), sex, HbA_{1c} (<8.5% and ≥8.5%), and institution [72]. Random allocation will be conducted via the Internet Data and Information Center for Medical Research cloud, provided by the University Hospital Medical Information Network, an internet-based central randomization system. A research co-investigator will access the University Hospital Medical Information Network Internet Data and Information Center for Medical Research cloud and input the required baseline information. The system will then securely generate the allocation result immediately before assigning each participant to a group. This process ensures that researchers cannot access or predict allocation results in advance, minimizing potential bias.

Intervention Process

The study (Table 4) consists of 5 events (E0-E4), a 2-week run-in period, a 12-week intervention period, and a 12-week observation period. Initial measurements will be taken at event E0. Questionnaires will be used to assess sleep behavior and gather patient feedback (Textbox 5).

Following randomization, the intervention begins. Before explaining the intervention, the researcher or CRC will administer the TPB Sleep Questionnaire and the Sleep-Related Behavior (SRB) Questionnaire to the intervention group. The researcher or CRC will then provide a diary customized for the intervention group. To establish a baseline bedtime, the researcher or CRC will average bedtimes recorded during the run-in period, considering any exclusions due to unusual circumstances in consultation with the patient. Patients will be informed that their ultimate goal is to shift their bedtime 1 hour earlier than the baseline, with an initial target of going to bed 10 minutes earlier during the first week. The researcher or CRC will help patients identify barriers preventing them from going to bed early and assist them in selecting up to 3 coping strategies tailored to these barriers for the first week. During this process, the researcher or CRC will facilitate discussions using the list in the diary as a reference. Patients may either choose strategies from the list or write their own in the diary. For the control group, the researcher or CRC will provide a diary similar to the one used during the run-in period but covering 12 weeks. Control group patients will be instructed to continue recording their bedtime and risetime as they did during the run-in period. The intervention period lasts 12 weeks, from E1 to E3. We will send reminder SMS text messages to both groups at the end of weeks 1 and 10 to encourage diary use. All equipment, including the diary, will be collected at E3 before the follow-up observation period begins.

For the intervention group, we will provide both daily and weekly feedback. Researchers will monitor the receipt of the Event time, and if it is missing, they will send a reminder asking the patient to report their bedtime via an SMS text message. If no bedtime is reported through either the Event record or SMS text message, the night will be considered a failure to achieve the target bedtime. At E2, 10 weeks after E1, we will send a reminder for participants to complete the TPB Sleep Questionnaire in the diary.

During the study, we will not restrict the use of supplements or drinks that may affect blood glucose and blood pressure. In both the intervention and control groups, T2D treatment—including oral T2D medications, insulin, glucagon-like peptide 1 receptor agonists, and medication dosage—may be adjusted at the discretion of the attending physician. We will collect information on T2D-related medication and medications affecting sleep at E1, E3, and E4.

Discontinuation is defined as a patient expressing a decision to withdraw or failing to record data for a continuous period of 7 or more days. If a participant discontinues during the intervention period, we will attempt to collect E3 measurement items. If discontinuation occurs during the observation period, we will attempt to collect E4 measurement items.

Table 4. Study events—1 measurement period and 4 visits spanning approximately 26 weeks.

Event	Focus	Time	Key activities
E0	Physical baseline assessments and initial registration	Enrollment: ≥7 days before the beginning of the intervention	• Collect consent • Collect demographic information: age, sex, date of type 2 diabetes diagnosis, smoking and drinking habits, macrovascular disease, diabetic retinopathy, periodontal disease, tinea pedis, diabetic neuropathy, and other medical history • Collect physical data: hemoglobin levels, albumin, uric acid, blood urea nitrogen, estimated glomerular filtration rate, creatinine, fasting blood glucose, HbA_{1c}[a], low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides, urine specific gravity, urinary protein, urine albumin-to-creatinine ratio, height, body weight, and blood pressure measurements • Collect medication status • Conduct screening surveys (STOP-J[b], ISI-J[c], IRLSQ-J version 2.2[d], AUDIT-C-J[e], PHQ-8-J[f], and TTM[g] Sleep Questionnaire) • Conduct PSQI-J[h] survey • Distribute actigraph (iAide2) and run-in period diary
Run-in	Baseline	From E0 for 2 weeks	• Patients record daily bedtime and risetime, with automated (blinded) measurements of sleep parameters and step count
E1	Registration, allocation, and beginning of the intervention	Beginning of the intervention	• Verify that run-in diary and iAide recording do not cause exclusion • Finalize registration and allocation • Collect medication status • Intervention only: conduct surveys (TPB[i] Questionnaire, SRB[j] Questionnaire) • Distribute the intervention diary or the control group diary • Check for malfunctions or adverse events during run-in
Intervention period	Ongoing measurement	From E1 for 12 weeks	• Patients record daily bedtime and risetime, with automated (blinded) measurements of sleep parameters and step count • Intervention only: daily feedback, weekly self-set barriers and coping strategies via diary, weekly personalized target bedtime setting via SMS text messages
E2	Ongoing measurement	End of 10 weeks from E1	• Intervention only: conduct TPB Questionnaire via diary
E3	End of the intervention	End of 12 weeks from E1	• Collect physical data: hemoglobin levels, albumin, uric acid, blood urea nitrogen, estimated glomerular filtration rate, creatinine, fasting blood glucose, HbA_{1c}, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides, urine specific gravity, urinary protein, urine albumin-to-creatinine ratio, body weight, and blood pressure measurements • Collect medication status • Conduct surveys (TTM Sleep Questionnaire, TPB Questionnaire, SRB Questionnaire, PSQI-J) • Intervention group: conduct survey (feedback survey) • Collect actigraph (iAide2) and intervention period diary • Check for malfunctions or adverse events
E4	End of follow-up	End of 24 weeks from E1	• Collect physical data: hemoglobin levels, albumin, uric acid, blood urea nitrogen, estimated glomerular filtration rate, creatinine, fasting blood glucose, HbA_{1c}, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides, urine specific gravity, urinary protein, urine albumin-to-creatinine ratio, body weight, and blood pressure measurements • Collect medication status • Conduct surveys (TTM Sleep Questionnaire, TPB Questionnaire, SRB Questionnaire, PSQI-J)

[a]HbA_{1c}: hemoglobin A_{1c}.

[b]STOP-J: Snoring, Tiredness, Observed Apnea, High Blood Pressure Screen, Japanese version.

[c]ISI-J: Insomnia Severity Index, Japanese version.

[d]IRLSQ-J version 2.2: International Restless Legs Syndrome Study Group Rating Scale, Japanese version.

[e]AUDIT-C-J: Alcohol Use Disorders Identification Test—Consumption, Japanese version.

[f]PHQ-8-J: Patient Health Questionnaire-8, Japanese version.

[g]TTM: Transtheoretical Model.

[h]PSQI-J: Pittsburgh Sleep Quality Index, Japanese version.

[i]TPB: Theory of Planned Behavior

[j]SRB: Sleep-Related Behavior.

Textbox 5. Assessment questionnaires and surveys.

- TPB (Theory of Planned Behavior) Sleep Questionnaire: assess individual components of TPB [32,33] relative to implementing an earlier bedtime
- SRB (Sleep-Related Behavior) Questionnaire: self-assessment of sleep over the past 2 weeks
- PSQI-J (Pittsburgh Sleep Quality Index, Japanese version): assess sleep quantity and quality [73,74]
- Feedback survey: collect feedback on the intervention

Monitoring, Quality Control, and Data Management

An auditor, independent of the departments involved in the trial, including those responsible for monitoring, will inspect the medical institution and other facilities to ensure the trial is conducted appropriately.

Ethical Approval

This trial will be conducted in compliance with the Declaration of Helsinki, the Pharmaceutical and Medical Device Act, the Ministerial Ordinance on Good Clinical Practice for Medical Devices, and all other relevant guidelines (jRCT1030230650). The study was approved by the Institutional Review Board of the University of Tokyo School of Medicine (approval number 2023336NI). We will obtain written informed consent from all study participants, and all patient data will be pseudonymized. Patients will receive compensation of JPY 30,000 (approximately US $200) at the end of E4.

The participant information materials and informed consent form are available from the corresponding author (KW) upon request. Any amendments to the protocol will be submitted for review and approval by the institutional review board. Study findings will be disseminated through peer-reviewed publications and conference presentations.

Outcome Measures

Primary Outcome

The primary outcome of this study is the between-group difference in the change in HbA_{1c} from baseline (E0) to either the end of the intervention period at week 12 (E3) or, for patients who discontinue before E3, the point of discontinuation. A reduction of 0.3 percentage points in HbA_{1c} is considered clinically significant [75,76].

Secondary Outcomes

Secondary outcomes (Table 5) include health measures, bedtime and sleep measurements, other behavior change assessments, and evaluations of actigraph and diary usage. We will also assess safety outcomes, including hypertension requiring medical assistance (evaluated from system records), subjective hypoglycemia, lower back pain, and pain in the lower extremities (tarsus, thighs, knees, calves, shins, ankles, and feet), as well as any other adverse events (all assessed through patient interviews).

Table 5. Secondary outcomes investigated in the study.

Measurements	Outcomes
Differences in changes	• Hemoglobin A_{1c} (%) (only after the end of the observation period)[a] • Weight (kg)[a] • BMI (kg/m^2)[a] • Systolic blood pressure/diastolic blood pressure (mmHg)[a] • Estimated glomerular filtration rate (mL/min/1.73 m2)[a] • Fasting blood sugar (mg/dL)[a] • Low-density lipoprotein cholesterol (mg/dL)[a] • High-density lipoprotein cholesterol (mg/dL)[a] • Neutral fat (mg/dL)[a] • Urine albumin-to-creatinine ratio (mg/gCr)[a] • PSQI-J[a,b]
Differences in the measured values	• Survey on past bedtimes[a]
Difference in proportions	• Behavior change questionnaire[a]
Observed data	• Elements of the bedtime questionnaire: attitude, subjective norms, perceived behavioral control, intention[c] • Sleep time calculated from iAide2's sleep data and diary data[d] • Time in bed calculated from bedtime and wake-up time recorded in the diary for each period[d] • Bedtime recorded in the diary for each period and bedtime sent from iAide[d] • Steps recorded by iAide2[d] • Achievement rate of target bedtime[e] • Number of barriers and coping strategies set and implemented in the diary for the intervention period[e] • Percentage of use of each drug[f] • Percentage of new additions for each drug since consent was obtained[g] • Changes in antidiabetic drugs since consent was obtained (strengthened, unchanged, or attenuated)[g]

[a]Evaluate the differences after the end of the intervention period (at 12 weeks) and after the end of the observation period (at 24 weeks) from the time of consent acquisition.

[b]PSQI-J: Pittsburgh Sleep Quality Index, Japanese version.

[c]Evaluate the differences in the measured values for the following items at 10 weeks and after the end of the observation period (24 weeks).

[d]Evaluate the differences in the average change from the trial period in the 2 weeks before the end of the intervention period.

[e]Evaluate the rates weekly during the intervention period, for the intervention group.

[f]Evaluate the differences in percentages at the time of consent acquisition, at the time of actual registration, after the end of the intervention period, and after the end of the observation period.

[g]Evaluate the difference in proportions after the intervention period and after the observation period.

Statistical Analysis

In this study, we define 3 analysis populations: the full analysis set (FAS), the per-protocol set (PPS), and the safety analysis set (SAS). The FAS includes all patients for whom the primary outcome was obtained. Following the intention-to-treat principle, we will analyze data based on the assigned group in the FAS analysis. The PPS consists of the FAS population, excluding patients who violated eligibility criteria after randomization, had 7 or more contiguous days of nonuse of the iAide2, or took medications affecting sleep. The SAS includes all patients who used the iAide2 at least once after randomization. In the safety analysis using the SAS, we will analyze data based on the intervention actually used by patients, regardless of allocation. The FAS will serve as the primary analysis population, while the PPS will provide supportive results. All safety analyses will be conducted using the SAS.

Patient characteristics will be presented as mean, SD, minimum, 25th percentile, median, 75th percentile, and maximum for continuous variables, and as frequency and proportion for categorical variables.

In the primary analysis, we will compare the change in HbA_{1c} from baseline (E0) to week 12 (E3; or the point of discontinuation, if earlier) between groups using analysis of covariance, with baseline HbA_{1c} (ie, HbA_{1c} at E0) included as a covariate in the FAS. For participants who discontinue the study, the most recent HbA_{1c} measurement before E3 will be used.

We will also conduct 2 subgroup analyses: one based on baseline HbA_{1c} at E0 (<8.5% or ≥8.5%) and the other based on age at initial registration (E0; <65 or ≥65 years). Subgroup analyses of the primary outcome will be performed in each analysis set to assess whether the efficacy of BedTime is consistent across these subgroups.

In the secondary analysis, changes in HbA_{1c} at week 12 (E3) and week 24 (E4) will be analyzed using the same approach as in the primary analysis. The proportion of patients with HbA_{1c} below 7% at E3 and E4 (or at the point of discontinuation, if earlier) will be compared between groups using the Fisher exact test. Changes from baseline in step counts, various laboratory test values, and questionnaire scores at E3 and E4 (or at the point of discontinuation, if earlier) will also be analyzed as key endpoints. Changes in T2D medications, categorized as weakened, unchanged, or strengthened, will be compared between groups using the Cochran-Mantel-Haenszel test. The proportion of newly added medications will be compared between groups using the Fisher exact test. A paired (2-sample) *t* test will be used for within-group comparisons of changes in TPB Questionnaire measurements over weeks 0 (E1), 10 (E2), 12 (E3), and 24 (E4). Changes in TPB Questionnaire and SRB Questionnaire measurements between week 12 (E3) and week 24 (E4) will be compared using a *t* test. A paired *t* test will also be used for within-group comparisons from week 0 (E1) to week 12 (E3) for goal achievement rate, goal increment rate, goal reduction rate, average number of coping strategies implemented per day, and the number of identified barriers.

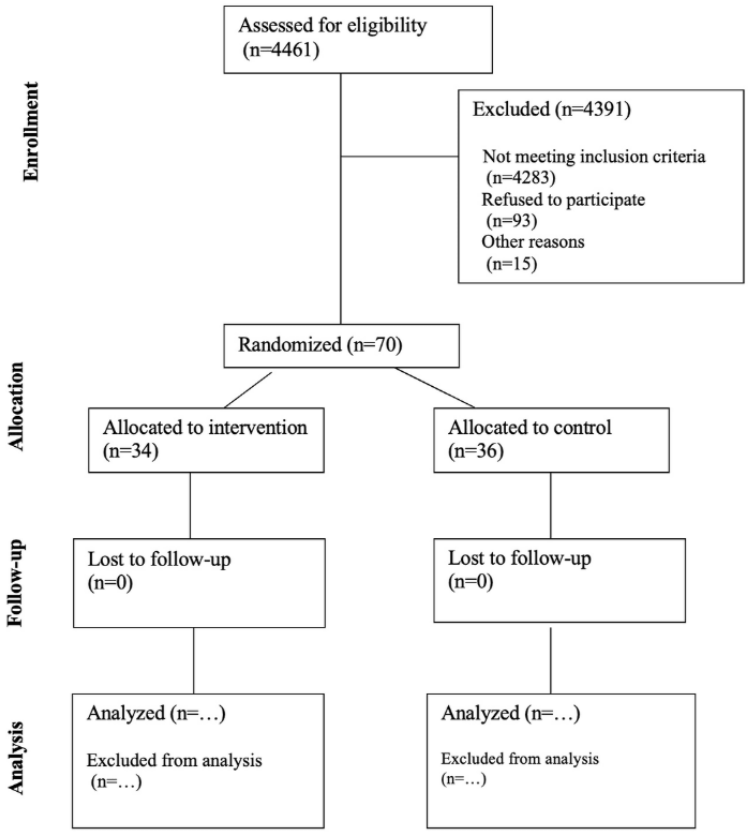
As an exploratory analysis, we will use linear regression to examine the relationship between the average number of coping strategies implemented per day and improvement in HbA_{1c} within the intervention group. The model will include the average number of coping strategies implemented per day and baseline HbA_{1c} as explanatory variables, with the change in HbA_{1c} as the response variable. Changes from baseline to week 12 (E3) and week 24 (E4) (or the point of discontinuation, if earlier) will be assessed.

We will perform a statistical analysis of safety outcomes by calculating the frequency, number of cases, and percentage of individuals experiencing adverse events during the trial, intervention, and observation periods. For the intervention and observation periods, data will be compiled separately for each group, and the percentages will be compared between groups using the Fisher exact test.

Results

Recruitment began on February 8, 2024, and ended on August 29, 2024. The intervention period concluded on December 6, 2024, and the observation period ended on February 26, 2025, with 70 participants completing the observation period (Figure 4). The analysis is currently underway, and we anticipate publishing the results in July 2025. Before commencing analysis, we will conduct a thorough review of all collected data and data entry.

Figure 4. CONSORT (Consolidated Standards of Reporting Trails) flow diagram depicting enrollment, allocation, follow-up, and analysis phases.



Discussion

We designed this study based on the foundational concept that it is a behavioral change intervention, despite measuring medical outcomes. The intervention is grounded in a specific theory of behavioral change (TPB) to provide a structured framework, ensure clarity on intervention targets, and maintain focus, avoiding a scattershot approach. We identified a specific, actionable target behavior—going to bed earlier—and developed a measurement and feedback system centered on this behavior. This focused approach provides clarity for both researchers and patients. By maintaining this focus, we can determine whether the intervention effectively changes sleep behavior while also evaluating its impact on sleep patterns and, ultimately, health outcomes. Demonstrating that a behavioral intervention improves HbA_{1c} is not enough, we need to understand the intermediate steps, particularly the behavioral response, to refine the intervention by enhancing effective components and eliminating ineffective ones. This study is designed to generate evidence on these intermediate stages.

Our study utilizes objectively measured data for all primary outcomes and many secondary outcomes. The intervention leverages wireless technology, enabling automatic synchronization of sleep and step count data to the server. These simple, passive features facilitate easy-to-use objective measurements, particularly for older patients.

Participants will be blinded to group assignments to minimize social desirability bias. To achieve this, they will not be informed that the study involves random assignment to 2 groups or that the intervention specifically targets advancing bedtime. Instead, patients will be told that the study examines the relationship between self-management of lifestyle habits (including exercise and sleep) and blood glucose control in individuals with T2D. They will also be informed that various lifestyle factors, including sleep, will be monitored. This approach minimizes the risk of unblinding in the control group by preventing participants from identifying the absence of an intervention. We believe that maintaining blinding offers significant scientific benefits by reducing potential bias and enhancing the validity of the study findings.

We selected the HbA_{1c} level as our primary outcome, as it is recognized as a global standard for assessing glycemic control and an appropriate indicator of T2D treatment effectiveness [77]. According to the Japan Diabetes Society's treatment guidelines, patients with T2D should aim to lower their HbA_{1c} level below 7% to prevent complications [78]. Therefore, in addition to analyzing absolute changes in HbA_{1c} levels, we examined the proportion of patients achieving an HbA_{1c} level below 7%. We acknowledge that T2D duration may influence the primary outcome. Although our recruitment process does not explicitly stratify participants by disease duration, this information is collected at registration and will be incorporated into the analysis to account for its potential impact on study outcomes.

In this study, we have chosen a "formidable" control [79], using the same devices as the intervention group. As an initial proof-of-concept study, our goal is to determine whether our specific behavior change intervention is more effective than simply having patients record their bedtime and risetime. Evidence suggests that providing patients with a pedometer can increase their activity levels [80], raising concerns that bedtime and risetime recording in the control group may similarly trigger behavioral changes, potentially making it more challenging to demonstrate the intervention's superiority statistically. By providing the control group with a diary but withholding the intervention functionality, we have designed the study to offer strong evidence of the intervention's effectiveness—should it indeed be effective.

Many behavior interventions demonstrate solid short-term gains that later fade [39]. This study includes a 12-week observation period following the intervention to assess whether the benefits persist or diminish. Behavior change maintenance is theorized to result from active, ongoing self-regulation, with habit formation emerging after a period of successfully regulating a new behavior [81]. Our goal is to foster sustainable behavior change, ensuring that the new pattern becomes an enduring habit.

A key aspect of our approach is providing patients with a strong introduction to the mechanics of the intervention. Given their busy lives, we strive to make participation clear and manageable. By offering thorough training and ensuring that all intervention messaging remains simple and focused, we maximize the likelihood that patients will engage with the tools as intended.

Another key aspect of our approach is prioritizing the needs of the patients the intervention is designed to serve. Rather than adopting a one-size-fits-all approach, we tailored the intervention for a specific target population, ensuring it aligns with their needs and preferences. Our previous study [39] highlighted the importance of considering cultural background and patient preferences in intervention design. Additionally, we recognize that socioeconomic background may influence sleep patterns. While our recruitment strategy does not explicitly target specific socioeconomic groups, the participating institutions serve patient populations whose demographics are representative of the general community.

Another key aspect of our approach is applying the intervention only to patients who are already motivated to change their behavior. We use the TTM stage as a filter, an approach that has proven highly effective in previous research [39,63]. Our intervention is specifically designed for highly motivated patients who need support in implementing their desired behavior changes, whereas low-motivation patients require a different intervention focused on enhancing motivation. Notably, a large proportion of patients with T2D in Japan exhibit high motivation, with one study indicating that 92% are in the contemplation-through-action stages of TTM for dietary behavior change [82]. There is a substantial pool of patients who could benefit from this targeted intervention. As a multicenter randomized controlled trial, this study enhances the generalizability of our findings to patients with T2D across Japan. Moreover, our techniques are broadly applicable, and there is strong reason to believe that these methods could be

adapted to increase sleep duration for patients with other conditions and in diverse health care settings worldwide.

This study has several limitations. The findings may be specific to the population studied and may not fully generalize to other groups. Our participants are likely to be older individuals of Japanese ethnicity, and differences in lifestyle and T2D pathophysiology between Japanese and other populations may limit broader applicability. Additionally, the study includes only patients capable of using mobile phones, introducing potential biases related to digital literacy. Furthermore, our baseline sleep measurements rely on actigraphy and sleep diaries provided to participants, which may overestimate true prestudy sleep levels. This effect is mitigated by the 2-arm design and the duration of our trial. However, it may lead to an underestimation of increases in sleep duration, potentially resulting in an overestimation of the per-hour-of-sleep impact on health outcomes.

This trial will provide important evidence on the efficacy of a TPB-based mHealth intervention in improving sleep duration and glycemic control in patients with T2D. If the intervention is proven effective and safe, this study could serve as a key step toward integrating mHealth into standard T2D treatment in Japan.

Acknowledgments

We thank Daniel Lane for his support in manuscript editing and scientific discussions. This research received no specific grant from any funding agency.

Data Availability

The data sets generated during or analyzed during this study can be obtained from the corresponding author on reasonable request.

Authors' Contributions

KW was responsible for conceptualization, methodology, project administration, resources, validation, and funding acquisition. Data curation was carried out by YB and RN, while RN also conducted the formal analysis and visualization. Software development was handled by YB and RN. The investigation was conducted by KW, AI, KM, HW, S Kato, HS, TM, YH, SS, SN, AT, MS, MT, S Kajino, KY, and YT. Supervision was provided by KW, TY, MN, and KO. The original draft was written by YB and KW, while AI, KM, HW, S Kato, HS, TM, YH, SS, SN, AT, MS, MT, S Kajino, KY, YT, KW, TY, MN, and KO contributed to the review and editing.

Conflicts of Interest

None declared.

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Abbreviations

ABC: actual behavioral control
CONSORT: Consolidated Standards of Reporting Trails
CRC: clinical research coordinator
FAS: full analysis set
HbA_{1c}: hemoglobin A_{1c}
mHealth: mobile health
PBC: perceived behavioral control
PPS: per-protocol set
SAS: safety analysis set
SRB: Sleep-Related Behavior
T2D: type 2 diabetes mellitus
TIB: time in bed
TPB: Theory of Planned Behavior
TTM: Transtheoretical Model

Edited by A Schwartz, T Leung; submitted 06.07.24; peer-reviewed by Y Yoshida, H Kurasawa; comments to author 24.12.24; revised version received 16.01.25; accepted 25.02.25; published 14.04.25.

Please cite as:
Ban Y, Waki K, Nakada R, Isogawa A, Miyoshi K, Waki H, Kato S, Sawaki H, Murata T, Hirota Y, Saito S, Nishikage S, Tone A, Seno M, Toyoda M, Kajino S, Yokota K, Tsurutani Y, Yamauchi T, Nangaku M, Ohe K
Efficacy of a Personalized Mobile Health Intervention (BedTime) to Increase Sleep Duration Among Short-Sleeping Patients With Type 2 Diabetes: Protocol for a Pilot Randomized Controlled Trial
JMIR Res Protoc 2025;14:e64023
URL: https://www.researchprotocols.org/2025/1/e64023
doi:10.2196/64023
PMID:

Protocol

Using Music to Promote Hong Kong Young People's Emotion Regulation and Reduce Their Mood Symptoms and Loneliness: Protocol for a Pilot Randomized Controlled Trial

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Abstract

Background: Mental health needs in the community surged during the pandemic, with concerning reports of increased negative mood symptoms among youth. At the same time, preventive psychoeducational interventions were insufficient within frontline youth mental health services in Hong Kong, and research specifically addressing youth loneliness remained limited on an international scale. Given the association between loneliness and other mental health symptoms, psychoeducational programs that empower adolescents to cope with emotions may help address both the research gap and local demand. As such, Tuned In, a previously validated intervention program originally developed in Australia, was introduced to the local context. Cultural adaptations and an added focus on loneliness were incorporated into the project to enhance its acceptability and test its effectiveness.

Objective: This study aims to evaluate an adapted version of the Tuned In music-based psychoeducation program, designed to reduce loneliness, depression, and anxiety symptoms among young people in Hong Kong by enhancing their emotion regulation skills.

Methods: Participants aged 16-19 years will be randomly assigned to either the experimental or control group. The experimental group will receive an online, group-based psychoeducation program focused on emotion recognition and management, delivered weekly over 4 consecutive weeks. The intervention is grounded in Russell's emotion circumplex model and music psychology, and program content included: The 2D model and characteristics of emotions from different quadrants (session 1); happiness and loneliness (session 2); high-arousal and negative-valence emotions, for example, stress and anxiety (sessions 3); and anxiety, perfectionism, and a celebration of achievement (session 4). Both therapist- and participant-selected music will be used in the intervention to provide a rich repertoire for group discussion, psychoeducation, reflection, and the practice of social skills. The main outcome measures will be assessed using the Emotion Regulation Questionnaire, the Difficulties in Emotion Regulation Scale, the Depression Anxiety Stress Scale, and the De Jong Gierveld Loneliness Scale. Feedback on the project arrangement will be gathered through qualitative input. A mixed methods analysis will be conducted following data collection.

Results: The project was successfully funded in February 2023 by the Health and Medical Research Fund in Hong Kong and commenced in August 2023. As of September 16, 2024, a total of 316 completed questionnaires had been received through Qualtrics for screening purposes, with 89 participants deemed eligible for the program. The project is scheduled to conclude in August 2025, with results to be published thereafter.

Conclusions: Participants are expected to show improvements in emotion regulation, along with reductions in mood symptoms and loneliness, following the intervention.

Trial Registration: ClinicalTrials.gov NCT06147297; https://clinicaltrials.gov/study/NCT06147297
International Registered Report Identifier (IRRID): DERR1-10.2196/67764

(JMIR Res Protoc 2025;14:e67764) doi:10.2196/67764

KEYWORDS

youth; adolescents; adolescence; teens; teenagers; music; moods; mood symptoms; loneliness; emotion regulation; emotions; Hong Kong; mental health; mental illnesses; mental disorders; randomized controlled trial; RCTs; protocol

Introduction

Significance of Study

Youth mental health is a significant concern in Hong Kong. Studies have reported that the prevalence of depression and anxiety among adolescents is approximately 11.3% locally [1]. Loneliness is also widespread among young people in Hong Kong, occurring at a higher rate than that reported for their counterparts in North America [2]. Around 39% of young people in Hong Kong reported feeling lonely—an increase of 55% from 2012 to 2018 [3]. Furthermore, the prevalence of loneliness rose to 47% among adolescents and young adults in 2020 due to the pandemic [4]. A recent survey found that loneliness was associated with symptoms of depression, anxiety, and stress, even after controlling for demographic factors and views on the COVID-19 pandemic [2]. These negative emotional states have also been shown to be linked to other issues, such as substance use [5]. The connection between negative experiences, low mood, and substance use problems may be partly explained by a lack of emotion regulation skills. Emotion regulation involves the ability to manage emotions within a social context, which includes expressing emotions appropriately and with suitable intensity [6]. The Transdiagnostic Emotion Vulnerabilities Model proposes that emotional vulnerability is a core transdiagnostic factor underlying major depression, anxiety, and tobacco smoking [7]. In particular, young people may believe that unhealthy coping mechanisms, such as smoking, help them to relax. Because of this pairing of mental distress and poor health habits, they are likely to engage in—or continue—smoking during times of distress [5]. By contrast, a meta-analysis by Schafer et al [8] found that healthy coping during distress was associated with reduced depressive and anxious symptoms (r ranging from –0.29 to –0.50) among adolescents and young adults.

Given the significant role that emotion regulation plays in promoting youth mental health, it is desirable for preventative interventions to equip young people with age-appropriate, healthy coping strategies that serve as protective factors against long-term emotional difficulties, health problems, addiction, or substance abuse. Unfortunately, few such interventions have been validated by research in Hong Kong [9]. The proposed pilot trial will evaluate the effectiveness of a music-based prevention program in reducing mood problems among young people by enhancing their emotion regulation skills. This project is supported by a seed grant to conduct a small-scale trial in preparation for future large-scale research.

To evaluate the validity and effectiveness of the project in the Hong Kong context, the following hypotheses will be tested:

- The emotion regulation skills of adolescents and young adults will be enhanced following participation in the music-based program (primary outcome).
- The depression and anxiety symptoms of adolescents and young adults will be reduced following participation in the music-based program (secondary outcome).
- The sense of loneliness experienced by adolescents and young adults will be reduced following participation in the music-based program (secondary outcome).

Definition of Terms of Music Interventions

Music, defined by The New Penguin English Dictionary as “any vocal, instrumental or mechanical sounds that have rhythm, melody or harmony” [10], can influence emotions in many ways. As such, music is often perceived as the language of emotion [11]. Distinct from the term song, which refers to a short composition combining both words and music, music is considered a hypernym of song. In other words, music is a broader term that encompasses a range of activities—from listening to background music to engaging in composition and improvisation [12]—whereas song specifically refers to music with lyrics that can be sung [13]. This broader definition of music is adopted by music therapists to allow greater flexibility in the use of music or sound during interventions, enabling them to meet clients where they are in the present moment [14].

Music interventions are broadly classified into 2 types: active and receptive [15]. In active interventions, clients participate in the process of music production. By contrast, receptive interventions involve clients receiving the music experience, with listening focused on the intellectual, emotional, or other aspects of the music [15,16]. Previous studies on group music interventions for young people have not found significant differences in treatment outcomes between the 2 approaches [17].

Music and Emotions

The activation of the limbic system—responsible for processing emotions—when the ears perceive music provides a biological foundation for music’s influence on emotions [18]. The emotions experienced by listeners result from an interplay of multiple factors, including elements of the music itself, the performance, and the surrounding environment. For example, structural features of music such as tempo and melody are known to influence emotional responses. It is widely accepted that tempo can directly affect the pleasantness of emotions and that melodies tend to be higher in pitch in happy music compared with sad music [19]. In addition to musical structural features, song lyrics are often used as a springboard for discussing life events that evoke emotions during interventions [16]. Lyrics play a vital role in eliciting emotions, particularly sadness [20].

Previous research has also found that engaging with self-selected music can foster a sense of connectedness [21].

Music Interventions, Youth Emotion Regulation, and Tuned In

Listening to music is an effective emotion regulation strategy [22-24], and existing literature supports its use in reducing symptoms of depression and anxiety. One study examining the use of online group music therapy to manage anxiety and stress among university students confirmed the effectiveness of this type of intervention [17].

Tuned In, a preventative program developed by 1 of the coinvestigators to address mild to moderate levels of psychological distress, has demonstrated positive psychological outcomes in both adolescents [25,26] and young adults in Australia [6]. A related intervention, Smoke into Sound, was found to be more effective in reducing cigarette cravings than the gold standard of cognitive behavioral therapy delivered via telephone, as shown in a randomized controlled trial (RCT) [27].

During the COVID-19 pandemic, young adults rated listening to music as the most effective coping mechanism [24]. The Tuned In program is based on Russell's [28] circumplex model of emotion, which categorizes emotions along 2 dimensions: valence and arousal. The theoretical foundation linking music and emotion in the Tuned In program draws from this 2D model [28,29], in which emotions are positioned along an arousal axis (ranging from high to low energy) and a valence axis (ranging from pleasant to unpleasant). It also incorporates the BRECVEMA (brain stem reflexes, rhythmic entrainment, evaluative conditioning, contagion [emotional contagion], visual imagery, episodic memory, musical expectancy, and aesthetic judgment) theory of music and emotion [30], which identifies mechanisms such as lyrical meaning, personal memories associated with music, and imagery evoked by music as key factors influencing emotional responses to listening. Although not explicitly stated in the program materials, this theoretical background is embedded in the content and activities—such as lyric analysis and imagery drawing tasks conducted while listening to music.

Through psychoeducation and experiential activities designed to explore and make meaning of emotions—such as locating emotions in the body, lyric analysis, drawing imagery while listening to music, and group discussions—participants in the program first learn to categorize their emotions in terms of intensity (ie, arousal level) and positivity (ie, valence). They then reflect on and develop a personalized list of songs they relate to, using these songs to increase or decrease the intensity and positivity of their emotions. In other words, participants practice monitoring their emotional states and using music to help modify how they feel.

In addition, music can enhance social connectedness—and potentially foster actual social connections—when shared with others [12]. Therefore, music serves as a universal and comprehensive tool for promoting emotion regulation and reducing feelings of loneliness, as well as depressive and anxious symptoms [24,25,31-33]. Furthermore, emerging local evidence supports the positive role of music listening as a promising strategy for enhancing mental health among adolescents in Hong Kong. In a large-scale cross-sectional survey, Leung and Cheung [34] found that music listening contributed to psychological well-being among young people by enhancing emotional awareness.

Music Interventions, Youth Loneliness, and Tuned In

In addition to depression and anxiety, loneliness is a socioemotional state that has attracted increasing research attention [35]. In 2019, 22% of young Chinese people reported experiencing feelings of loneliness [36]. Recent data also suggest that loneliness is associated with poor health habits—such as smoking—among young Chinese individuals [36].

Although lonely young people may have friends and families, everyday interactions often provide limited opportunities for deep connection and personal sharing within a trusting environment for this age group [37]. This is echoed by recent research findings showing that 76% of lonely adolescents and young adults feel they are not well understood by others—a situation that could potentially be addressed through the empathic effects of music [21,31].

Feelings of empathy or being understood can arise not only through human interactions but also through listening to comforting music, suggesting a promising mechanism for reducing loneliness in young people [21]. Schafer and colleagues [21] found that listening to self-selected music improved participants' self-reported mood following a sad mood induction, regardless of the type of music chosen. They proposed that self-selected (ie, familiar) music acts as a surrogate listener, helping individuals feel that their emotions are being "heard," thereby providing a comforting effect. These soothing effects of music could be leveraged to address a key issue underlying loneliness among young people.

However, there is limited research on interventions aimed at reducing loneliness among young people in Hong Kong. This scarcity is also evident in the broader literature. A recent meta-analysis and systematic review found that certain group-based psychological interventions can be effective in reducing loneliness [38,39].

One psychoeducation group intervention found no significant decrease in loneliness at follow-up [40], while other interventions—such as online dancing and various psychoeducation-based group programs—reported reductions in loneliness [41-43]. These mixed results highlight the need for more promising and effective programs to reduce loneliness, both locally and within the broader research literature.

Nevertheless, there is preliminary evidence that the Tuned In program has positive effects in reducing loneliness among young people. Coinvestigator GD and her team (email communication, February 18, 2025) completed a study applying the original program in a passive control design with 35 English-fluent international students in Australia. They found a significant interaction between time and condition, resulting in a reduction in self-reported loneliness among participants—with a moderate effect size (η^2_p=0.12)—compared with the waitlist group. This

overall positive effect is attributed to the synergy of the program's core components: psychoeducation, group work, and music. Each serves as an essential therapeutic element, and together they form the comprehensive Tuned In intervention.

Undeniably, adopting an active control would be more ideal. However, due to limited resources and the need to maintain fidelity to the original program, a waitlist control design was chosen for practical reasons. The primary aim of this study is to examine whether this combination of elements can produce desirable outcomes in the Hong Kong context. Investigating the specific role and contribution of each component, as well as comparing the effectiveness of this combination with other types of interventions, represents a valuable direction for future research.

Theoretical Framework for Tuned In

The Tuned In program was developed as an alternative to cognitive behavioral therapy and is grounded in emotion theory and music psychology research on the links between music listening and emotional responses [25-27]. The 4 sessions primarily aim to not only address negative emotions—such as depression, loneliness, anxiety, and anger—but also explore ways to enhance positive emotions or states such as motivation, happiness, and calmness. Each session begins with the facilitator describing the components and functions of emotions (eg, physiological responses and common thoughts), followed by participant sharing and group discussion about songs they currently listen to—or could listen to—that elicit or help regulate those emotions.

As engagement in music does not require participants to have prior knowledge or skills in music [17], a receptive intervention has been chosen for the current project. According to Juslin's BRECVEMA model [30], the meaning of lyrics is one of several mechanisms that link music listening with emotional responses. The model identifies multiple pathways through which a musical event can influence emotions, including brain stem reflex, rhythmic entrainment, evaluative conditioning, emotional contagion, visual imagery, episodic memory, musical expectancy, and aesthetic judgment [30].

Although some experimental evidence suggests that melody has a stronger influence than lyrics on emotional responses to music [44], this effect is highly individualized—some people focus more on melody, while others are more affected by lyrics. Therefore, both instrumental music and songs will be used in this project. In alignment with both the original program and guidelines for receptive music interventions, instrumental music may be used for imaginal and somatic listening, with the flexibility to adjust based on participants' emotional states and feedback. Songs, by contrast, will be used for lyric discussions. Given that the current project is psychoeducational, with music serving as a tool for relationship building and emotional regulation, the inclusion of both songs and instrumental music allows for greater acceptance of diverse musical styles and gives participants the freedom to share and appreciate various kinds of music. Discussions about song components (eg, lyrics) can also deepen participants' understanding of the physiological and cognitive aspects of different emotions. The intention is that, by the end of the program, participants will be able to assess their emotional valence and arousal, and they will have a personalized playlist they can use to enhance or regulate their emotional states. In other words, they will be "tuned in" to their emotions.

Building on the existing evidence, the proposed study aims to establish an effective music-based program to enhance emotion regulation skills among young people in Hong Kong. This approach complements current practices in the region, which often focus on areas such as self-esteem, resilience, social competence, problem-solving, and communication [1,9]. Notably, the proposed study introduces a new session targeting "loneliness"—an addition to the original Tuned In program implemented in Australia [6]. This new component directly addresses the rising prevalence of loneliness among adolescents in Hong Kong [3,4].

The program will be facilitated by a registered music therapist and a research assistant, both under the supervision of the primary investigator. The research assistant will receive training from the coinvestigator and original developer of Tuned In before delivering the groups, along with ongoing supervision from her. This arrangement ensures the standardized delivery of both the music-based activities and the psychoeducational content. Because of previous COVID-19–related restrictions, the program was initially proposed to be conducted online. However, with the loosening of COVID-19 restrictions, the study has incorporated an introductory session where participants can meet each other and the facilitator in person. This session is intended to build rapport and foster a sense of group identity, which is expected to enhance engagement during the subsequent online group sessions while preserving the flexibility of the program format [45,46].

Aims and Objectives

The ultimate aim of this study is to test and validate a music-based program designed to improve emotion regulation among adolescents and young adults in Hong Kong, with the broader goal of reducing symptoms of depression, anxiety, and loneliness.

The objective of the proposed project is to evaluate the effects of a music-based program on young people in Hong Kong. The hypotheses to be tested are listed below.

The primary outcome is as follows:

- The emotion regulation skills of adolescents and young adults will be enhanced following participation in the music-based program.

The secondary outcomes are as follows:

- Symptoms of depression and anxiety among adolescents and young adults will be reduced following the program.
- Feelings of loneliness among adolescents and young adults will be reduced following the program.

Methods

Ethical Considerations

Ethical approval for the study was obtained from The University of Hong Kong (approval number EA230395) and The Hong

Kong Polytechnic University (approval number HSEARS20221024004). Ethical approval was either exempted or not required by other participating universities for the distribution of advertisement materials.

In adherence to the ethical regulations of the university, signed active parental consent will be obtained for participants under the age of 18 years. All participants are required to sign a physical consent form before participating in the intervention. Participation is entirely voluntary, and all participants have the right to withdraw from the project at any time without any negative consequences.

Study Design

The study adopts a waitlist RCT design. Participants are randomly assigned to either the intervention group, who will receive the program immediately, or the waitlist control group, who will receive the intervention after a 4-week waiting period. The main assessment time points are pre- and postintervention for the intervention group, and baseline and postwaiting period for the control group. Additionally, the control group will be invited to complete an optional postintervention survey following their participation, which will be used for secondary data analysis. The postintervention surveys for both groups will contain identical items to ensure comparability. It is also planned that all participants who complete the intervention will be invited to take part in an optional qualitative interview to gain deeper insights into their experiences using the strategies taught in the program.

Given the project's strong emphasis on psychoeducation, participants' application of the strategies taught serves as an indicator of the program's acceptability. Qualitative inquiry offers valuable insights into the extent to which participants have internalized and consolidated the healthy coping strategies introduced during the intervention. This approach enables exploratory interpretations of the project's outcomes and helps uncover the nuanced, individualized experiences of participants. Therefore, qualitative research is considered appropriate to capture the subjective and personal dimensions of the intervention's impact.

Online delivery was chosen in response to the prevailing pandemic conditions at the time. This decision not only aligned with the original program design but also helped overcome geographical barriers. By eliminating distance as a constraint, the online format significantly enhanced the accessibility of the program. While this mode of delivery presented challenges—such as difficulty in maintaining participants' attention and limited nonverbal communication—it also expanded the potential of digital platforms to support mental health through digital expressive arts and peer support [47]. Moreover, the web-based design increased the mobility and flexibility of the intervention [48]. Previous studies have shown that online group interventions can be effective in reducing mental health symptoms such as depression [43,48], and Draper and Dingle [49] found that virtual groups were effective in addressing psychological needs.

Material and Personnel Preparation

The group sessions are cofacilitated by 2 individuals: a research assistant with a background in a mental health–related discipline and a registered music therapist. The research assistant takes the lead in delivering the psychoeducational content, while the music therapist facilitates the musical experiential activities and supports group discussions. Both facilitators employ techniques such as encouraging participants to be "good group members" to manage group dynamics effectively. For instance, during ice-breaking activities or group discussions led by the research assistant, the music therapist may participate as though they are a group member. This approach helps to foster rapport and strengthen the connection between the facilitators and participants. The same roles and techniques also apply to the research assistant during music activities. Additionally, the research assistant serves as the main point of contact for participants and is responsible for participant follow-up and distribution of reimbursement. The follow-up, limited to the scope of the project, includes administrative liaison (eg, responding to participant inquiries, delivering materials, arranging logistics) and crisis intervention. Crisis intervention involves providing appropriate community crisis support resources and information and making an informed decision regarding the participant's eligibility to continue with the group intervention.

To enhance project fidelity, the English manual from the original program was revised and translated into Chinese. The music selections from the original program were also adapted by the music therapist to better suit the local context. The incorporated music in this project is intended to produce equivalent therapeutic effects while maintaining consistency in music type with the original selections. For instance, Shawn Mendes' *A Little Too Much* [50] from the original program was replaced with Eason Chan's *Today* [51], which is more culturally relevant and relatable for local youth.

The manuals will be printed and distributed to participants and facilitators before the sessions. In cases where distributing hard copies is not feasible, an electronic version will be provided instead. To enhance readability and engagement during session presentations, PowerPoint (Microsoft Corporation) slides aligned with the manual content will also be used.

A session checklist outlining the key components of each session was prepared for facilitators to log the completion of intervention activities. These entries serve as records to support program fidelity and ensure consistency across sessions.

Recruitment

The recruitment process began in August 2023 and will continue until August 2025. Various strategies have been implemented to improve the accessibility of project information across all regions of Hong Kong.

Three main recruitment channels have been used:

- Social Media Platforms: project posters, welcome messages, and links to detailed information were posted on Instagram (Meta Platforms, Inc.), Facebook (Meta Platforms, Inc.), and Social Career (Social Career Limited), which are widely

used by local youth. Additionally, project details were published on the university website to reach the general public.

- Existing Partnership Networks: Information about the project was shared with 3 local universities, a local integrated children and youth services center, and several secondary schools that either have existing collaborations with the principal investigator (YC) or have expressed partnership interest. These institutions helped disseminate project details to their students or service users (eg, the ELCHK Lutheran Academy).
- Exploratory cold calls and emails: The research assistant reached out to additional secondary schools and integrated children and youth services centers via phone and email. These contacts were selected based on alignment between their service targets, institutional missions, and the goals of the project. Project information and partnership invitations were conveyed either verbally or in writing.

Randomization and Blinding

Participants will be randomly assigned to either the intervention or waitlist control group using a computer-generated randomization procedure. The Random Allocation Software developed by Dr. Mahmood Saghaei [52] will be used to facilitate this process. Block randomization will be implemented to ensure balanced group sizes, with a maximum of 8 participants per group. Randomization will be carried out by an independent researcher who is not part of the current research team or is listed as an author. The principal investigator remains blinded to group assignments to maintain objectivity and reduce potential bias. Outcome measures are managed by a separate research assistant who is not involved in the delivery of the intervention, ensuring independence and reducing potential bias. Once a sufficient number of eligible participants have been recruited, randomization will be conducted, typically 2 weeks before the intervention start date. Participants will then be informed of their group allocation, along with the schedule of their assigned group sessions, by the designated research assistant. In alignment with the ongoing recruitment process and rolling admission, the intervention will be delivered to participants as they are randomized and assigned to groups.

Participants

The target population for this study comprises post–high school students and adolescents aged 16-19 years. This age range aligns with international guidelines, such as those from the World Health Organization, which defines adolescence as ranging from 10 to 19 years, and the United Nations, which considers individuals aged 15-24 years as adolescents and young adults. Recruitment materials for the project will be disseminated to students in their final year of high school as well as recent graduates who maintain connections with their schools. Young adults, primarily those in their first year of undergraduate studies (typically aged 17-19 years in the Hong Kong context), will be recruited through posters displayed on university campuses and word-of-mouth referrals. A snowball sampling method will also be used to expand participant recruitment. Consistent with the approach used by Dingle and Fay [6], this study will include youth who self-report experiencing symptoms of low mood, anxiety, or loneliness.

Inclusion criteria for participation are (1) self-reported difficulties with low mood, anxiety, or loneliness; and (2) a score of 3 or above on the 12-item General Health Questionnaire (GHQ-12), indicating the presence of psychological distress. Exclusion criteria are the presence of severe mental health symptoms, such as self-harm or suicidal ideation, as the Tuned In program has not yet been trialed with individuals experiencing more acute mental health conditions.

Interested participants who do not meet the inclusion criteria will be provided with an information sheet about community counseling services. Eligible participants who confirm their enrollment will be randomized.

Sample Size Calculation

Dingle and Fay [6] found a medium effect size (η^2_p=0.076) for improved emotion regulation after the music intervention with young adults, compared with the control group. Based on this medium effect size, at least 98 participants are needed to detect a significant group × time interaction effect (P<.05). However, based on previous trials, some dropout is expected after the intervention has commenced. The estimated attrition rate is 15%. Besides, considering that partnerships with middle schools have only recently begun to develop, while many university students have already expressed interest in committing to the project, we expect to recruit more university participants. Therefore, we aim to recruit over 100 participants for the randomization stage, including around 50 adolescents and 65 young adults, to account for possible dropouts before the intervention begins.

Contingency Plan

Based on prior trials of Tuned In, we expect a high retention rate among youth [6]. However, some attrition may occur among adolescents [25]. Even with that attrition rate, we anticipate retaining at least 30 adolescents at the postintervention stage, providing sufficient data from this pilot study to inform future large-scale trials. In the event of significant challenges in recruiting adolescents, our backup plan is to recruit additional youth from the university community for this trial.

Because of the online mode of intervention, the study design minimizes potential disruptions arising from any local changes in the COVID-19 pandemic situation. If difficulties or delays in participant recruitment arise, we will place advertisements on social media as an additional recruitment channel.

Considering the risk of potential emotional disturbances, a page listing several 24-hour community crisis support hotlines has been incorporated into the manual to provide participants in need with an additional channel to external resources. Alongside the distribution of these resources, the research assistant will also give instructions on how to use them during the group contracting phase and explicitly encourage participants to seek help and notify the research assistant immediately if they experience emotional distress during the session.

In situations where psychological distress is identified either by a facilitator or self-reported by a participant, the research assistant will separate the individual from the rest of the group, while the music therapist continues to lead the remaining activities. The research assistant will provide immediate emotional support and conduct a timely risk assessment, and the principal investigator will be informed of the situation. Based on the participant's condition, appropriate referrals will be made as necessary.

The research assistant will follow up with individuals who disclose intentions or actions related to self-harm, suicide, harm to others, or breaches of the law, and will discuss with them the appropriateness of continuing in the project or the available options for discontinuation.

Description of the Intervention

The project consists of 5 weekly sessions: 1 introductory (preassessment) session followed by 4 psychoeducational sessions. Each session lasts approximately 60-90 minutes.

In the introduction session, participants sign the informed consent forms after being informed about the program's content and expectations by the main group facilitator (ie, the research assistant). For participants under 18 years of age, parental consent will also be obtained during the session. Following the signing of consent, the baseline survey will be distributed and collected. Participants' demographic information will be gathered through the survey. This includes, but is not limited to, age, gender, education level, household income, region of residence, living arrangement, and employment status.

Each week, participants will receive WhatsApp (Meta Platforms, Inc.) text message reminders about upcoming sessions and other important announcements.

The psychoeducational sessions differ in theme but follow a similar structure. Session 1 focuses on emotions located in various quadrants of the 2D model, such as high-arousal and negative-valence emotions. Session 2 explores happiness and loneliness, with the new component of loneliness added to this session. Sessions 3 and 4 address high-arousal emotions, such as stress and anxiety. An example session plan is provided in Multimedia Appendix 1 for reference (Table 1).

Table 1. Summary of session content.

Session	Content
Session 1	Emotions located in various quadrants of the 2D model, such as high-arousal and negative-valence emotions
Session 2	Happiness and loneliness
Session 3	High-arousal and negative-valence emotions, such as stress and anxiety
Session 4	High-arousal emotions, such as perfectionism and anxiety (continue) and achievement

For the new loneliness component, in addition to discussing songs that evoke a sense of receiving empathy, psychoeducation will be provided on the positive effects of music sharing in building and strengthening emotional bonds in relationships [12]. The group sessions will offer a safe and pleasant environment where participants can talk about music, using this topic as a channel to foster new connections with fellow group members. In session 2, participants will be guided to discuss how they can apply this skill outside of the program to strengthen existing relationships and build new connections.

Participants are also expected to select music for themselves during the group sessions. These self-selected songs serve to evoke the target emotions for each session and support group discussions and experiential psychoeducation—specifically, increasing awareness of the bodily or physiological changes that accompany each emotion as elicited by music. As music appreciation is used as a tool to support psychoeducation about emotions, rather than being a goal in itself (ie, the program is not intended to enhance musical understanding), we believe that participant-selected songs are more appropriate than those prescribed or suggested by the program facilitators. This is also in line with literature supporting the benefits of using self-selected and familiar music [21]. As such, participants' sharing of their self-selected music is incorporated as a core element in the sessions. The music submitted by participants spans a wide range of styles, reflecting their individual tastes, and includes Cantonese pop songs, classical music, movie soundtracks, and more.

Each session begins with a music check-in led by the music therapist, followed by participants listening to their self-selected music. This music listening and sharing segment takes approximately 15-20 minutes. Once the target emotions are evoked, the research assistant provides psychoeducation on the theme emotion and facilitates a group discussion on coping strategies. Around 10-15 minutes are allocated for this group discussion. Next, the music therapist guides participants through a core music activity designed to support reflection and reconnection with the theme emotion. Selected music activities include body scan, drawing, and lyric analysis. Each activity takes approximately 15 minutes. Each theme emotion is paired with its own specific psychoeducational content and corresponding music activity. The session concludes with a summary and debriefing provided to participants.

By the end of the last session, participants will be invited to complete the postquestionnaire. Individuals who complete both the prequestionnaire and postquestionnaire will receive a reimbursement of HK $200 (US $25.77) in cash. Reimbursement will be provided in person, and participants will be required to sign a receipt for record-keeping purposes. The intervention for the control group will be delivered after the final session of the experimental group and upon completion of the postquestionnaire by its participants. A flowchart outlining the project has been included in Multimedia Appendix 2.

Outcome Measures

Overview

The following measures of emotion regulation (primary outcome), mood symptoms (secondary outcome), and loneliness (secondary outcome) will be administered pre- and postintervention via Qualtrics (Silver Lake Technology Management, L.L.C.).

Primary Outcome: Emotion Regulation

- The Emotion Regulation Questionnaire is a widely used measure with subscales assessing 2 styles of emotion regulation: cognitive reappraisal and expressive suppression. It has been translated and validated for use in Hong Kong (Cronbach α=0.80-0.83) [53]. A child and adolescent version of the scale has also been translated into Chinese [54]. Given that the primary focus of the Tuned In program is to encourage the outward expression of emotion through music, it is anticipated that changes will be observed in expressive suppression scores, but not necessarily in cognitive reappraisal scores, following the program.
- The Difficulties in Emotion Regulation Scale (DERS) is a more comprehensive measure that assesses emotional awareness, emotional acceptance, impulse control, and emotion regulation strategies among both adolescents and adults. This scale has also been validated for use with Chinese participants (Cronbach α=0.68-0.89) [55]. Given its comprehensive nature, the DERS is considered the primary outcome measure in this study.
- To measure confidence in managing emotions, items from the program evaluation tool used by Dingle and Carter [27], which explicitly asks participants to rate their self-confidence in managing both positive and negative emotions, will also be included.

Secondary Outcomes: Mood Symptoms And Loneliness

- The 21-item Depression Anxiety Stress Scale (DASS-21), which has been used with Chinese participants [56], will be used to measure mood symptoms. Recent research has demonstrated the scale's validity for assessing emotional distress among young people in Hong Kong [57].
- The Hong Kong version of the 6-item De Jong Gierveld Loneliness Scale (Cronbach α=0.76) [58] will be used to assess loneliness.

Additional Measure

We will use the Music USE (MUSE) Questionnaire [59] to assess each participant's typical music listening habits, including whether they play a musical instrument and if they have received formal musical training. This scale was successfully used in a study involving 1318 adolescents in Hong Kong [34], making it a valuable tool for describing participants' engagement with music.

For demographic information such as gender and socioeconomic status collected in the survey, tests will also be conducted across the 2 conditions to examine whether the results differ.

The effect of the intervention on reducing anhedonia will also be explored using the Chinese version of the Snaith-Hamilton Pleasure Scale [60]. Data collected from this scale will be used for future outcome analysis.

The Tuned In program's acceptability among Hong Kong adolescents will be examined using a combination of quantitative and qualitative approaches. Satisfaction ratings will be collected from participants using a 7-point Likert scale. With "strongly disagree" at 1 point and "strongly agree" at 7 points, the ratings will capture the extent to which participants agree with the positive statements. The questions will address the perceived usefulness of the program, the level of interest in the program, the likelihood of recommending the program to other adolescents, and the likelihood of continuing to use music as an emotion regulation strategy in the future [25]. The aforementioned areas of investigation regarding the project's acceptability are framed into 4 separate rating questions, all of which are included in the postintervention survey. The quantitative questions are provided in Multimedia Appendix 3.

In addition, we will include open-ended qualitative questions to gather feedback from participants on their experiences with the program and to collect suggestions for improvements for a future RCT. Written responses are expected from participants. As feasibility indicators, we will also record the recruitment rate and dropout rate for this trial. The qualitative questions are incorporated into the postintervention survey, to be completed by participants at the end of the final session.

To explore participants' continued use of music for emotion regulation after the program, invitations to qualitative interviews will be sent at the 1-month follow-up. All participants who received the intervention will be invited. Open-ended and probing questions will be used to gather descriptive data on participants' views of the program and their music listening habits. Data saturation is expected to be reached by the conclusion of the project. Please refer to Multimedia Appendix 3 for the interview and postintervention survey questions.

Data Analysis

For the main outcome evaluation measures, mixed measures ANOVAs will be performed. The between-participants factor is group (intervention vs control), and the within-participants factor is time (pre- vs postintervention). Before the main analyses, independent samples *t* tests (2-tailed, paired) will be conducted on the baseline demographic variables to identify any significant differences between the 2 groups. Any variables that show statistically significant differences will be included as covariates in the subsequent main analyses. It is expected that the treatment group will demonstrate improved emotion regulation and reduced mood symptoms and loneliness following the music intervention, compared with the control group. A medium effect size is anticipated for the significant group × time interaction effect.

All verbal and written feedback will be analyzed using thematic analysis [61]. The qualitative analysis software NVivo (QSR International) will be used to assist with the process. Content analysis will be conducted following the transcription and coding of the data.

Results

The successful funding outcome of this project was announced in February 2023. Participant recruitment began in January 2024, and as of September 16, 2024, a total of 316 responses had been received through Qualtrics. Upon submission of the questionnaire, all participants are promptly notified of its receipt. Those deemed eligible receive a basic information sheet, while individuals who are ineligible are provided with a list of supporting resources. Of the responses received, 89 participants were considered eligible for the program. The project is scheduled to conclude in August 2025, with results to be published thereafter.

Discussion

Expected Findings

This proposal focuses on examining the short-term impact of a music-based emotion regulation program for young people in Hong Kong. For this trial, we expect the intervention group to demonstrate improved emotion regulation and reduced mood symptoms and loneliness after completing the Tuned In program, compared with the control group. This expectation is based on previous successful trials of Tuned In conducted in Australia [27]. Furthermore, in line with the Transdiagnostic Emotion Vulnerabilities Model, enhanced emotion regulation may help alleviate a range of mood-related issues [7].

Qualitatively, we expect that participants will describe their reduced loneliness and enhanced mental well-being as being directly and indirectly related to music. For example, they may resonate with the music and experience a sense of being understood [12]. We also anticipate that participants will appreciate the use of self-selected music throughout the program [21]. In the future, we plan to conduct longitudinal studies to examine the medium- to long-term impacts of the intervention.

Strengths

The study demonstrates notable strengths, including the involvement of 2 cofacilitators—a registered music therapist and a trained research assistant with a mental health background—ensuring both clinical expertise and research rigor in program delivery. Additionally, the inclusion of a new session component specifically targeting “loneliness” enhances the intervention by building upon and extending the established “Tuned In” program previously conducted in Australia, thereby addressing an important psychosocial issue with a tailored and evidence-informed approach.

Limitations

As this study is a pilot RCT, the primary focus is on assessing the feasibility and effectiveness of the intervention. The long-term effects can be explored in future, larger-scale trials. It is acknowledged that the outcome measures used are self-reported. This method was chosen to capture participants’ subjective experiences and perceptions. Additionally, the study does not account for individual differences that may influence outcomes. Factors such as the impact of life events or levels of alexithymia may potentially influence the outcomes of the program and should be taken into account in future research. Subsequent studies could incorporate additional forms of assessment, such as physiological measures or reports from family members, to provide a more comprehensive and corroborated evaluation.

As coping through emotions mediates the relationship between resilience and youth well-being [62], equipping young people with adaptive strategies to manage stress and difficult emotions helps consolidate learning and builds greater internal resources and capacity. This, in turn, positively influences both their short- and long-term mental health. Healthy coping also acts as a protective factor for their future emotional well-being.

Although this project does not investigate the medium- to long-term effects of the intervention on youth mental health due to resource constraints, future research could adopt a longitudinal perspective to explore the factors that help sustain the positive outcomes. Future studies could also incorporate an active control design and examine the individual contribution of each component to the overall effectiveness of the program.

Conclusions

This project aims to examine the short-term effects of a music-based emotion regulation program for young people in Hong Kong. We expect positive outcomes from this trial, and the preliminary results will inform the planning of future studies to better understand the underlying mechanisms and longer-term impacts.

From a practical perspective, the project will provide valuable insights into the use of music and psychoeducation in youth mental health work in Hong Kong. From a research and theoretical perspective, it may offer evidence regarding the effectiveness of combining music, psychoeducation, and group work in improving youth mental health. Building on the current project, future studies are encouraged to explore innovative ways to enhance the cost-effectiveness, outcome magnitude, reliability, and sustainability of the intervention.

Acknowledgments

This project is funded by the Health and Medical Research Fund, Health Bureau, The Government of the Hong Kong Special Administrative Region (reference number 10211636), and the Seed Fund for Basic Research for New Staff from the University of Hong Kong. DHKS is supported by internal funding from The Hong Kong Polytechnic University.

Authors' Contributions

YC designed the study, contributed to the intervention design, and was responsible for funding acquisition. DTLS and DHKS contributed to the program evaluation and participant recruitment planning. RT and GD contributed to the intervention design

and program evaluation planning. YC and DCWL drafted earlier versions of the paper. YS contributed to paper revisions. All authors reviewed and edited the final manuscript before submission.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Tuned In group session plan (session 5).
[DOCX File , 13 KB - resprot_v14i1e67764_app1.docx]

Multimedia Appendix 2
Project flowchart.
[PNG File , 279 KB - resprot_v14i1e67764_app2.png]

Multimedia Appendix 3
Survey and interview questions.
[DOCX File , 17 KB - resprot_v14i1e67764_app3.docx]

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Abbreviations

BRECVEMA: brain stem reflexes, rhythmic entrainment, evaluative conditioning, contagion (emotional contagion), visual imagery, episodic memory, musical expectancy, and aesthetic judgment
DASS-21: 21-item Depression Anxiety Stress Scale
DERS: Difficulties in Emotion Regulation Scale
GHQ-12: 12-item General Health Questionnaire
MUSE: music USE
RCT: randomized controlled trial

Edited by J Sarvestan; submitted 22.10.24; peer-reviewed by WLS Cheng, G Wadley; comments to author 31.01.25; revised version received 27.02.25; accepted 28.03.25; published 16.04.25.

Please cite as:
Cao Y, Shi Y, Low DCW, Shek DTL, Shum DHK, Tanksale R, Dingle G
Using Music to Promote Hong Kong Young People's Emotion Regulation and Reduce Their Mood Symptoms and Loneliness: Protocol for a Pilot Randomized Controlled Trial
JMIR Res Protoc 2025;14:e67764
URL: https://www.researchprotocols.org/2025/1/e67764
doi:10.2196/67764
PMID:

Original Paper

High-Intensity Interval Training for Individuals With Isolated Impaired Fasting Glucose: Protocol for a Proof-of-Concept Randomized Controlled Trial

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Abstract

Background: Standard lifestyle interventions have shown limited efficacy in preventing type 2 diabetes among individuals with isolated impaired fasting glucose (i-IFG). Hence, tailored intervention approaches are necessary for this high-risk group.

Objective: This study aims to (1) assess the feasibility of conducting a high-intensity interval training (HIIT) study and the intervention acceptability among individuals with i-IFG, and (2) investigate the preliminary efficacy of HIIT in reducing fasting plasma glucose levels and addressing the underlying pathophysiology of i-IFG.

Methods: This study is a 1:1 proof-of-concept randomized controlled trial involving 34 physically inactive individuals (aged 35-65 years) who are overweight or obese and have i-IFG. Individuals will undergo a 3-step screening procedure to determine their eligibility: step 1 involves obtaining clinical information from electronic health records, step 2 consists of completing questionnaires, and step 3 includes blood tests. All participants will be fitted with continuous glucose monitoring devices for approximately 80 days, including 10 days prior to the intervention, the 8-week intervention period, and 10 days following the

intervention. Intervention participants will engage in supervised HIIT sessions using stationary "spin" cycle ergometers in groups of 5 or fewer. The intervention will take place 3 times a week for 8 weeks at the Aerobic Exercise Laboratory in the Rehabilitation Hospital at Emory University. Control participants will be instructed to refrain from engaging in intense physical activities during the study period. All participants will receive instructions to maintain a eucaloric diet throughout the study. Baseline and 8-week assessments will include measurements of weight, blood pressure, body composition, waist and hip circumferences, as well as levels of fasting plasma glucose, 2-hour plasma glucose, and fasting insulin. Primary outcomes include feasibility parameters, intervention acceptability, and participants' experiences, perceptions, and satisfaction with the HIIT intervention, as well as facilitators and barriers to participation. Secondary outcomes comprise between-group differences in changes in clinical measures and continuous glucose monitoring metrics from baseline to 8 weeks. Quantitative data analysis will include descriptive statistics, correlation, and regression analyses. Qualitative data will be analyzed using framework-driven and thematic analyses.

Results: Recruitment for the study is scheduled to begin in February 2025, with follow-up expected to be completed by the end of September 2025. We plan to publish the study findings by the end of 2025.

Conclusions: The study findings are expected to guide the design and execution of an adequately powered randomized controlled trial for evaluating HIIT efficacy in preventing type 2 diabetes among individuals with i-IFG.

Trial Registration: Clinicaltrials.gov NCT06143345; https://clinicaltrials.gov/study/NCT06143345

International Registered Report Identifier (IRRID): PRR1-10.2196/59842

(JMIR Res Protoc 2025;14:e59842) doi:10.2196/59842

KEYWORDS

isolated impaired fasting glucose; prediabetes; high-intensity interval training; fasting hyperglycemia; diabetes incidence; fasting glucose; glucose; diabetes; proof of concept; interval training; type 2 diabetes; hyperglycemia; overweight; obese; weight; insulin; feasibility

Introduction

The prevalence of type 2 diabetes is increasing globally [1-3], driven predominantly by a rising number of individuals with prediabetes [2]. Globally, an estimated 860 million (8.4%) adults are living with prediabetes, a condition that increases the risk of developing type 2 diabetes [2], micro- and macrovascular complications, and mortality [4].

Prediabetes is not a singular entity but rather a heterogeneous group of metabolic defects that often precede type 2 diabetes [5-7]. Prediabetes phenotypes include isolated impaired fasting glucose (i-IFG), isolated impaired glucose tolerance (i-IGT), and IFG + IGT. Each prediabetes phenotype exhibits distinct pathophysiological abnormalities [5-7]. i-IFG is marked by impaired early-phase insulin secretion and hepatic insulin resistance. Conversely, i-IGT involves impairments in both early- and late-phase insulin secretion and skeletal muscle insulin resistance [5,7]. IFG + IGT presents a combination of defects observed in both i-IFG and i-IGT [5,7]. i-IFG accounts for a substantial portion of the global prediabetes population, ranging from 43.9% to 58% among Caucasian individuals and 29.2% to 48.1% among Asian individuals, depending on the diagnostic criteria [8]. Individuals with i-IFG exhibit a 4 to 5.5 times higher rate of progression to type 2 diabetes, depending on the diagnostic criteria, compared to those with normoglycemia [9].

Individuals with prediabetes are typically advised to adopt standard lifestyle interventions that emphasize improving diet quality with a modest calorie restriction and increasing moderate-intensity physical activity to reduce the risk of developing type 2 diabetes [10,11]. However, recent research highlights the varied effectiveness of these interventions among different prediabetes phenotypes. While these approaches prove highly effective for individuals with i-IGT and IFG plus IGT, their efficacy is notably limited for those with i-IFG [6,12,13]. Thus, there arises a necessity for alternative lifestyle intervention strategies tailored specifically to individuals with i-IFG.

One of the promising approaches is high-intensity interval training (HIIT), recognized as a time-efficient exercise option with significant benefits for metabolic health [14]. HIIT entails alternating short bursts of high-intensity exercise with periods of less active or passive recovery [15]. It is noteworthy that HIIT represents a more intensive exercise regimen compared to the current physical activity recommendations for individuals with prediabetes [10,11].

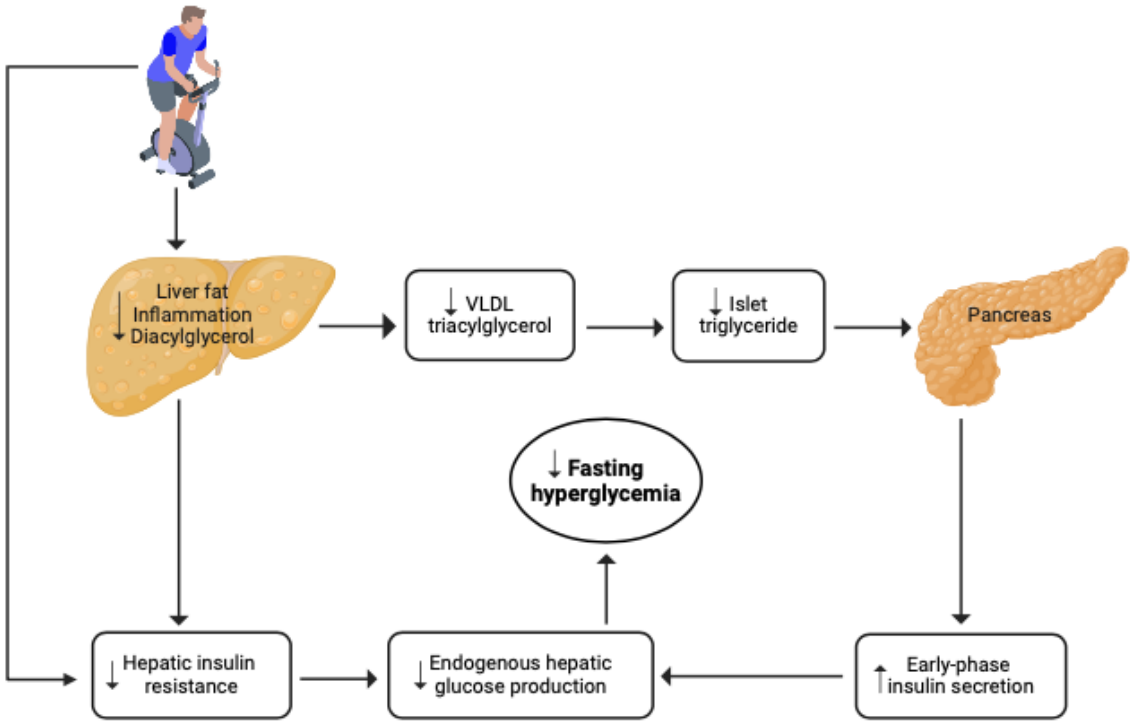
HIIT has been shown to effectively reduce hepatic insulin resistance and improve early-phase insulin secretion in individuals with type 2 diabetes [16-20], leading to significant reductions in fasting plasma glucose (FPG) levels [17,21-25]. Given that i-IFG shares these same pathophysiological defects [5-7], it is reasonable to hypothesize that HIIT could also be effective in individuals with i-IFG, as depicted in Figure 1. However, this hypothesis has yet to be tested in a randomized controlled trial (RCT). This is a critical investigation, as reducing fasting hyperglycemia is key to preventing the progression of type 2 diabetes in those with i-IFG [6,26]. To inform the design and implementation of this RCT, we propose conducting a proof-of-concept study among individuals with i-IFG, with the following objectives.

- Primary objectives (feasibility and acceptability): (1) assess the feasibility of recruiting and retaining participants and executing study procedures; (2) examine the feasibility, acceptability, and appropriateness of the HIIT intervention for participants; and (3) investigate participants' experiences, perceptions, and satisfaction with the HIIT

intervention, and identify facilitators and barriers to participation.

- Secondary objective (preliminary efficacy): Investigate the preliminary efficacy of HIIT in reducing FPG levels and addressing the underlying pathophysiology of i-IFG.

Figure 1. Potential pathways through which high-intensity interval training sessions may address the pathophysiological abnormalities and fasting hyperglycemia in individuals with isolated impaired fasting glucose. VLDL: very low-density lipoprotein.

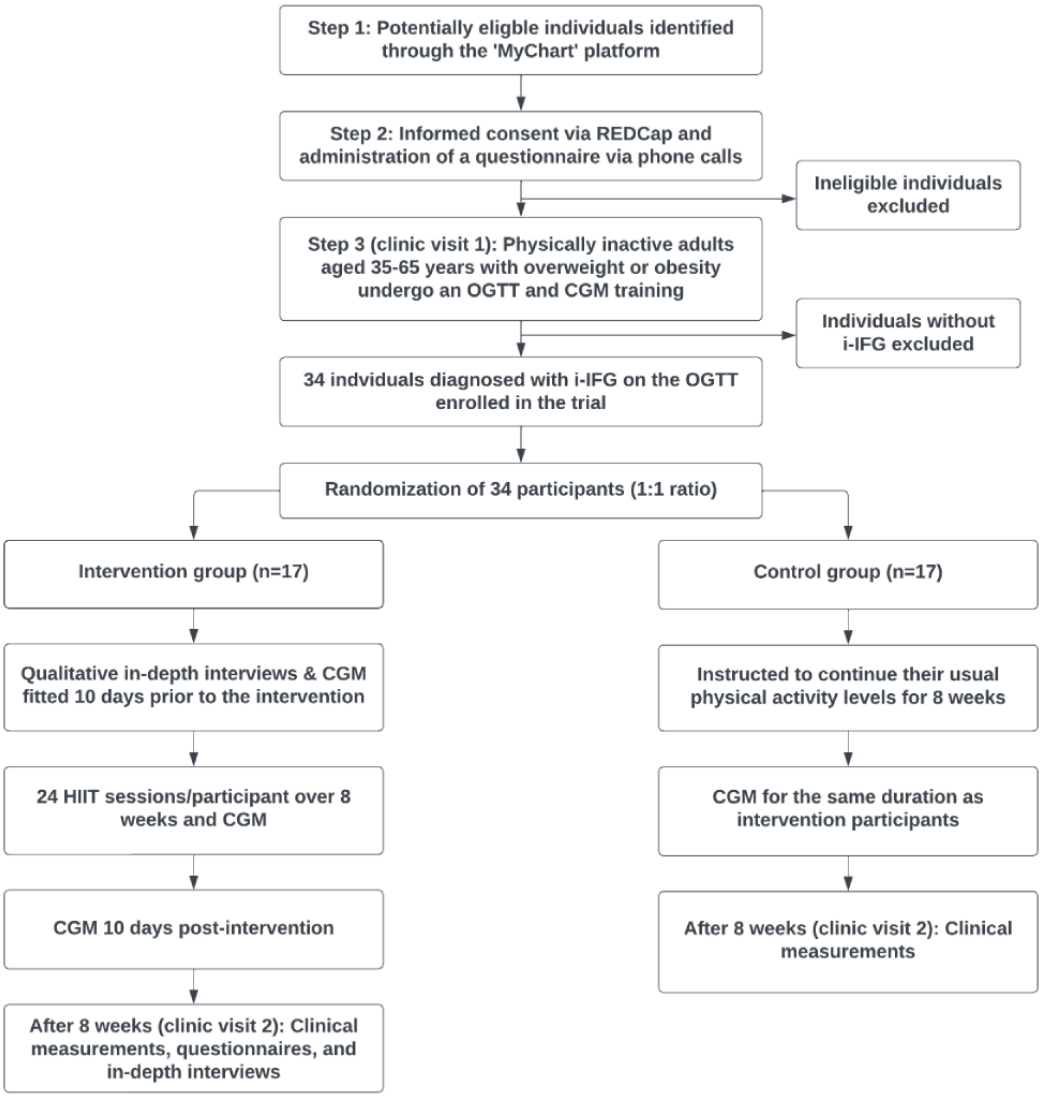


Methods

Study Design, Study Setting, and Participants

The study will be reported in accordance with the CONSORT (Consolidated Standards of Reporting Trials) guidelines for randomized pilot and feasibility trials [27]. This is a "proof-of-concept" 1:1 parallel-group RCT involving 34 physically inactive individuals aged 35-65 years who are overweight or obese and have i-IFG. Figure 2 presents the study's CONSORT diagram. The Georgia Clinical Research Center (GCRC) at Emory University Hospital will serve as the site for participant recruitment and conducting study procedures. A highly trained and experienced study coordinator will recruit participants through a comprehensive 3-step screening procedure.

Figure 2. CONSORT (Consolidated Standards of Reporting Trials) flow diagram. CGM: continuous glucose monitoring; HIIT: high-intensity interval training; i-IFG: isolated impaired fasting glucose; OGTT: oral glucose tolerance test; REDCap: Research Electronic Data Capture.



Step 1: Screening (via Electronic Health Records)

Potential participants will be identified using Emory's electronic health care records system, known as "MyChart." Queries within this database will target individuals aged 35-65 years with a BMI≥25 kg/m^2 (≥23 kg/m^2 if Asian descent) [28], who have been diagnosed with prediabetes (hemoglobin A_{1c} [HbA_{1c}] 5.7%-6.4%) [29] within the last 12 months, have no diagnosis of diabetes (FPG≥126 mg/dL or 2-hour plasma glucose ≥200 mg/dL or HbA_{1c}≥6.5% or currently taking antidiabetic drugs) [29], not currently taking weight-loss medications, not currently taking drugs known to influence glucose tolerance (steroids and antipsychotics), not currently taking beta-blockers and calcium channel blockers (individuals taking these drugs will not reach heart rate (HR) targets for the HIIT sessions), did not undergo bariatric surgery, no anemia (anemia may limit the exercising capacity), and have no chronic illnesses (cardiovascular disease, stroke, cancers, chronic respiratory diseases, and mental health disorders). Individuals meeting these criteria will receive an invitation through the MyChart platform to participate in the second screening step.

Step 2: Screening (via Phone Calls)

Those expressing interest in participating in the study through MyChart will be contacted via phone. During these calls, individuals will receive a comprehensive explanation of the study and have any questions addressed. They will then be asked to sign an electronic consent form via Emory's REDCap (Research Electronic Data Capture; Vanderbilt University) platform [30]. Following consent, potential participants will complete a questionnaire to assess their eligibility for step 3 screening based on the following criteria.

- Physically inactive (less than 150 minutes per week of moderate-intensity physical activity, less than 75 minutes per week of vigorous-intensity physical activity, and <600 metabolic equivalent task–minutes per week) [31] assessed by the International Physical Activity Questionnaire (IPAQ) [32].
- Available to participate in the HIIT group sessions.
- No history of smoking (smoking is associated with reduced insulin secretion and increased insulin resistance) [33].
- Not enrolled in weight loss programs in the past 6 months.

- Not enrolled in any regular exercise programs in the past 6 months.
- Not currently following a specific diet (eg, ketogenic and Mediterranean).
- No plans to undergo bariatric surgery during the study period.
- No plans to relocate outside the study area during the study period.
- Not pregnant.
- Not breastfeeding.

Step 3: Screening (via In-Person Clinic Visits)

Individuals meeting the step 2 criteria will be invited to visit the GCRC at Emory University Hospital after fasting overnight for a minimum of 8 hours [29]. During the visit, participants will complete standard questionnaires to collect sociodemographic information (education, occupation, and marital status) [34,35] and details on alcohol consumption [34,35] and dietary intake [36]. Additionally, physical measurements will be conducted using standardized instruments in accordance with the World Health Organization's STEPwise approach to noncommunicable disease risk factor surveillance (STEPS) protocol [37]. Following these assessments, individuals will undergo an oral glucose tolerance test (OGTT) and provide blood samples for insulin. Individuals diagnosed with i-IFG, defined by the American Diabetes Association criteria as FPG between 100-125 mg/dL and 2-hour plasma glucose<140 mg/dL [29], will be deemed eligible to participate in the study. Individuals without i-IFG will be excluded from further participation in the study. They will receive a summary report of their test results and general healthy lifestyle advice and will be referred to their general practitioner if they have IGT or undiagnosed diabetes for further management.

Randomization and Blinding

Participants will be equally randomized into either the intervention or control group after completing baseline assessments and being found eligible, using a computer-generated randomization sequence by a statistician not involved in the trial. Given the nature of the study, only specific personnel such as nursing staff, laboratory personnel, and the data analyst will be blinded to participant allocation to the study groups. Participants, the study coordinator, the HIIT intervention instructor, and the principal investigator will not be blinded to participation allocation.

Intervention

Following the recommendation of the American College of Sports Medicine [38], participants in the intervention group will be required to obtain medical clearance from their general practitioner before starting the HIIT sessions. These sessions, led by a qualified exercise physiologist (the instructor) and adhering to standard protocols [39,40], will take place in the Aerobic Exercise Laboratory at Emory University's Rehabilitation Hospital. Using "spin cycle ergometers" (Schwinn), sessions will be conducted in small groups of 5 or fewer participants at specified times on Mondays, Wednesdays, and Fridays, spanning 8 weeks. Each participant will undergo a maximum of 24 HIIT sessions. Each session will consist of a 5-minute warm-up, followed by an interval-based workout phase with steady up-tempo cadences, sprints, climbs, and interspersed recovery periods. A 5-minute cooldown will conclude each session. The workout sessions will initially last 20 minutes and will progressively increase in time based on participants' tolerance and instructor recommendations. Each session will include "active rest" periods where resistance is reduced to lower HR, alternating with high-intensity intervals featuring sprints or climbs to elevate HR. The duration of active rest versus high-intensity intervals will be adjusted according to individual responses and target HR. To monitor and maintain intensity within the target HR range, participants will wear Polar H10 chest strap HR sensors [41]. The target HR will be calculated using the Karvonen method [42]. Exercise intensity will begin at 75% of the estimated maximum HR reserve (HRR) and will increase by 5% every week, as tolerated or deemed necessary by the instructor, over the 8-week intervention period. During the workout phase, the target HRR reserve will be maintained by averaging increases and decreases in intensity or HR with a target to maintain within a 10% offset from the HRR goal [39,40]. Participants will need to adhere to within-session HR targets at an 80% rate (or greater) for a session to be counted as attended and participants will need to attend 19 out of 24 sessions to be included as a "completer" in the final data analysis. To date, our interventions have yielded a within-session adherence rate to the prescribed intervention of 91% (as measured by HR) and a retention rate of 85% [40,43-45]. Participants' weight and body composition will be measured weekly.

To ensure high compliance in session attendance, the instructor will hold weekly one-on-one meetings with participants to provide personalized feedback and encouragement. Participants' HR data will also be reviewed during these meetings. Additionally, the study coordinator will remind participants of their scheduled sessions 1 day in advance through phone calls or texts. Attendance in sessions will be closely monitored, and records of attended exercise sessions will be maintained. Participants who miss sessions will be contacted via phone calls to encourage attendance.

Any adverse events occurring during or after HIIT sessions will be documented, with medical advice sought if necessary. Both intervention and control participants will receive instructions to maintain a eucaloric diet throughout the study. Dietary adherence will be monitored biweekly by a registered dietitian using the Automated Self-Administered 24-Hour Dietary Assessment Tool (National Cancer Institute) [36]. This tool will be administered via phone calls 3 times a week, covering 2 weekdays and 1 weekend day. Additionally, control participants will be instructed to refrain from engaging in intense physical activities during the study period. Physical activity adherence will be assessed biweekly using the short form of IPAQ, also administered via phone calls [32].

Procedures

The details about the measurements, study tools, and timelines are outlined in Table 1.

Table 1. Measurements, study tools, and study timeline.

Variables	Components	Study tools	Baseline	8 weeks
Study feasibility	Response rate, screening yield, enrollment rate, time to enrollment, intervention compliance, resource use, and retention rate	REDCap[a] database	✓	✓
Intervention feasibility	Qualitative and quantitative research	Feasibility of Intervention Measure [46]	✓	✓
Intervention feasibility	Qualitative and quantitative research	In-depth interviews	✓	✓
Intervention acceptability	Qualitative and quantitative research	Theoretical Framework of Acceptability questionnaire [47]	✓	✓
Intervention acceptability	Qualitative and quantitative research	In-depth interviews	✓	✓
Intervention appropriateness	Qualitative and quantitative research	Intervention Appropriate Measure [46]	✓	✓
Intervention appropriateness	Qualitative and quantitative research	In-depth interviews	✓	✓
Participants' expectations of and experiences with the intervention	Qualitative research	In-depth interviews	✓	✓
Sociodemographics	Age, sex, marital status, education, and occupation	WHO STEPS[b] [34] and NHANES[c] questionnaires [35]	✓	x[c]
Eligibility criteria	Inclusion and exclusion criteria[e]	Short-form IPAQ[f] [32]	✓	x
Behavioral measures	Dietary habits	ASA24[g] dietary assessment tool [36]	✓[h]	✓[h]
Behavioral measures	Physical activity	Short-form IPAQ [32]	✓[i]	✓[i]
Behavioral measures	Smoking	WHO STEPS [34] and NHANES questionnaires [35]	✓	✓
Behavioral measures	Alcohol consumption	WHO STEPS [34] and NHANES questionnaires [35]	✓	✓
Physical measures	Height	Stadiometer	✓	x
Physical measures	Weight	Digital weighing scale	✓	✓
Physical measures	Waist circumference	Inelastic measuring tape	✓	✓
Physical measures	Hip circumference	Inelastic measuring tape	✓	✓
Physical measures	BP[j]	DINAMAP BP apparatus	✓	✓
Physical measures	Body composition	Bioimpedance analysis	✓	✓
Biochemical measures	OGTT[k] (0, 30, and 120 minutes)	Enzymatic assays	✓	✓
Biochemical measures	Insulin levels at 0 and 30 minutes	Immunoassays	✓	✓
CGM[k]	Proportion of time and mean time spent in nocturnal (00:00-06:00) normoglycemia (60 to <100 mg/dl) [48]	Dexcom G6 Pro (DexCom, Inc)	✓[l]	✓[l]

[a]REDCap: Research Electronic Data Capture.

[b]WHO STEPS: World Health Organization STEPwise approach to noncommunicable disease risk factor surveillance.

[c]NHANES: National Health and Nutrition Examination Survey.

[d]x: the particular variable will not be collected during that particular timepoint.

[e]Inclusion criteria: aged 35-65 years, overweight or obese (body mass index ≥25 kg/m² [≥23 kg/m² if Asian descent]), physically inactive (less than 150 minutes per week of moderate-intensity physical activity and less than 75 minutes per week of vigorous-intensity physical activity and <600 metabolic equivalent task–minutes per week), and a diagnosis of isolated impaired fasting glucose (fasting plasma glucose 100-125 mg/dL and 2-hour plasma glucose<140 mg/dL). Exclusion criteria: diagnosis of diabetes, diagnosis of other chronic illnesses (eg, cardiovascular disease, stroke), current smoker, history of anemia, currently enrolled in weight loss programs, currently enrolled in any regular exercise programs, currently following a specific diet (eg, ketogenic diet, Mediterranean diet), currently taking weight-loss medications or drugs known to influence glucose tolerance (steroids and antipsychotics), currently taking beta-blockers or calcium channel blockers, underwent bariatric surgery or plans to undergo the surgery during the study period, plans to relocate outside the study area during the study period, pregnant, or breastfeeding.

[f]IPAQ: International Physical Activity Questionnaire.

[g]ASA24: Automated Self-Administered 24-Hour Dietary Assessment Tool.

[h]Dietary habits will be assessed biweekly throughout the study duration.

[i]Physical activity of control participants will be assessed biweekly throughout the study duration.

[j]BP: blood pressure.

[k]OGTT: oral glucose tolerance test.

[l]All participants will be fitted with the continuous glucose monitoring device 10 days before the intervention, and they will be trained to replace the device every 10 days until 10 days post intervention.

Study Feasibility

Table 2 shows the study feasibility metrics. Continuous data collection on feasibility parameters, such as response rate, screening yield, enrollment rate, time to enrollment, intervention compliance, resource use (cost and staff time), and retention rate, will be conducted throughout the study.

Table 2. Study feasibility metrics.

Parameters	Calculations
Response rate	• Number of individuals responded to the invitation/number of individuals invited
Screening yield	• Number of individuals diagnosed with i-IFGa/number of individuals screened
Enrollment rate	• Number of individuals enrolled/number of individuals diagnosed with i-IFG
Time to enrollment	• Average time taken from sending the invitation to enrolling one participant in the trial
Intervention compliance	• Number of HIITb sessions attended/Total number of HIIT sessions
Resource use	• Program costs: Includes screening cost, cost of procedures, intervention cost, participant incentives, and other costs. • Staff time: Time spent screening and recruiting participants, time spent delivering the intervention, time spent making phone calls to participants, time spent implementing the study procedures, and time spent on baseline and follow-up assessments.
Retention rate	• Number of participants attended follow-up visits/number of participants enrolled

[a]i-IFG: isolated impaired fasting glucose.

[b]HIIT: high-intensity interval training.

Intervention, Feasibility, Acceptability, and Appropriateness

The Feasibility of Intervention Measure (FIM) will evaluate the feasibility of the intervention, encompassing questions regarding its implementability, possibility, doability, and ease of use [46]. The acceptability of the intervention will be assessed through the Theoretical Framework of Acceptability (TFA) questionnaire, which explores affective attitude, burden, ethicality, perceived effectiveness, intervention coherence, self-efficacy, opportunity costs, and general acceptability [47]. The Intervention Appropriate Measure (IAM) will evaluate the appropriateness of the intervention, including questions about its fittingness, suitability, applicability, and alignment with participants' needs [46]. Responses to the questions in all 3 questionnaires will be recorded on a Likert scale of 1 to 5. The mean total score for each of these scales will be calculated by combining the individual Likert points of each scale. Higher scores on the FIM, TFA, and IAM scales indicate greater feasibility, acceptability, and appropriateness, respectively, among participants.

Continuous Glucose Monitoring

By providing 288 glucose measurements per day throughout the 8-week intervention and 10-day follow-up, continuous glucose monitoring (CGM) can track the dynamic changes in fasting glucose levels induced by HIIT [48]. This can help identify when the effects of HIIT on fasting glucose levels become evident and whether these effects are sustained after the intervention, which may not be captured by a single blood glucose measurement taken after 8 weeks. All participants, regardless of their assigned treatment, will be fitted with a CGM device on their abdominal area upon enrollment. The CGM device, Dexcom G6 Pro CGM system (DexCom, Inc), will be used in blinded mode to minimize bias and ensure that it does not influence the study outcomes. Participants will be instructed to eat their last meal by 10 PM daily after the CGM fitting. They will wear CGM devices for approximately 80 days, including 10 days prior to the intervention, the 8-week intervention period, and 10 days following the intervention. Participants will be trained on how to replace the device every 10 days, using the instructions provided in the manual [49], during the first study visit. The adequacy of CGM data will be evaluated using the following criteria: a minimum of 80% of the potential 288

glucose values per day should be present for any 7 consecutive days, commencing from the day following sensor insertion [50].

Clinical Measures

Data on health behaviors, physical measurements, and biochemical measurements will be collected at both baseline and 8 weeks.

Health Behaviors

Physical activity levels will be assessed using the short form of IPAQ [32] and dietary intake with the Automated Self-Administered 24-Hour Dietary Assessment Tool questionnaire [36]. Data on smoking and alcohol use will be obtained using questions adapted from the WHO STEPS [34] and the National Health and Nutrition Examination Survey questionnaires [35].

Physical Measures

Physical measurements will be taken following standard protocols [37,51]. Height will be measured using a stadiometer (Welch Ally—Scale-Tronix) with an accuracy of 0.1 cm. Weight will be assessed using a digital weighing scale (Welch Ally—Scale-Tronix) with precision to the nearest 0.1 kg. Waist and hip circumferences will be measured using an inelastic measuring tape (BaumGartens) with a precision of 0.1 cm. Blood pressure will be measured using the DINAMAP automatic blood pressure apparatus (GE HealthCare). Body composition measures, including fat mass, muscle mass, fat-free mass, visceral adipose tissue mass, and fat percent, will be obtained using the bioimpedance analysis.

Biochemical Measures

Participants will undergo an OGTT following standard protocols [52,53]. The test will be conducted after an overnight fast of at least 10 hours, with the session scheduled between 7 and 9 AM. Venous blood samples will be collected at 0, 30, and 120 minutes after ingesting a 75-g oral glucose load dissolved in 250-300 mL of water, consumed over 5 minutes. Additionally, blood samples for insulin will be obtained at 0 and 30 minutes after glucose load ingestion. Blood samples will be processed and analyzed at the Emory Medical Laboratory (EML). EML is a fully accredited and licensed clinical laboratory, actively participating in the College of American Pathologists Laboratory Accreditation Program. Additionally, it holds Clinical Laboratory Improvement Amendments certification through the Centers for Medicare and Medicaid Services. EML is also duly licensed by the state of Georgia. Glucose levels will be assessed through enzymatic assays and insulin levels via immunoassays based on the EML protocol [53]. All these analyses will use kits provided by Beckman Coulter Inc and will be performed on a Beckman Coulter analyzer.

Indices of ß Cell Function and Insulin Resistance

Table 3 provides details on the indices of ß Cell function and insulin resistance derived from glucose and insulin levels. Early-phase insulin secretion will be assessed using the insulinogenic index [54], while total ß cell function with be evaluated with the oral disposition index [55] and homeostatic model assessment of ß cell function [56]. Whole-body insulin resistance will be determined using the Matsuda index [57] and homeostatic model assessment of insulin resistance [56], while tissue-specific insulin resistance will be assessed with the hepatic insulin resistance index [58] and muscle insulin sensitivity index [58].

Table 3. Indices of ß-cell function and insulin resistance.

ß cell function or IR[a] and components	Indices	Formula
ß cell function		
Early-phase insulin secretion:	IGI[b] [54]	$(I_{30}^{c}–I_0^{d})/(G_{30}^{e}–G_0^{f})$
ß cell function	DI_O^{g} [55]	$([I_{0\text{-}30}/ G_{0\text{-}30}]\times[1/I_0])$ • I0 in µU/l • G0 in mmol/l
ß cell function	HOMA-B[h] [56]	$(20\times I_0)/(G_0–3.5)$ • I0 in µU/l • G0 in mmol/l
Insulin resistance		
Whole-body insulin sensitivity	Matsuda index [57]	$10{,}000 /\sqrt{((G_0\times I_0)\times(G_{mean}^{i}\times I_{mean}^{j}))}$
Insulin resistance	HOMA-IR[k] [56]	$(I_0\times G_0)/22.5$ • I0 in µU/L • G0 in mmol/l
Hepatic insulin resistance	HIRI[l] [58]	$(G_0–G_{30}[AUC^{m}]\times I_{0\text{-}30}[AUC])$ • G0 in mg/dl • I0 in µU/ml
Muscle insulin resistance	MISI[n] [58]	$(dG/dt^{o})/\bar{I}^{p}$

[a]IR: insulin resistance.

[b]IGI: insulinogenic index.

[c]I_{30}: mean insulin at 30 minutes during the oral glucose tolerance test.

[d]I_0: mean insulin at 0 minutes during the oral glucose tolerance test.

[e]G_{30}: mean glucose at 30 minutes during the oral glucose tolerance test.

[f]G_0: mean glucose at 0 minutes during the oral glucose tolerance test.

[g]DI_O: oral disposition index.

[h]HOMA-B: homeostatic model assessment of ß cell function.

[i]G_{mean}: mean glucose during the 2-hour oral glucose tolerance test.

[j]I_{mean}: mean insulin during the 2-hour oral glucose tolerance test.

[k]HOMA-IR: homeostatic model assessment of insulin resistance.

[l]HIRI: hepatic insulin resistance index.

[m]AUC: area under the curve during the first 30 minutes of the oral glucose tolerance test.

[n]MISI: muscle insulin sensitivity index.

[o]dG/dt: slope of the regression line from the peak of the plasma glucose curve to its nadir (mmol/L/min).

[p]$\bar{I}$: mean insulin concentration over the 2-hour duration of the oral glucose tolerance test (pmol/L).

Qualitative Research

Participants assigned to the intervention group will be invited to take part in in-depth interviews both before and after the HIIT intervention. Trained interviewers will administer these interviews either in person during scheduled study visits or via Zoom within 1 week of the visits if participants are unable to attend in person. The interviews will be guided by interview guides specifically developed for the study and piloted with members of the study team. Preintervention interviews will delve into participants' prediabetes history, physical activity and dietary habits, perceptions of body size and image, as well as their comfort levels, perceived difficulty, confidence, and expectations regarding the HIIT intervention. Post-intervention interviews will focus on participants' experiences with the intervention. Every effort will be made to interview both dropouts and active participants to ensure a comprehensive understanding of program acceptability and to identify barriers and facilitators to adherence. All interviews will be audio recorded, transcribed verbatim, and deidentified for analysis.

Outcomes

Primary Outcomes

- Quantitative measures: (1) feasibility metrics and (2) mean FIM, TFA, and IAM scores.

Qualitative measures: participants' experiences, perceptions, and satisfaction with the HIIT intervention, and facilitators and barriers to participation.

Secondary Outcomes

- Between-group differences in changes in the following parameters from baseline to 8 weeks: (1) mean FPG and insulin levels, (2) indices of β cell function and insulin resistance, and (3) weight, body composition, waist and hip circumferences, and blood pressure.
- CGM metrics: (1) between-group differences in the proportion of time and mean time spent in nocturnal (12 to 6 AM) [50] normoglycemia (60 to <100 mg/dL) during the 8-week intervention period and the 10 days following the intervention, and (2) within-participant differences in the proportion of time and mean time spent in nocturnal (12 and 6 AM) normoglycemia (60 to <100 mg/dL) between exercise and non-exercise days during the 8-week intervention period.

Data Management

The study coordinator will enter questionnaire data, as well as physical and biochemical measurements directly into Emory University's REDCap database [30]. This database will feature validation checks to ensure data accuracy, along with skip patterns facilitated by branching logic functions. The principal investigator (ST) will constantly review the data for any errors, promptly flagging any errors for correction by the study coordinator. Upon completion of data entry and cleaning, a master copy of the data set will be generated and securely stored within the REDCap database. CGM raw data (in CSV file format per participant) will be downloaded from the DexCom Clarity software and uploaded to REDCap. Access to these datasets will be limited to the study coordinator and the principal investigator for confidentiality and data security purposes.

Sample Size Calculation

Assuming a Cohen *d* of 0.3 to <0.7 (medium standardized effect size) [25,59] for FPG in the planned main trial, with an alpha of 5% and a power of 90%, a sample size of 15 participants per treatment group is deemed necessary for this pilot study. Factoring in a 10% loss to follow-up in each group, the total sample size was estimated to be 34 participants (17 per group).

Statistical Analysis

Quantitative Research

Objective 1

Continuous variables will be summarized using either mean (SD) or median (IQR), depending on their distribution, which will be visually assessed through histograms. Categorical variables will be presented as counts (n) and percentages (%).

Objective 2

The analyses will adhere to the "intention-to-treat" principle. Between-group differences in changes in continuous variables from baseline to 8 weeks will be analyzed using mixed-effects linear regression models, while categorical variables will be assessed with log-binomial models. Skewed variables will be log-transformed prior to analysis. Fixed effects will include the study group (intervention vs control), timepoint (follow-up vs baseline), and the interaction between the study group and timepoint. Random effects will be specified for participants to account for the correlation between repeated measurements on the same individual. The *P* value for the study group-by-timepoint interaction will be used to evaluate the difference in changes between the study groups. The correlation between changes in fasting glucose levels and the indices from baseline to 8 weeks will be assessed using either Pearson or Spearman correlation coefficients, depending on the nature of the data distribution. Mixed-effects linear regression models will be used to compare CGM metrics between study groups, adjusting for baseline values. These models will also examine within-participant differences in CGM metrics between exercise and non-exercise days. Statistical significance will be considered with a 2-sided *P* value<.05 with no adjustments for the multiplicity of comparisons. All analyses will be conducted using Stata (version 18.0; StataCorp LLC).

Qualitative Research

In-depth interviews will be conducted with intervention group participants and dropouts. All interviews will be audio recorded and transcribed verbatim for analysis. The qualitative analysis plan involves 2 main components: a framework-driven analysis of intervention acceptability data and a thematic analysis focusing on participant expectations, experiences, barriers, and facilitators in undergoing the HIIT intervention. For the framework-driven analysis, a deductive codebook containing the TFA dimensions will be applied to both baseline and postintervention interview data. This approach aims to provide a comprehensive and longitudinal understanding of HIIT acceptability among program users, comparing results across timepoints and between those who remained in the program and study dropouts. Additionally, an inductive approach will be used to create a codebook of inductive codes around other aspects of acceptability, program barriers, facilitators, experiences, and sustainability through a close reading of the transcripts. Once the data is coded, thick descriptions of individual codes will be developed, including structured comparisons such as between baseline and postintervention interviews, program adherents and dropouts, men and women, and older and younger participants. These comparisons will guide data reporting and program adaptation for further trials, providing insights into the diverse experiences and perspectives of participants.

Challenges and Mitigation Strategies

The potential challenges that could be encountered at various stages of the study and the corresponding mitigation strategies are outlined in Table 4.

Table 4. Potential challenges and proposed mitigation strategies.

Study stage	Challenges	Mitigation strategies
Identifying potential participants	Insufficient number of potentially eligible individuals	• We will use physician referrals as an additional recruitment strategy.
Screening	Low yield of screening	• The 3-step screening procedure was carefully designed, drawing upon insights from our previous research and existing literature, to target individuals who are likely to have i-IFG[a].
Intervention	Low HIIT[b] compliance	• The study coordinator will remind participants of their scheduled exercise sessions through phone calls. Additionally, the coordinator will regularly review the attendance log, providing motivation and support to participants with low attendance levels. • The exercise instructor will hold weekly one-on-one meetings with participants to review their progress and provide motivation, specifically targeting those with low attendance levels.
Procedures	Periodic data gaps with CGM[c] whenever the receiver is located more than 5 feet	• The CGM data will be assessed for adequacy based on the following criteria: Data points must be present for at least 80% of the possible 288 glucose values per day for any 7 consecutive days, starting on the day after sensor insertion.
Follow-up	Low retention rate	• Compensation for time and parking: (1) participants will receive a US $50 gift card upon completion of the study and (2) parking fees at study sites will be covered. • Building rapport: study staff will create a warm and supportive environment during study visits, fostering a sense of trust and comfort. • Ongoing support: the study coordinator will provide continuous support through regular phone calls. This proactive approach ensures that participants feel connected to the study outside of scheduled visits. The study coordinator will address any concerns, answer queries, and offer encouragement, reinforcing a sense of partnership between participants and the research team.

[a]i-IFG: isolated impaired fasting glucose.

[b]HIIT: high-intensity interval training.

[c]CGM: continuous glucose monitoring.

Ethical Considerations

The study protocol was approved by the institutional review board of Emory University, Atlanta, USA (MOD001-STUDY00005855). All participants will provide written informed consent prior to study participation. Participant identifiers will be kept strictly confidential in a secure REDCap database, accessible only by the principal investigator and study coordinator. Data will be deidentified before analysis. Participants will receive a US $50 gift card as compensation for their participation.

Results

Table 5 shows the study timeline. Recruitment for the study is scheduled to begin in February 2025, with follow-up expected to be completed by the end of September 2025. We plan to publish the study findings by the end of 2025.

Table 5. Study timeline[a].

	2023		2024				2025			
	May	July-December	January-March	April-June	July-September	October-December	January-March	April-June	July-September	October-December
Received funding	✓									
Finalizing the study protocol and study tools		✓								
Clinical trial registration		✓								
Obtaining approvals: NIH[b], NCATS[c], and IRB[d]			✓	✓	✓					
REDCap database setup						✓				
Screening and recruitment							✓	✓		
Baseline assessments							✓	✓		
Baseline in-depth interviews							✓	✓		
HIIT[e] intervention							✓	✓		
8-week assessments									✓	
In-depth interviews at 8 weeks									✓	
Data entry							✓	✓	✓	
Data analysis									✓	✓
Study report and publications										✓
Conferences and scientific meetings										✓

[a]The cells colored in gray showing the timeline for various activities.

[b]NIH: National Institutes of Health.

[c]NCATS: National Center for Advancing Translational Sciences.

[d]IRB: institutional review board.

[e]HIIT: high-intensity interval training.

Discussion

Expected Findings

This proof-of-concept study will generate data on the feasibility and acceptability of the HIIT intervention, as well as participants' experiences and satisfaction levels. Additionally, the study will offer preliminary estimates on the efficacy of HIIT in reducing FPG levels and addressing the pathophysiology of i-IFG.

Strengths and Limitations

To our knowledge, this study will be the first to assess the feasibility and acceptability of a HIIT intervention exclusively among individuals with i-IFG. Additionally, we adhered to the PRISMA-P (Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols) statement [60] when reporting the details of this study protocol. However, there are some limitations. We will assess the pathophysiological abnormalities in i-IFG using indices derived from the OGTT and fasting insulin levels instead of gold-standard methods like the intravenous glucose tolerance test and glycemic clamps [61-63]. However, these indices have demonstrated strong correlations with estimates obtained from the gold-standard methods [61-63]. Additionally, our reliance on a single OGTT may be subject to day-to-day variability in glucose tolerance status. Nevertheless, strict adherence to standardized protocols for conducting the OGTT [52,53] should help minimize this variability to a significant extent.

Conclusions

The results of this study are expected to guide the design and implementation of an RCT to assess the efficacy of HIIT intervention in reducing diabetes incidence and achieving remission in individuals with i-IFG.

Acknowledgments

This study was supported by the Georgia CTSA's Pilot Program, funded by the Robert W Woodruff Health Science Center at Emory University and the National Center for Advancing Translational Sciences of the National Institutes of Health (NIH; award UL1TR002378). The qualitative research component of the study was supported by the National Institute of Diabetes and Digestive and Kidney Diseases of the NIH (award P30DK111024). ST was partially supported by a grant (75D30120P0742) from the Centers for Disease Control and Prevention, Atlanta. RB was partly funded by the NIHR Applied Research Collaboration West Midlands. The content is solely the responsibility of the authors and does not necessarily represent the official views of the Robert W Woodruff Health Science Center or the NIH. The funder had no role in the conceptualization, design, data collection, analysis, decision to publish, or preparation of the manuscript.

Authors' Contributions

ST, LS, FL, MLMS, MDS, FJP, and JRN conceived the idea; ST received funding; ST, TRZ, MBW, LS, FL, MLMS, MDS, FJP, and JRN designed the study methodology; ST wrote the first draft of the manuscript; TRZ, MBW, LS, FL, MLMS, MDS, AV, RB, FEF, MP, SK, RJT, JES, FJP, and JRN reviewed the manuscript draft and provided critical comments. All authors have read and agreed to the published version of the manuscript.

Conflicts of Interest

FP received research support from Dexcom, Ideal Medical Technologies, Tandem Diabetes Care, and Novo Nordisk, and consulting fees from Dexcom and Insulet (paid to his institution). None of these entities were involved in the development of this manuscript, and none had editorial oversight.

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Abbreviations

CGM: continuous glucose monitoring
CONSORT: Consolidated Standards of Reporting Trials
EML: Emory Medical Laboratory
FIM: Feasibility of Intervention Measure
FPG: fasting plasma glucose
GCRC: Georgia Clinical Research Center
HbA1c: hemoglobin A1c
HIIT: high-intensity interval training
HR: heart rate
HRR: heart rate reserve
i-IFG: isolated impaired fasting glucose
i-IGT: isolated impaired glucose tolerance
IAM: Intervention Appropriate Measure
IPAQ: International Physical Activity Questionnaire
OGTT: oral glucose tolerance test
PRISMA-P: Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols
RCT: randomized controlled trial
REDCap: Research Electronic Data Capture
STEPS: STEPwise approach to noncommunicable disease risk factor surveillance
TFA: Theoretical Framework of Acceptability

Edited by A Schwartz; submitted 23.04.24; peer-reviewed by C Farrell; comments to author 02.08.24; revised version received 16.08.24; accepted 09.10.24; published 20.02.25.

Please cite as:
Thirunavukkarasu S, Ziegler TR, Weber MB, Staimez L, Lobelo F, Millard-Stafford ML, Schmidt MD, Venkatachalam A, Bajpai R, El Fil F, Prokou M, Kumar S, Tapp RJ, Shaw JE, Pasquel FJ, Nocera JR
High-Intensity Interval Training for Individuals With Isolated Impaired Fasting Glucose: Protocol for a Proof-of-Concept Randomized Controlled Trial
JMIR Res Protoc 2025;14:e59842
URL: https://www.researchprotocols.org/2025/1/e59842
doi:10.2196/59842
PMID:

Protocol

Weighted Blankets for Agitation in Hospitalized Patients with Dementia: Protocol for a Randomized Controlled Trial

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Abstract

Background: There are limited therapies approved for the treatment of aggression and agitation in patients with dementia. While antipsychotics and benzodiazepines are commonly used, these medications have been associated with significant side effects and US Food and Drug Administration (FDA) boxed warnings. Weighted blankets have been associated with decreased anxiety and improved sleep. Weighted blankets are potentially a nonpharmacologic option to reduce agitation in hospitalized patients with dementia.

Objective: The aim of this study is to investigate the effect of weighted blankets on aggression and agitation in hospitalized patients with dementia.

Methods: A pilot study will be conducted on a total of 30 hospitalized patients with a documented clinical diagnosis of dementia and ongoing agitated behaviors admitted to a medicine or psychiatry service. Patients will be randomly allocated to receive either a weighted blanket for 3 nights or continued usual care. The primary outcome is the change in the observational version of the Cohen-Mansfield Agitation Inventory (CMAI-O) over the course of the 3-night study period. The secondary outcomes are changes in Edmonton Symptom Assessment System Revised (ESAS-r) and Clinical Global Impression (CGI) scores, hours of sleep, use of antipsychotics and benzodiazepines, and incidence of delirium. Identical study assessments will be completed for both the usual care and the weighted blanket study groups. At 5 study time points (baseline, postnight 1, postnight 2, postnight 3, and a final assessment 48-72 h after the last use of the weighted blanket), patients will be assessed with the CMAI-O, ESAS-r, and CGI tools. All assessments will be completed by the bedside nurse or patient care assistant caring for the patient each day. Within 2 to 4 weeks post discharge from the hospital, study coordinators will contact the patient's legally authorized representative (LAR) to assess for continued use of the weighted blanket.

Results: Enrollment of participants began on April 23, 2023. As of November 2024, a total of 24 participants have been enrolled in the study. Baseline characteristics of enrolled participants will be analyzed and reported upon completion of enrollment. We anticipate completing data collection by March 2026.

Conclusions: The study will determine the effect of weighted blankets on agitation in hospitalized patients with dementia. Insights into the effect of weighted blankets on sleep will also be gained. The results of this study will be relevant in the setting of increasing numbers of older adults with dementia exhibiting agitation, leading to increased hospitalizations, caregiver burden, and health care costs.

Trial Registration: ClinicalTrials.gov NCT03643991; http://clinicaltrials.gov/ct2/show/NCT03643991

International Registered Report Identifier (IRRID): DERR1-10.2196/57264

(JMIR Res Protoc 2025;14:e57264) doi:10.2196/57264

KEYWORDS

dementia; hospitalized dementia patients; agitation; aggression; behaviors; sleep; weighted blankets; nonpharmacologic strategy; pilot study; inpatients; occupational therapy

Introduction

Background

Many patients with dementia develop neuropsychiatric symptoms and somewhere between 40% and 76% of patients demonstrate agitation and aggression [1,2]. Agitated behaviors are often disruptive and difficult to manage, and are associated with increased caregiver burden and burnout, increased hospitalizations, and elevated health care costs [1,3]. Agitation includes a range of behaviors, including restlessness, pacing, physical aggression, and verbal agitation [4].

Nonpharmacologic strategies are the first line in the prevention and treatment of neuropsychiatric symptoms of dementia, including agitation. Limited pharmacologic options exist in this setting. In fact, no pharmacologic therapies were approved by the Food and Drug Administration (FDA) for this indication until the recent approval of the atypical antipsychotic brexpiprazole for the treatment of agitation associated with dementia due to Alzheimer disease [5]. Other antipsychotics are commonly used, particularly in emergency and acute care settings when agitated or aggressive behaviors threaten either patient or caregiver [6]. These medications, however, are associated with significant serious long- and short-term side effects including akathisia and restlessness [7], and carry an FDA-boxed warning for increased risk of mortality [8]. The 2016 American Psychiatric Association practice guidelines recommend that antipsychotic medications be reserved for severe, dangerous, or significantly distressing symptoms and used at the lowest effective dose due to concern for side effects [9]. The management of agitated and aggressive symptoms without primary reliance on antipsychotics remains a challenge. Benzodiazepines are typically avoided due to the risk of cognitive impairment, falls, and respiratory depression [10].

Weighted blankets are filled with plastic pellets or beads and are commercially available in weights ranging from 5 to 30 pounds. Weighted blankets have been used in occupational therapy as a form of noninvasive deep-pressure stimulation, which appears to increase parasympathetic arousal and decrease anxiety [11-13]. Weighted blankets have been studied in patients with psychiatric diagnoses in both the inpatient and outpatient settings, and they appear to be associated with decreased anxiety and improved sleep [14,15]. Weighted blankets have also been associated with improved chronic pain and reduced anger scores [16,17]. Currently, however, there are no studies investigating the use of weighted blankets to address agitation in hospitalized patients with dementia.

Objectives

The aim of this study is to investigate the effect of weighted blankets on aggression and agitation in hospitalized patients with dementia. We hypothesize that compared to controls, patients with agitation in the setting of dementia will show reduced agitation, reduced anxiety, and potentially improved sleep while hospitalized when provided with a weighted blanket.

Methods

Design and Randomization

To address this question, we designed a pilot study (ClinicalTrials.gov NCT03643991) with 1:1 randomization of hospitalized patients with dementia and evidence of agitated behaviors to receive either a weighted blanket for 3 nights or continued usual care.

Study Population and Recruitment

Patients will be recruited from a single large tertiary care hospital. Participants are eligible for inclusion if they are 60 years or older, have a documented clinical diagnosis of dementia, and are currently admitted to either a medicine or psychiatry primary service. All participants are required to have ongoing agitated behaviors at the time of enrollment as demonstrated by an elevated CMAI-O with a score of 2, 3, or 4 on at least one aggression-related item (items 1-11 or 22-24) [18]. Patients will be excluded if they have severe pain likely to be exacerbated by the use of the weighted blanket, have significant burns or wounds for which weighted blanket use could potentially be detrimental, or are admitted on a 72-hour involuntary hold. Participants can be enrolled at any point during their hospitalization. Hospitalizations will not be prolonged for the purpose of the study. To reflect real-world conditions, all other usual medical care will be continued at the discretion of the primary medical or psychiatric team.

Intervention

Participants will be randomized 1:1 to either the usual care group or the weighted blanket group. The weighted blankets used are commercially available and purchased for the study. Patients randomized to the weighted blanket group will be provided with either a 10 lb, 15 lb, or 20 lb weighted blanket, ensuring that the weight is not more than 10% of the participant's body weight. Participants will be withdrawn from the study if they refuse the blanket or are unable to tolerate it for more than 2 hours on the first night after enrollment. Participants can also be withdrawn from the study at any time if the primary team feels that further participation will jeopardize patient safety. Enrolled participants will use the blanket for a total of 3 consecutive nights, or until the time of discharge if that occurs sooner. Following participation in the study, participants will be allowed to keep the weighted blanket for future personal use. To reduce potential bias, the data analysis team will remain blinded to group assignment during statistical analyses, although investigators administering the questionnaires will not be blinded due to the nature of the intervention.

Primary Outcome

The primary end point will be the change in CMAI-O over the course of the 3-night study period. The CMAI-O is a validated scale published in 2020 by Griffith et al [18] to quantify neuropsychiatric behavior in patients with dementia. Observers rank the frequency of 29 behaviors grouped into categories: physical aggressive behaviors (questions 1-11), physical nonaggressive behaviors (questions 12-21), verbal aggressive behaviors (questions 22-24), and verbal nonaggressive behaviors (questions 25-29). The frequency of each behavior is ranked as 1 (never), 2 (less than once per h), 3 (once per h), and 4 (several times per hour).

Secondary Outcomes

Secondary end points will include change in Edmonton Symptom Assessment System Revised (ESAS-r) score and change in Clinical Global Impression (CGI) score as well as hours of sleep, use of antipsychotics and benzodiazepines, and incidence of delirium.

The ESAS-r was originally designed as a self-report tool in which patients rate the severity of 9 symptoms on a scale from 0 to 10 (10 being the most severe) [19]. The tool assesses the following nine symptoms: pain, tiredness, drowsiness, nausea lack of appetite, shortness of breath, depression, anxiety, and well-being. This assessment tool has been commonly used in palliative medicine and oncology settings, translated into several languages, and is well received by patients and nursing staff [19]. The ESAS-r captures the pattern of a patient's severity of symptoms at a point in time and may be repeated to track changes over time. Since patients with a diagnosis of dementia vary significantly in their ability to report symptoms, we have standardized the protocol by using caregiver (nurse or patient care assistant) input to complete the ESAS-r assessment tool [19].

The CGI scale is a brief, independent assessment initially designed to summarize a caregiver's view of a patient's global functioning before and after initiating an intervention [20]. The CGI consists of 2 one-item measures that evaluate the severity of psychopathology and change from the initiation of treatment on a 7-point scale. The CGI may be used to track clinical progress over time [20].

Further clinical data will be extracted from the medical record. Caregiver staff will estimate hours of sleep. Use of antipsychotics and benzodiazepines will be recorded based on the medical administration records. The incidence of delirium will be estimated based on documentation of a newly positive Brief Confusion Assessment Model (bCAM) assessment [21]. Delirium Triage Screen and bCAM assessments are performed to screen for delirium every 12 hours (once per nursing shift) in the hospital where this study will be conducted.

Study Timeline and Follow-Up

Identical study assessments will be completed by the patient's caregiver (either registered nurse or patient care assistant) for both the usual care group and the weighted blanket study group. Cohen-Mansfield Agitation Inventory (CMAI-O), ESAS-r, and CGI scores will be collected at 5 study time points (baseline, postnight 1, postnight 2, postnight 3, and a final assessment 48-72 hours after the last use of the weighted blanket). A total of 3 nights were determined to be sufficient for assessing trends in agitation, anxiety, and sleep, while also testing the feasibility of the intervention in a real-world clinical environment. Within 2-4 weeks following hospital discharge, study coordinators will contact the patient's legally authorized representative (LAR) to assess for continued use of the blanket. Refer to the patient timeline (Table 1).

Table 1. Patient timeline.

Assessment	Baseline (enrollment)	WB[a] day 1	WB day 2	WB day 3	Final within 72 hours of last use of WB (cohort 1) or no WB (cohort 2)	Within 2-4 weeks post discharge
CMAI-O[b]	✓	✓	✓	✓	✓	
ESAS-r[c]	✓	✓	✓	✓	✓	
CGI[d]	✓	✓	✓	✓	✓	
Posthospitalization phone call to assess continued weighted blanket use						✓

[a]WB: weighted blanket.

[b]CMAI-O: Cohen-Mansfield Agitation Inventory.

[c]ESAS-r: Edmonton Symptom Assessment System Revised.

[d]CGI: Clinical Global Impression.

Sample Size

We will target an enrollment of 30 participants in this pilot study. This sample size was chosen to balance the need for gathering preliminary data with the constraints of patient availability, time, and resources within our hospital setting. The sample size of 30 is sufficient to provide preliminary insights into the effects of weighted blankets on agitation, allowing us to explore trends and estimate effect sizes for future studies. Recruitment will be facilitated by daily review of hospital-wide behavior emergency response team activations and patient referrals from inpatient medicine and psychiatry primary services.

Data Collection, Management, and Confidentiality

Participants will be randomized 1:1 to the treatment and usual care groups via computer-generated sequence which will be concealed until after each patient's enrollment. Given the nature of the study, blinding of caregivers and study coordinators to treatment groups is not feasible.

Data will be collected by study personnel in a manner consistent with patient confidentiality. For patients withdrawn from the study, no further data will be collected but existing study data to the point of withdrawal will be included in the final analysis which will be performed based on intention to treat.

All data obtained will be entered into REDCap (Research Electronic Data Capture), a secure electronic database that is password-protected and accessible only to the study team. Each participant will be assigned a unique identification code to protect their identity, and only the code will be used for forms, reports, and data analysis. Paper records containing protected health information will be maintained in locked file cabinets in a secure room accessible only to research personnel. All patient information will be kept confidential and managed according to the Health Insurance Portability and Accountability Act of 1996 requirements.

Data Analysis

A per-protocol analysis will be used. Baseline characteristics of participants will be reported using percentages for categorical variables and mean with SD for continuous variables. Differences between the 2 treatment groups for the descriptive variables will be compared using chi-square tests for categorical variables and Kruskal-Wallis tests for continuous variables. The medications and dosages taken during the study will also be reported. The primary outcome of the CMAI-O score will be described at each of the 5 time points (baseline, day 1, day 2, day 3, and day 72 follow-up). A linear mixed effects model with time as a random effect will be used to analyze changes in the CMAI-O score over time. Both the unadjusted and an adjusted model with age, sex, and unit type as covariates will be reported. Age and sex were included as covariates as they are standard demographic factors that can influence behavioral outcomes. Unit type (medicine vs psychiatry) was included as it may impact patient management practices and potentially influence study outcomes. This model also allows for missing data which occurs in the dataset when a patient was discharged before the end of the study period. Secondary outcomes of ESAS-r and CGI scores will be analyzed in a comparable way with a linear mixed model. The end-of-study survey results will be described for each question. A per-protocol analysis will evaluate only the enrolled patients who followed protocol.

Monitoring

The principal investigator will conduct weekly meetings with the study coordinator and research team to review the status of the study, recruitment and enrollment of participants, protocol adherence, safety issues, and overall conduct of the study. The principal investigator will monitor, track, and report any adverse events, protocol deviations, and progress reports or continuing reviews to the institutional review board (IRB) with research regulations.

Ethical Considerations

This study follows the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) guidelines for reporting (see Multimedia Appendix 1). The study protocol was approved by the Mayo Clinic IRB (IRB 17-009951) and was registered with ClinicalTrials.gov (NCT03643991). Amendments to the protocol will be submitted to the Mayo Clinic IRB for approval before implementation. Written informed consent approved by the IRB will be obtained from the participant's LAR, who will be provided sufficient information regarding the risks and benefits of the study to make an informed decision about the participation of their loved ones in the study. The LARs will be fully informed about their right to withdraw participation at any time. No compensation is being provided to participants, although individuals randomized to the weighted blanket group are permitted to keep the weighted blanket. Study investigators will have access to the final dataset, which will include deidentified participant information only as outlined above in the "Data Collection, Management, and Confidentiality" section. Results will be submitted to a peer-reviewed journal and scientific conferences for the advancement of clinical care.

Results

Enrollment of participants began on April 23, 2023. As of November 2024, 24 participants have been enrolled in the study. Baseline characteristics of enrolled participants will be analyzed and reported upon completion of enrollment. We anticipate completing data collection by March 2026. The study results will be reported in a peer-reviewed journal upon completion.

Discussion

Primary and Secondary Outcomes

We hypothesize the use of a weighted blanket will reduce patients' behaviors and agitation; therefore, patients' CMAI-O scores will decrease. In addition, we anticipate patients' ESAS-r and CGI scores will decrease with the use of a weighted blanket. We hope with reduced behaviors and agitation that patients will have reduced antipsychotic and benzodiazepine administrations and decreased incidence of delirium.

Strengths and Limitations

There are several strengths of this study. This study is a randomized controlled trial being performed in both medical and psychiatric inpatient settings at an academic medical center. The study's intervention is a nonpharmacologic option that has minimal potential side effects. The study is a pilot study that can offer opportunities for further research studies. A couple of the study's limitations are the small sample size and performed at a single organization. In addition, the investigators are nonblinded and could lead to a potential bias. It is unclear if the results will be generalizable to all patients with agitation and dementia, other health care organizations, and outpatient settings.

Conclusions

This study addresses the important clinical issue of agitation in hospitalized patients with dementia. This study will contribute to the growing body of knowledge on nonpharmacological management of behavioral symptoms in older adults with dementia. This is important as the management of agitated and aggressive symptoms without primary reliance on antipsychotics and benzodiazepines remains a challenge. We anticipate that these study results will be used to inform health care professionals, caregivers, and family members regarding the potential usefulness of weighted blankets as a nonpharmacologic method to decrease agitation and distress in hospitalized older adults with dementia.

Acknowledgments

This is an investigator-initiated clinical trial by MIL. MIL is supported in part by a grant (R01AG061100) from the National Institute on Aging and has no financial relationships to disclose. The study is made possible by the generous support of a benefactor through Mayo Clinic Development, which serves as the primary source of funding for this research. Additional support is provided by the Mayo Clinic Center for Translational Science Activities through a grant (UL1 TR000135) from the National Center for Advancing Translational Sciences, a component of the National Institutes of Health (NIH). The study is supported by the Mayo Clinic Department of Medicine Research Hub and the Division of Hospital Internal Medicine. Its contents are solely the responsibility of the authors and do not necessarily represent the official views of the NIH. The funders have no role in study design, data analysis and interpretation, in the writing of the report, and in the decision to submit the manuscript for publication. The findings do not necessarily represent the views of the funders. Artificial intelligence was not used in any portion of this manuscript generation.

Data Availability

The datasets generated or analyzed during this study are available from the corresponding author on reasonable request.

Authors' Contributions

HAS, AKP, NBS, DKL, KMF, MIL, and RED contributed to conceptualization. DKL, KMF, MIL, and RED performed data curation. KMF, MIL, and RED were involved in formal analysis. MIL was responsible for funding acquisition. HAS, AKP, NBS, DKL, MIL, and RED participated in the investigation. HAS, AKP, NBS, DKL, KMF, MIL, and RED performed the methodology. HAS, AKP, NBS, DKL, MIL, and RED handled project administration. HAS, AKP, NBS, DKL, KMF, MIL, and RED were involved in writing–original draft, review and editing.

Conflicts of Interest

None declared.

Multimedia Appendix 1
SPIRIT Outcomes 2022 checklist.
[PDF File (Adobe PDF File), 265 KB - resprot_v14i1e57264_app1.pdf]

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Abbreviations

bCAM: Brief Confusion Assessment Model
CGI: Clinical Global Impression
CMAI-O: Cohen-Mansfield Agitation Inventory
ESAS-r: Edmonton Symptom Assessment System Revised
FDA: US Food and Drug Administration
IRB: institutional review board
LAR: legally authorized representative
REDCap: Research Electronic Data Capture
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials

Edited by A Schwartz; submitted 09.02.24; peer-reviewed by R de Filippis, UA Snigurska; comments to author 25.09.24; revised version received 29.12.24; accepted 17.01.25; published 26.02.25.

Please cite as:
Schenzel HA, Palmer AK, Shah NB, Lawson DK, Fischer KM, Lapid MI, DeFoster RE
Weighted Blankets for Agitation in Hospitalized Patients with Dementia: Protocol for a Randomized Controlled Trial
JMIR Res Protoc 2025;14:e57264
URL: https://www.researchprotocols.org/2025/1/e57264
doi:10.2196/57264
PMID:

Protocol

Research Participants' Engagement and Retention in Digital Health Interventions Research: Protocol for Mixed Methods Systematic Review

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Abstract

Background: Digital health interventions have become increasingly popular in recent years, expanding the possibilities for treatment for various patient groups. In clinical research, while the design of the intervention receives close attention, challenges with research participant engagement and retention persist. This may be partially due to the use of digital health platforms, which may lack adequacy for participants.

Objective: This systematic literature review aims to investigate the relationship between digital health platforms and participant engagement and retention in clinical research. It will map and analyze key definitions of engagement and retention, as well as identify design characteristics that influence them.

Methods: We will carry out a mixed methods systematic literature review, analyzing qualitative and quantitative studies. The search strategy includes the electronic databases PubMed, IEEE Xplore, CINAHL, Scopus, Web of Science, APA PsycINFO, and the ACM Digital Library. The review will encompass studies published between January 2018 and June 2024. Criteria for inclusion will be the presence of digital health care interventions conducted through digital health platforms like websites, web and mobile apps used by patients, and informal caregivers as research participants. The main outcome will be a narrative analysis with key findings on the definitions of participant engagement and retention and critical factors that affect them. Quality assessment and appraisal will be done through the Mixed-Methods Assessment Tool. Data analysis and synthesis will follow the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) 2020 flow diagram. Quantitative data will be qualified and integrated into qualitative data, which will be analyzed using thematic analysis and synthesis.

Results: The study expects to map and summarize critical definitions of participant engagement and retention, and the characteristics of digital health platforms that influence them. The systematic review is expected to be completed in June 2025.

Conclusions: This systematic review will contribute to the growing discussion on how the design of digital health intervention platforms can promote participant engagement and retention in clinical research.

Trial Registration: PROSPERO CRD42024561650; https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=561650

International Registered Report Identifier (IRRID): PRR1-10.2196/65099

(JMIR Res Protoc 2025;14:e65099) doi:10.2196/65099

KEYWORDS

clinical research informatics; participant engagement; participant retention; clinical research; mobile application; digital platforms; mobile phone

Introduction

In 2022, over 100,000 health care mobile apps were available in Apple and Google app stores combined [1]. Digital health care has transformed care delivery through a diverse fleet of technologies, from mobile apps and wearable devices to biosensors and the Internet of Things [2]. It offers a myriad of innovative ways to provide treatments, monitor health conditions, assist, and empower patients with diverse needs to be more in charge of their health, and enable health care professionals to deliver better service [3]. Following the expansion of the digital health care range, digital health (DH) interventions have also increased exponentially (Textbox 1). DH interventions are interventions delivered through digital technology for the treatment or management of physical or mental conditions [4].

Textbox 1. Key concepts.

Digital health intervention

- Interventions are delivered through digital technologies such as smartphones, websites, wearables, video games, or text messaging [2,5,6]. A digital health intervention offers guidance, information, and support for a diversity of physical or mental health conditions through a digital platform. Also commonly referred to as health informatics or eHealth interventions [7]; they are designed to help people avoid, recover from, or cope with disease and disability or to improve the quality and safety of health care [8], for example, as self-help or self-guided eHealth interventions [9,10].

Digital health platforms

- Websites, web-based or mobile apps used to access digital health interventions.

Digital clinical research

- Clinical research is conducted through digital health platforms. It may include digital health interventions, digital data collection, and electronic Case Report Forms, among other resources. Only digital clinical research encompassing digital health interventions will be considered for this study.

Research participant

- Recipients of intervention; for example, patients or informal caregivers.

Participant engagement

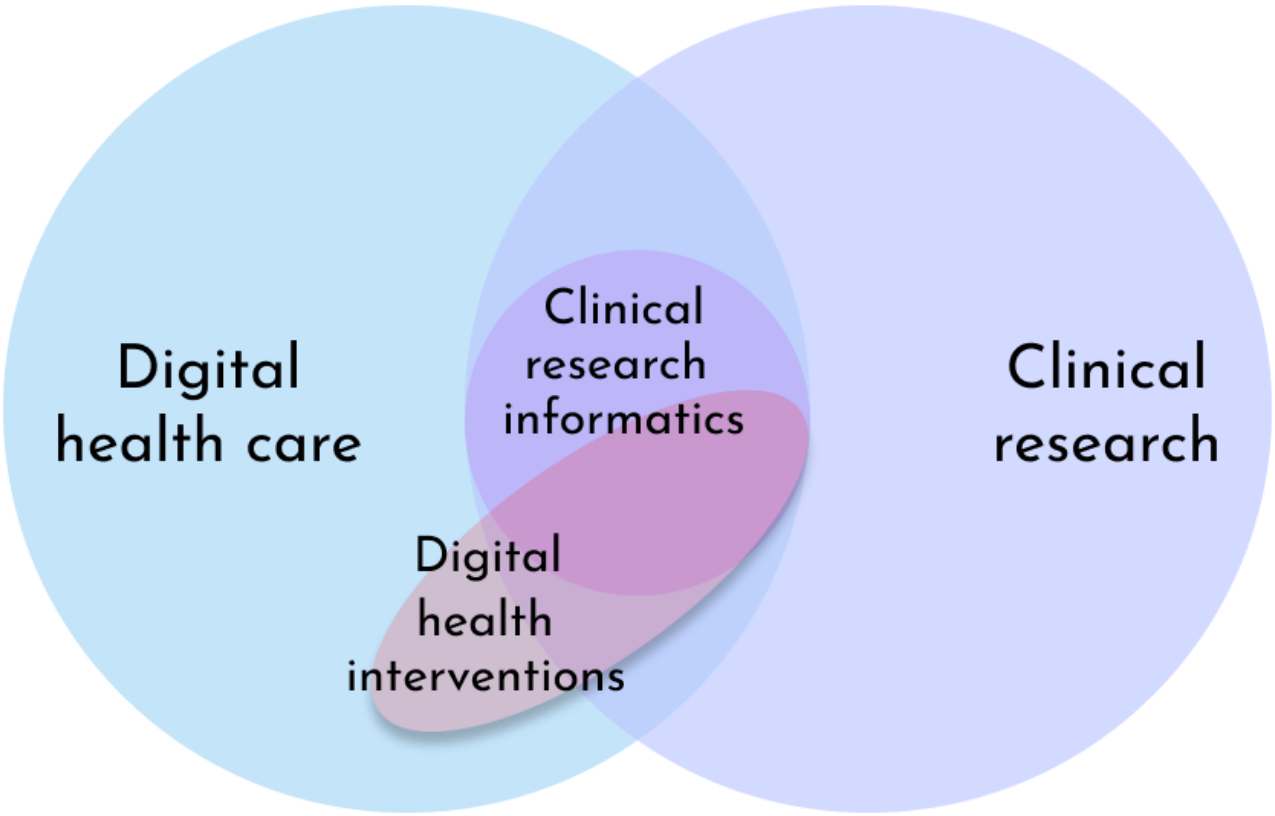
- Length and depth of participant's involvement with the digital health intervention.

Participant retention

- Duration and continuity of the participant's involvement with the digital health intervention.

Through online treatments, DH interventions promise to improve health care, enhancing accessibility, effectiveness, and personalization [2,11]. DH interventions are available in commercial applications, as easily accessible health care, and as part of clinical research (Figure 1). When conducted as part of clinical research, they share the same benefits as general digital health care. DH interventions also allow for the development of effective treatments for more patients [11], are more community-inclusive [12], decrease health disparities [13], and improve study generalizability and validity [14,15]. Successful clinical research generates evidence that, in turn, promotes health care improvements [16].

Figure 1. Digital health interventions are part of general digital health care and clinical research. The latter can be delivered through clinical research informatics or commercial health platforms and software.



In clinical research, DH interventions are designed following the principles of clinical research informatics (CRI) [4]. CRI is the use of informatics principles and techniques to conduct clinical research [4]. DH interventions have the potential to accelerate the process from initial research to "real world" outcomes, contributing to increasing scale and distribution, cost and resource optimization, and facilitating financial auditing processes [12,16-18]. These principles could also be applied to DH interventions.

Both engagement and retention of clinical research participants are crucial intervention research outcomes, but the concepts have varying definitions. Frequently, different terms for engagement are used interchangeably, like involvement, participation, acceptability, and completion rates, among others. Engagement can be described as the extent and manner in which people actively use a resource [19]. Perski et al [20] define engagement as two main concepts: (1) a subjective experience, meaning a state of focus and interest with a temporal dissociation, and (2) a behavior, described as usage over time. It is often connected to concepts like adherence, duration, and frequency that can be quantified through concrete measurements like opening or using a mobile app, frequency of times, or the duration of the use [21]. Participant retention, in turn, refers to the proportion of recruited participants who remained in the study until its end and at an optimal proportion that does not compromise the study's validity [22,23].

In DH intervention research, both engagement and retention can vary considerably. Intervention dropout from internet-based treatment for psychological disorders, for example, fluctuates between 30% and 50% [24]. While poor engagement or retention may be due to the intervention quality or outside factors, an often-overlooked component is the design of DH platforms. Appraising the DH platforms' design choices and how they impact participant engagement and retention could help make DH interventions better. In this context, there is an untapped opportunity to explore the practical factors that affect intervention success. This systematic literature review will focus on DH platforms' design choices concerning engagement and retention and their relationship with research participants' behavior.

The relationship between DH platforms and research participants is receiving growing interest, as evidenced by the increase in research. Studies have examined participant engagement and retention across various settings, for example, mHealth or web-based platforms [21,25], focusing on particular patient groups, for example, older adults with dementia or digital mental health interventions [26-29].

Still, a comprehensive literature review on the relationship between DH interventions and participant engagement and retention in digital clinical research has yet to be conducted. This review aims to fill the gap by studying DH platforms that have been used in digital clinical research. We will map the various definitions that capture the engagement and retention of research participants in DH interventions. We will further identify platform design factors and features that hinder or promote participants' engagement and retention. The key concepts relevant to the review are defined in Textbox 1.

Methods

This systematic review was submitted for registration with the International Prospective Register of Systematic Reviews (PROSPERO) on June 8, 2024 (CRD42024561650), to avoid bias in conducting and reporting findings. According to the study's progress, amendments will be made if necessary [30].

Review Question

The review question was elaborated using the Population-Exposure-Outcome (PEO) statement, as outlined in Textbox 2. We chose to apply the PEO as it is regarded as the more appropriate approach for qualitative inquiries [31]. It is also more suitable for the definition of associations between particular exposures and factors and related outcomes [32]. The overall review question is: What factors and aspects promote research participants' engagement with and retention in DH interventions in digital clinical research? This was further broken down into 2 specific research questions:

Research question 1: How are engagement and retention of research participants defined in DH interventions conducted for clinical research?

Research question 2: What user interface elements, interaction design, and platform characteristics influence research participants' engagement and retention in DH interventions?

Textbox 2. Population-exposure-outcome structure.

Population-exposure-outcome element and description
Population
Research participants who are patients, informal or family caregivers.
Exposure
User interface, interaction elements, and platform characteristics of digital health interventions conducted in clinical research.
Outcomes
Engagement and retention of research participants.

Methodology Choice Rationale

The choice to perform a mixed methods systematic literature review is due to the number of individual studies that have already been conducted in digital health care and DH interventions, providing substantial evidence for the review.

The methodology selected for this systematic literature review is the mixed methods systematic review (MMSR) [33]. It is a standard approach that allows to systematically combine qualitative and quantitative data [34]. By integrating the findings of effectiveness (quantitative data) with findings on participants' experiences (qualitative data), MMSR offers a comprehensive evaluation with balanced data insights [35].

We plan to carry out the MMSR as we expect both data types to be prevalent in the reviewed studies. By including both data types, we will adopt a holistic approach to defining engagement and retention. For instance, qualitative data can shed light on the context, patient and informal caregivers' experiences, and barriers to engagement and retention, which quantitative data alone may not fully capture.

Search Strategy

We will analyze studies that (1) offered a DH intervention; (2) used a DH platform component, such as a mobile app, website, or text-messaging process; (3) collected engagement and retention-related measurements–quantitative, qualitative, or both; and (4) presented a digital interface to the research participants—patients, and informal caregivers—to interact with the DH intervention. The DH platforms can be designed specifically for clinical research or not. Commercially available health applications will be considered if they are used for clinical research purposes.

The search strategy for this systematic literature review was developed in collaboration with Görel Sundström, a librarian from Uppsala University, and the researchers involved in this study, LT, AK, MH, and MIM.

The PEO statement was used to construct the search strategy (Table 1). The keywords refinement process involved different approaches: tests conducted by the librarian, consultation of referenced articles to analyze the keywords they used, and expert reviews conducted by the research team. The keywords selection process was performed to ensure the search would capture studies using various terminologies to address the same research questions (Multimedia Appendix 1).

Table 1. Preliminary Web of Science search strategy (to be adapted for the other databases).

Search number	Database search algorithm
User engagement, user retention, and metrics	
1	(“active user*” OR Attrition OR “Click rate” OR “Completion rate*” OR “Frequency of use” OR “Follow up” OR Login OR “log in” OR “Returning user*” OR “Session duration” OR “Sign in” OR “Study complet*” OR “Time spent” OR usage OR “User actions” OR “Use Rate*” OR “User metric*” OR “user session*”)
2	((Caregiver* OR “Healthy Volunteer*” OR “Research Subject*” OR participant* OR patient* OR subject* OR user*) NEAR/3 (accept* OR activit* OR adher* OR attitude* OR barrier* OR challeng* OR complian* OR discontinu* OR Disengagement* OR Dropout* OR Efficien* OR Effectiveness OR engag* OR evalutation* OR experience* OR Finish* OR involvement* OR interaction* OR obstacle* OR participation* OR perception* OR perspective* OR retention* OR satisf* OR visit* OR view*))
3	1 OR 2
Clinical research informatics and digital care	
4	(“Clinical informat*” OR “Clinical research informat*” OR “Clinical trials informatic*” OR CRI OR “digital care” OR eHealth OR e-health OR etherap* OR “e-Mental health” OR “Health informati*” OR iCBT OR “Internet Cognitive Behavioral Treatment*” OR “medical informatics*” OR mHealth OR m-health OR mtherap* OR m-therap* OR “Online Clinical Trial*” OR telerehabilitation)
5	((“clinical research” OR “clinical trial*” OR “medical research” OR health OR intervention* OR psychotherap* OR therap* OR “self-help program*” OR treatment*) NEAR/3 (Computer* OR cyber OR Digital OR electronic OR informatics OR Internet OR Mobile OR Online OR Smartphone OR “Technology Based” OR “Web based”))
6	4 OR 5
Design and aspects of software or digital platform	
7	(“Interaction design*” OR Interface OR Usability OR “User centered design*” OR “Visual design*”)
Combining all topics	
8	3 AND 6 AND 7

The search will be conducted across a range of electronic databases: PubMed, IEEE Xplore, CINAHL, Scopus, Web of Science, APA PsycINFO, and the ACM Digital Library. These databases are chosen based on their relevance to the research topic and their widespread use in academic and research communities.

In addition to the electronic database searches, the research team will use additional search methods to identify potential studies that may not be captured through the database searches. It includes hand search, which involves manually scanning relevant journals; back-forward citation tracking, where we examine the references of identified articles; and reference checking to ensure no valuable sources are overlooked during the review process.

This systematic literature review will not involve collecting sensitive personal data.

Study Selection Criteria

The PEO statement was used to outline the eligibility criteria for study inclusion and exclusion, delineating them by population, exposure, and outcomes (Table 2).

Table 2. Population-exposure-outcome inclusion and exclusion criteria.

PEO[a]	Inclusion criteria	Exclusion criteria
Population	Research participants, study participants, patients, informal caregivers, carers, caregivers, and users. No exclusion based on age or gender.	Researchers, physicians, doctors, nurses, social care workers, social workers, dentists, and health care professionals.
Exposure or environment	User interface and interaction design of DH platforms.	Engagement and experience related to the intervention or treatment itself. Experience with content quality (text and multimedia content).
Outcomes	Engagement and retention to the study.	Efficacy of the treatment, efficacy related to the intervention or treatment itself.
Study methods	Qualitative methods, quantitative methods, mixed methods.	Reviews (systematic, scoping, meta-analysis, etc)
Publication types	Formally published peer-reviewed journal articles, conference papers.	Grey literature, opinion pieces, protocols, reviews
Geographical considerations	Initially not limited to any geographical area.	

[a]PEO: Population-exposure-outcome.

Types of Studies

Qualitative Studies

Qualitative interviews, focus group discussions, usability studies, participatory research, participatory design, case studies, grounded theory research, thematic and content analysis of textual data, phenomenological studies, narrative research, and ethnographic observations.

Quantitative Studies

Randomized controlled trials, cohort studies, longitudinal studies, experimental studies, case-control studies, cross-sectional studies, and observational studies.

Mixed Methods Studies

Studies integrating qualitative and quantitative data collection and analysis methods within a single research design, encompassing but not restricted to convergent design, sequential explanatory design, and sequential exploratory design.

In the case of studies addressing the same DH intervention and cohort of individuals, only the study with more detailed data regarding engagement and retention-based measurements will be considered, unless the studies present different aspects of the 2 mentioned subjects.

Studies such as gray literature, editorials, letters, opinion papers, and theses and dissertations will be excluded.

Time Period

The study will consider articles published from January 2018 to June 2024. This 7-year publication window was chosen because of the rapid evolution in the technology and health informatics domain. The timeframe also covers DH intervention platforms developed before and after the COVID-19 pandemic [36].

Language

Due to resource constraints, the study will exclusively include articles published in English. The research team acknowledges that this approach limits the inclusion of studies performed in different parts of the world and published in other languages.

Study Screening

First, a search conducted by an independent librarian will identify potentially eligible studies based on predefined keywords that consider the inclusion and exclusion criteria. The results from this initial search will undergo deduplication: Duplicates will be identified and removed using EndNote (version 21; Clarivate), using the Bramer et al [37] guidelines. The remaining studies will then be imported into Covidence [38]. There, data will be screened in two steps: (1) title and abstract screening, and (2) full-text screening. During the first step, at least 2 reviewers will independently review the titles and abstracts, blinded to the authors' names, and each other's review decisions (ie, double-blinded) [38]. After, the potential articles will have their full text screened, filtered, and categorized according to the predefined inclusion and exclusion criteria. In the event of disagreements between the 2 reviewers, at either stage of the review process, a third reviewer (LT) will be consulted to reach a consensus.

Data Extraction

The data extraction will use a standardized data extraction form elaborated by the research team. The form is designed to capture study information such as (1) identification: study ID, authors, year, country, publication type, and analysis type (qualitative, quantitative, and mixed-methods); (2) characteristics: research participants' characteristics, age, sample size, intervention description, digital platform or software, and the medium used; (3) results: engagement and completion measurements, results and findings presented in qualitative and quantitative data, and measurement tools.

Other information may be added as the research team considers it relevant to the analysis. One reviewer will independently extract the data, and a second reviewer will check it for accuracy and completion. The extracted information will be organized in a previously formatted table in Microsoft Excel. Qualitative data regarding results and findings will also be collected. The qualitative data will be analyzed using NVivo (version 14; Lumivero) afterward.

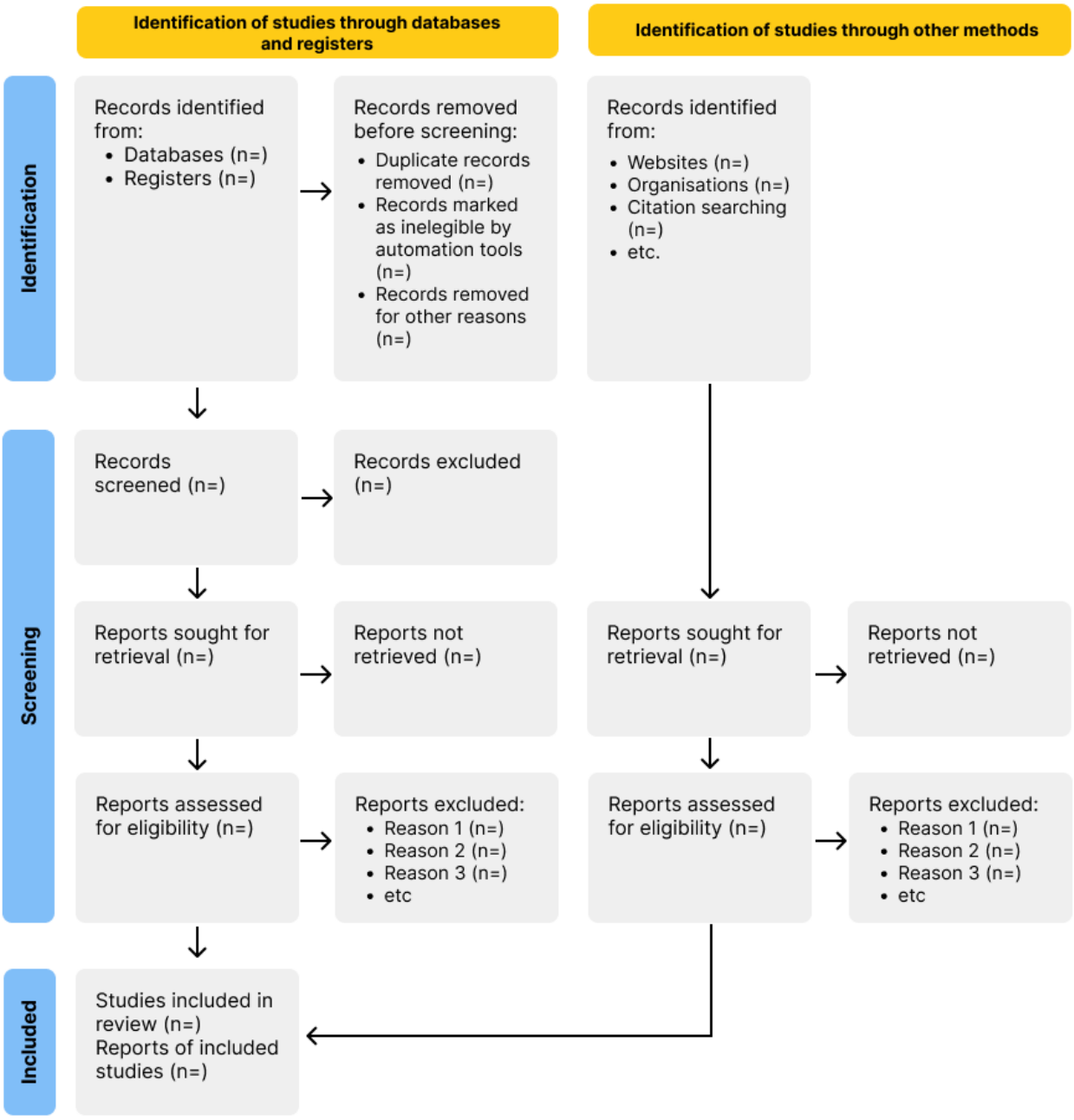
Quality Assessment and Appraisal

The study plans to use the mixed-methods assessment tool (MMAT) for quality assessment and critical appraisal [39]. MMAT provides a systematic approach to assessing quality criteria on a variety of study designs, such as qualitative studies, quantitative randomized controlled trials, quantitative nonrandomized, quantitative descriptive, and mixed-methods studies [40]. Using MMAT, we will evaluate the studies' clarity of the research question, appropriateness of the study design, data collection methods, data analysis, and interpretation of results.

Data Analysis and Synthesis

The study selection procedure will be visualized through the PRISMA 2020 flow diagram, as seen in Figure 2 [41].

Figure 2. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram.



Data related to the identification of a given study and its characteristics will be organized in summary tables. As the review question stipulates the inclusion of a wide range of research designs, including qualitative and quantitative designs, the main results from our investigation will be organized into major themes and subthemes, and key findings on terms will also be presented. If significant differences and patterns arise, such as those related to health conditions, age, or digital literacy, thematic clusters for analysis will be delineated. Since the data will potentially arise from diverse study designs, quantitative data will be submitted to a data transformation process to be qualitized to be converted into qualitative data in the form of themes and categories and afterward summarized in a narrative synthesis to allow further integration with qualitative data [35,42,43]. Once qualitative and quantitative data are integrated, they will be compiled through a thematic analysis in order to identify the main concepts regarding engagement and retention. The codes for this investigation will be developed by one of the reviewers and checked by at least 1 member of the research team. The codes will be built using the Persuasive System Design framework developed by Oinas-Kukkonen and Harjumaa as a basis [44]. Kelders et al [25] have already applied this framework in the digital health area. A total of 2 independent reviewers will conduct the coding, and discrepancies and new codes will be discussed between the 2 reviewers. If no agreement is reached, a third reviewer will be consulted to reach a consensus. Afterward, the major themes and subthemes will be summarized in a narrative synthesis. One of the authors will compose the narrative synthesis, and a second author will assess and provide appraisal.

Dissemination Strategy

The results of this study will be disseminated as a scientific publication in a peer-reviewed journal and presented at conferences. Plain-language summaries will also be produced to share in various channels, such as social media, ResearchGate, and technology and health care websites.

Ethical Considerations

According to the Ethical Review Data (2003:460) by the Swedish Ethical Review Authority, ethical approval will not be required for this research.

Results

As of June 2024, the literature review has conducted 2 pilot searches to test and refine keywords and verify the initial quality of results. The results are expected to be published as a systematic literature review and submitted for publication in June 2025.

Discussion

Principal Findings

In light of the potential benefits of technology in clinical research, DH intervention design demands further investigation, to mediate the relationship between research participants and the technology. As highlighted by Johnson [45], connected technologies have provided many new opportunities in clinical research in recent years, such as increasing research awareness, recruitment options, and delivering interventions and treatments. Achieving a high rate of participation required to ensure the quality of an investigation is still a challenge. To meet these opportunities, CRI researchers and developers becoming more aware of the importance of developing adequate software for research participants to expand intervention. Although a "user-centric" approach has increased through participant-centered initiatives, digital clinical research is still on the journey to find ways to reduce the time and labor requirements that hinder participant involvement [14,46]. Offering a proper setting to a plurality of participants is fundamental to guaranteeing clinical research quality; otherwise, CRI risks increasing health care inequalities and disparities. DH interventions that do not consider socioeconomic factors such as financial situation, race, ethnicity, age, education, and digital literacy present higher chances of producing intervention-generated inequalities, increasing the digital divide, and may only benefit the already more advantaged populations [6,9,47].

Intervention researchers have long experimented with strategies for engagement and retention. Intervention factors like acceptability and feasibility of devices and technology, system usability, visual design, content, and adaption to literacy levels have been found to affect participant behaviors. These factors commonly influence access conditions by minimizing attrition but do not necessarily guarantee engagement, retention, and adherence. Importantly, engagement and retention may be promoted by factors that pertain to the particular characteristics of the digital platforms and software. Here are included platform usability and design, but also and others are research-based strategies, such as compensation, incentives, or rewards [21]. Interaction features can also incentivize participant's engagement and retention. These could be in the form of (1) gamification, (2) reminders or notifications, (3) social support provided within the DH intervention, (4) personalization, and (5) content tailored to participants' physical and cognitive abilities [21,25,26]. Understanding how platform design choices interact with participant behavior in DH interventions has become a crucial consideration for intervention research.

Limitations

Summarizing the key DH platform factors that affect participant engagement and retention given the variability of intervention designs, target participant groups and DH platform mediums may be challenging. Given the heterogeneity of the reviewed studies, we may have to focus only on some participant populations or DH platforms or include only broad trends in the narrative synthesis. Preliminary research, however, showed that concepts like personalization and fit to participants' conditions and needs are commonly important design factors, as discussed in previous literature [11].

Implications

We foresee that this review will serve as a useful resource to those developing DH interventions, but may not be versed in DH platform design. By summarizing key platform design characteristics that affect participant behavior on the platform and, by proxy, the intervention, the review will be particularly relevant to intervention researchers.

Conclusions

Systematic reviews are considered one of the most informative sources of research evidence and have supported decision-making in health care in recent decades [40,48]. Acknowledging the relevance of this resource, this review aims to contribute to the growing field of digital clinical research and patient-centered design, providing a comprehensive reference for developing more engaging and effective digital platforms and software for clinical research.

Acknowledgments

The authors would like to thank Görel Sundström for assisting with the search strategy.

This work was supported by U-CARE, which is a strategic research environment funded by the Swedish Research Council (dnr 2009–1093).

Data Availability

Data sharing is not applicable to this article as no datasets were generated or analyzed during this study.

Authors' Contributions

LT, AK, and MH contributed to the idea conception. LT wrote the initial manuscript draft. Manuscript revision was performed by LT, AK, MH, and MIM, Visualization was done by LT. All authors reviewed and edited the manuscript and approved the final version of the manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
String searches.
[PDF File (Adobe PDF File), 135 KB - resprot_v14i1e65099_app1.pdf]

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Abbreviations

CRI: clinical research informatics
DH: digital health
MMAT: mixed-methods assessment tool
MMSR: mixed-methods systematic review
PEO: population-exposure-outcomes
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PROSPERO: Prospective Register of Systematic Reviews

Edited by A Schwartz; submitted 09.08.24; peer-reviewed by L Uchtmann; comments to author 08.10.24; revised version received 22.10.24; accepted 12.11.24; published 03.01.25.

Please cite as:
Terceiro L, Mustafa MI, Hägglund M, Kharko A
Research Participants' Engagement and Retention in Digital Health Interventions Research: Protocol for Mixed Methods Systematic Review
JMIR Res Protoc 2025;14:e65099
URL: https://www.researchprotocols.org/2025/1/e65099
doi:10.2196/65099
PMID:

Protocol

Value Cocreation and Codestruction in Digital Health Services: Protocol for a Systematic Review

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Abstract

Background: To successfully design, develop, implement, and deliver digital health services that provide value, they should be cocreated with patients. However, occasionally, the value may also be codestructed. In the field of health care, the concepts of value cocreation and codestruction still need to be better established within emerging digital health services. Studying these concepts is essential for developing effective and sustainable patient-centered care.

Objective: The aim of the study is (1) to understand the antecedents, decisions, and outcomes of value cocreation and codestruction in digital health services, (2) to define the dynamics between value cocreation and codestruction, and (3) to map future research areas of value cocreation and codestruction within digital health services.

Methods: The systematic review will be conducted in accordance with the Joanna Briggs Institute methodology for mixed method systematic reviews and the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement. The review considers scientific qualitative, quantitative, or mixed method studies published in English, Finnish, or Swedish that concern either value cocreation or codestruction in digital health services. Studies focusing on physical robotics and online health communities, as well as non–peer-reviewed and nonscientific papers, will be excluded. The searches were conducted using Scopus and MEDLINE during this protocol creation. Critical appraisal will be done using suitable checklists for qualitative, quantitative, and mixed method studies. The review will adhere to a convergent integrated approach as outlined in the Joanna Briggs Institute methodology for mixed methods systematic reviews.

Results: The searches resulted in a total of 837 records. The antecedents, decisions, and outcomes of value cocreation and codestruction in the context of digital health services will be described in a finalized systematic review. In the outcomes, our main interest is the effect on patient outcomes and experiences and professional experiences.

Conclusions: Since our study involves diverse scientific fields, there is a risk that our search does not capture all relevant papers. To mitigate this risk, we used 2 large databases for the searches. In addition, the value cocreation or codestruction terms may not have been used in all studies focusing on the collaborative roles of patients and providers, especially in the medical field, and that may be difficult to capture. The review reveals the current understanding of value cocreation and codestruction in digital

health services and shapes the research agenda for these phenomena. Value cocreation can be used to both design and efficiently use digital health services trying to maximize the value for patients.

International Registered Report Identifier (IRRID): DERR1-10.2196/63015

(JMIR Res Protoc 2025;14:e63015) doi:10.2196/63015

KEYWORDS

value cocreation; value codestruction; telemedicine; eHealth; systematic review

Introduction

Value cocreation and customers' interactive roles in the service exchange have been essential to understanding how value is created in services [1]. Rapid technological advances and digital transformation are transforming the context in which value is created [2]. Health care services had a significant transformation as digital health services rapidly expanded during the COVID-19 pandemic [3,4]. Digital health services can be defined as the use of information and communication technologies in health care products, services, and processes [5]. Digital services, including telemedicine interventions, mobile health apps, and remote monitoring devices, have been suggested as a potential solution to tackle issues related to accessibility, availability, and health care costs [6,7]. In addition to the technical development, it also changes the way of thinking and how services are provided and perceived [4].

Cocreation, a burgeoning paradigm within management literature, facilitates the joint creation of value by enterprises and consumers through interactive processes [8]. Since the onset of the 21st century, the concept of cocreation has proliferated extensively, evidenced in scholarly discourse and empirical inquiries, thereby challenging established tenets of capitalist economies. In such economies, value traditionally tends to be predetermined prior to market transactions [8,9]. Health care is a complex service where defining and operationalizing value presents significant challenges [10,11]. Since Porter [12] introduced the idea of measuring health care value as patient-relevant outcomes per costs associated with the health problem, the concept has been widely discussed for its potential to unify the objectives of various stakeholders [11]. In the context of digital health services, value may be more closely related to outcomes and experiences, with costs being more pertinent at the system level.

From the standpoint of cocreation, suppliers and customers are no longer perceived as adversaries but rather as collaborators engaging with each other to foster the emergence of novel business prospects [13]. During the last decade, Yi and Gong [14] established the significance of value cocreation behavior, which provides a multidimensional framework encompassing diverse value cocreation activities, such as information seeking, information sharing, responsible behavior, and personal interaction, that help explain how customers and firms, or patients and health care providers in this case, interact and collaborate.

Additionally, the digitalization of services within health care ecosystems is altering how value is created, delivered, experienced, and evaluated [15,16]. Understanding value cocreation and the interactive roles of customers in the service exchange is crucial for comprehending how value is created in services [1], with value cocreation being conceptualized as a joint problem-solving process [17]. For instance, value cocreation in digital health services can be depicted through customer engagement, encompassing emotional, active, and cognitive dimensions [18].

However, value is not always cocreated. Value codestruction signifies that not all interactions and relationships yield positive or value-creating results; occasionally, these engagements may even lead to adverse outcomes [19,20]. Value codestruction refers to an interactive process between service systems that leads to a reduction in the well-being of at least 1 of the systems, which can affect either individuals or organizations depending on the nature of the service system [20]. For example, value codestruction may manifest in the inability to search for, understand, and use health information gathered on the web [21]. Additionally, the assumption that telemedicine can negatively impact doctor-patient relationships inevitably leads to value-in-use destruction [21].

As digital services differ significantly from traditional services, there is a need to understand how to enhance value cocreation between a service provider and its users in digital services [22,23]. Tuunanen et al [23] identified 5 mechanisms to support value cocreation in the design of digital services, namely social use, customer orientation and decision-making, service experience, service use context, and customer values and goals.

In response to evolving population needs, it is evident that the role of patients within digital health services and health care at large has transitioned toward a collaborative partnership between professionals and patients [24,25]. According to Huber et al [26], the definition of health is also changing from "complete mental, physical, and social well-being" toward "the ability to self-manage and adapt." According to van Druten et al [27], a similar multifaceted approach to Huber's concept of positive health was shared by many perspectives. Nevertheless, upon closer examination, it was observed that the core elements of positive health, namely "the ability to adapt and to self-manage," were also acknowledged in other health concepts, regardless of perspective. These health concepts described "the ability to adapt" as, for instance, adjusting to changing physical conditions like aging, illness, or disability, maintaining emotional balance, and viewing health as a dynamic state requiring adaptation to circumstances. "The ability to self-manage" was often described as autonomy or independence. Through the value cocreation process, professionals and patients can make a significant contribution to health outcomes as partners [28]. For example, patients can provide perspectives on areas of the care process

that are invisible to health care professionals [29,30]. Previous literature has discussed many consequences of value cocreation related to health outcomes, service experience, perceived service quality, and service engagement [31].

While value cocreation has also been studied in health care, less attention has been given to the investigation of value codestruction [29,32]. As the field of health care is constantly becoming more digitalized, examining value cocreation and value codestruction in digital services would provide valuable insights into developing such services. Peng et al [31] conducted a systematic review of value cocreation in health care and digital services before the COVID-19 pandemic. They also encouraged researchers to explore further opportunities for value cocreation in both web-based and hybrid environments. Even so, the review by Peng et al [31] did not address value codestruction, which, in conjunction with value cocreation, could aid in enhancing the efficiency of digital health services. Several authors have highlighted the necessity of gaining a more comprehensive understanding of value codestruction and integrating it with the research on value cocreation [33,34]. Considering the pandemic's impact on digital service expansion [3,4], increasing resource constraints due to rising chronic illnesses, and aging populations [35,36], conducting a new systematic literature review could provide a contemporary perspective on value cocreation in health care. Furthermore, this review aims to provide a more comprehensive understanding of value codestruction.

So as to gain a more current understanding of both value cocreation and value codestruction in digital health services, this review seeks to identify scientific studies published between 2020 and 2024, using the Joanna Briggs Institute's (JBI) guidance for mixed method systematic reviews [37] and adhering to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) checklist for reporting systematic reviews [38] The objectives of the review will be (1) to understand the antecedents, decisions, and outcomes (ADO) of value cocreation and value codestruction, (2) to define the dynamics between value cocreation and value codestruction in digital health services, and (3) to map future research areas of value cocreation and value codestruction within digital health services. To answer the first research question, this review uses a systematic literature review framework, namely, the ADO framework by Paul and Benito [39]. The ADO framework aims to identify the known aspect of any phenomenon, which in the case of this review is value cocreation and value codestruction in the context of digital health services. Our research questions are (1) What are the ADO of value cocreation and value codestruction in digital health services? (2) What are the dynamics between value cocreation and value codestruction in digital health services? (3) What are the most promising future research areas in value cocreation and value codestruction within digital health services?

Methods

Overview

The systematic review will be conducted in accordance with the JBI methodology for mixed method systematic review [37] and the PRISMA statement [38,40] (Multimedia Appendix 1). This protocol has been registered in PROSPERO (International Prospective Register of Systematic Reviews; 549303). During this review protocol, the searches have been conducted, but the screening, quality assessment, and analysis will be carried out in the finalized systematic review.

Search Strategy

Using the search strategy developed by Peng et al [31] as a foundation, adjustments were made to include value codestruction. The search strategy aimed to identify peer-reviewed scientific studies and was conducted in 3 steps. First, to ensure an optimal search strategy for both value cocreation and value codestruction, an initial limited search of MEDLINE and Scopus was conducted on May 21, 2024, which resulted in 48 and 247 papers, respectively. MEDLINE and Scopus were selected since they collectively provide extensive coverage of publications on digital health services, value cocreation, and value codestruction. Second, relevant papers were identified through title, abstract, and index term analysis. An information specialist was consulted during the development of the final search strategy. Keywords were truncated as necessary, and index terms such as MeSH were used in MEDLINE (Multimedia Appendix 2). Additionally, the reference lists of all included studies will be screened to identify additional relevant studies.

Eligibility Criteria

This study will include studies that investigate either value cocreation, value codestruction, or both in digital health services. This review will consider scientific qualitative, quantitative, or mixed method studies. Papers published in English, Finnish, and Swedish will be eligible for inclusion. Only papers published between January 1, 2020, and the present (June 2024) concerning value cocreation were considered, as an earlier review covered the period from 2008 to 2019 [31]. Regarding value codestruction, the limitation period extends from January 1, 2008, to December 31, 2008, since the earlier review did not address value codestruction. Studies focusing on physical robotics, as well as non–peer-reviewed and nonscientific papers, will be excluded.

Study Selection

The results of the search are presented in a PRISMA flow diagram [38]. All citations identified through the described search strategy were compiled and uploaded into Rayyan (Al Rayyan Company), which was also used to remove duplicate entries. Titles and abstracts will then undergo independent screening by 2 team members (NH and JP) using predefined inclusion and exclusion criteria. For papers lacking abstracts, the full text will be obtained. Following the title and abstract screening, potentially relevant studies will be retrieved in full. Two independent reviewers (NH and JP) will thoroughly assess these studies and determine their suitability based on the inclusion criteria. Exclusion reasons will be documented for studies that do not meet the inclusion criteria. Any discrepancies during the study selection or any other process will be resolved through discussion or by consulting a third team member (EL

and PT). All search methods, strategies, and sources will be detailed or named in the final report, ensuring replicability.

Assessment of Methodological Quality

Before being included in the review, papers will undergo evaluation by 2 separate reviewers (EL and M Vanhanen) to ensure methodological soundness. We will use the JBI checklists for qualitative and quantitative studies and the Mixed Methods Appraisal Tool for mixed method studies [41]. In cases where necessary, authors of papers will be contacted to request missing or additional data to ensure clarity. The outcomes of critical appraisal will be presented both in narrative form and in a table format. Data extraction and synthesis will be conducted for all studies, irrespective of their methodological quality assessment outcomes, whenever feasible.

Data Extraction and Synthesis

Two independent reviewers (EL and M Vanhanen) will extract both quantitative and qualitative data from the studies included in the review. The extracted data will encompass specific details about populations, study methods, phenomena of interest, context, and outcomes relevant to the review questions. Quantitative data will include outcomes derived from descriptive and inferential statistical tests. Additionally, qualitative data will comprise verbatim themes or subthemes accompanied by corresponding illustrations and will be assigned a level of credibility. Authors of papers will be contacted up to a maximum of 2 times to request missing or additional data, as necessary.

Data Transformation

The quantitative data will undergo a process of "qualitization," which entails transforming it into textual descriptions or narrative interpretations that directly address the review questions.

Data Synthesis and Integration

This review will adhere to a convergent integrated approach as outlined in the JBI methodology for mixed methods systematic reviews. This approach involves integrating the qualitized data with the qualitative data. The assembled data will be categorized and pooled based on similarity in meaning, ultimately generating a set of integrated findings presented as the line of action statements. We will classify the data using the ADO framework [39]. Additionally, we will synthesize the current knowledge of each dimension and formulate a future research agenda based on the findings.

Ethical Considerations

Since concept analyses solely rely on secondary publicly available data sourced from primary research studies, there is no requirement for research ethics approval.

Validity and Rigor

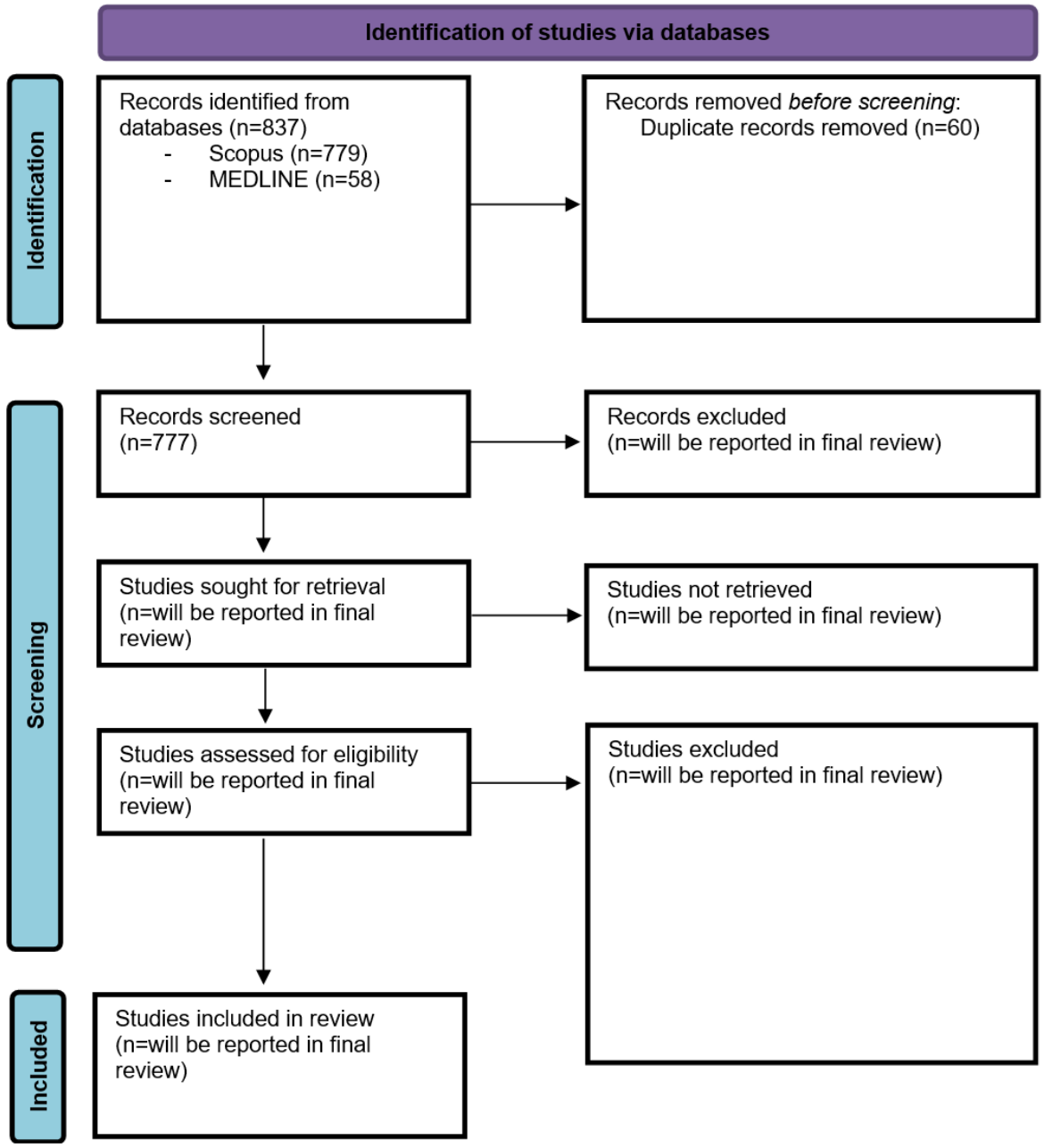
The following activities will be performed to enhance the review's validity and rigor:

1. Method: The systematic review will be conducted following the JBI guidelines [37] and following the PRISMA statement [38].
2. Search: To increase the reliability of the review, an information specialist with expertise in health care, value cocreation, and value codestruction will be consulted. Additionally, several database sources will be included in the final search to ensure the richness of the data to be analyzed.
3. Screening, data extraction, and synthesis: Each of the previously mentioned phases will be conducted independently by at least 2 independent team members (NH and JP), which will enhance the reliability of the review.
4. Process: The research team members (EL, TT, M Vanhanen, NH, JP, MJ, M Vesinurm, and PT) will continuously review the paper during ongoing meetings throughout the process.

Results

The review started in May 2024 and will be completed in a time frame of 8 months. This time phase includes the following phases: screening, data extraction, quality assessment, and data synthesis. The literature search was conducted entirely during the review protocol process and reported in the PRISMA diagram. The final search in MEDLINE and Scopus on June 6, 2024, resulted in 58 and 770 papers, respectively (Figure 1). As Peng et al [31] omitted value codestruction in their search, a supplementary search focusing exclusively on value codestruction was conducted on September 19, 2024, covering the years 2008 to 2019. This search yielded 9 papers from Scopus and none from MEDLINE. In total, 837 records were detected. The systematic review is anticipated to be ready for submission by December 2024.

Figure 1. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram.



Discussion

Principal Findings

Our review will reveal the current understanding of value cocreation and codestruction in digital health services and shape the research agenda for these phenomena. In their review, Peng et al [31] focused on studies published prior to the COVID-19 pandemic, a period after which the number of digital health services has significantly increased. Consequently, our review will provide the most recent insights into value cocreation and value codestruction within digital health services. The ADO framework [39] assists in producing a knowledge map outlining the associations between ADO of value cocreation and codestruction in the context of digital health services. The ADO of value cocreation and codestruction will be described. In the outcomes, our main interest is the effect on patient outcomes and experiences and professional experiences. The more detailed results will be determined based on the finalized review.

Value cocreation can be used in both designing as well as the efficient use of digital health services trying to maximize value for patients. In other digital services, value cocreation and codestruction have been studied more thoroughly, as most of the services nowadays are digital, and the world has already been described as digital-first [42].

As the field of health care is constantly more digitalized, examining value cocreation and codestruction in digital services would provide valuable insights into developing such services. To support the cost-effectiveness of the services and try to minimize the effects of digital exclusivity, it is crucial to understand value cocreation and codestruction better in digital health services.

Strengths and Limitations

Since our study is crossing the scientific fields, there is a risk that our search does not capture all relevant papers. To mitigate this risk, we include multiple databases for the searches. However, only peer-reviewed studies will be included in this review, which excludes gray literature [43]. In addition, the value cocreation or codestruction terms may not have been used in all studies focusing on the collaborative roles of patients and providers, especially in the medical field, and that may be difficult to capture.

Acknowledgments

The authors would like to thank Aalto University Library for consulting with the search strategy. Open access is funded by the Helsinki University Library.

Data Availability

The datasets generated and analyzed during this study are available from the corresponding author on reasonable request.

Authors' Contributions

The review protocol was conceived and supervised by EL and PT. EL, TT, MJ, M Vanhanen, NH, JP, M Vesinurm, and PT planned the review and formed the aim and research question. PT, NH, and JP developed the search strategy and conducted the search. EL, NH, JP, and PT screened papers. EL and PT drafted the main text. All authors contributed revisions.

Conflicts of Interest

None declared.

Multimedia Appendix 1
PRISMA-S (Preferred Reporting Items for Systematic reviews and Meta-Analyses Literature Search Extension) checklist.
[DOC File , 159 KB - resprot_v14i1e63015_app1.doc]

Multimedia Appendix 2
Search strategy.
[DOC File , 164 KB - resprot_v14i1e63015_app2.doc]

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Abbreviations

ADO: antecedents, decisions, and outcomes
JBI: Joanna Briggs Institute
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PROSPERO: International Prospective Register of Systematic Reviews

Edited by A Schwartz; submitted 11.06.24; peer-reviewed by R Arriaga; comments to author 04.09.24; revised version received 15.10.24; accepted 03.12.24; published 14.01.25.

Please cite as:
Laukka E, Tuunanen T, Jansson M, Vanhanen M, Hirvonen N, Palukka J, Vesinurm M, Torkki P
Value Cocreation and Codestruction in Digital Health Services: Protocol for a Systematic Review
JMIR Res Protoc 2025;14:e63015
URL: https://www.researchprotocols.org/2025/1/e63015
doi:10.2196/63015
PMID:

Protocol

Evaluating Online and Offline Health Information With the Patient Education Materials Assessment Tool: Protocol for a Systematic Review

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Abstract

Background: The Patient Education Materials Assessment Tool (PEMAT) is a reliable and validated instrument for assessing the understandability and actionability of patient education materials. It has been applied across diverse cultural and linguistic contexts, enabling cross-field and cross-national material quality comparisons. Accumulated evidence from studies using the PEMAT over the past decade underscores its potential impact on patient and public action.

Objective: This systematic review aims to investigate how the quality of patient education materials has been assessed using the PEMAT.

Methods: This review protocol follows PRISMA-P (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols) guidelines. PubMed, MEDLINE, Cumulative Index to Nursing and Allied Health Literature (CINAHL), APA PsycInfo, and Web of Science Core Collection will be searched systematically for articles published since September 2014. Two independent reviewers will conduct the search to yield a list of relevant studies based on the inclusion and exclusion criteria. Rayyan QCRI software will be used for screening and data extraction.

Results: The results will be included in the full systematic review, which is expected to start in September 2024 and be completed to be submitted for publication by early 2025.

Conclusions: The findings are expected to identify the quality of materials evaluated by the PEMAT and the areas under evaluation. This review can also highlight gaps that exist in research and practice for improving the understandability and actionability of the materials, offering deeper insights into how existing materials can facilitate patient and public action.

International Registered Report Identifier (IRRID): PRR1-10.2196/63489

(JMIR Res Protoc 2025;14:e63489) doi:10.2196/63489

KEYWORDS

patient education; health communication; health information; behavior change; understandability; actionability Patient Education Materials Assessment Tool; PEMAT; medical information; health literacy; patient education materials

Introduction

Patient education materials, such as brochures, websites, videos, and apps that provide health and medical information to patients and the general public, are used in various clinical and public health areas. Given the known relationship between health literacy and health outcomes [1], assessing the quality and usefulness of the materials to patients or general public is

worthwhile. Particularly, Healthy People 2030 emphasized organizational health literacy [2], which represents organizational competencies that enable people to access, understand, appraise, and use health information and services [3].

Therefore, medical institutions, companies, and government agencies providing health care information need to produce higher quality materials to support the health behaviors of patients and the general public.

A range of tools have been designed to assess the effectiveness of patient education materials. Garner et al [4] outlined a three-step process that characterizes the audience's interaction with such materials: (1) reading to the end, (2) constructing a coherent understanding, and (3) responding to the content. In response to these processes, they introduced an evaluation framework of readability, comprehensibility, and communicative effectiveness [4]. Among these 3 factors, readability formulas, which focus on the aspect of "reading to the end," have been used since the 1930s. Later, following the establishment of the concept of health literacy, comprehensibility indicators were developed to assess whether materials align with audience's health literacy demands. These indicators consider not only the wording of the material but also its structure and style; notable examples include suitability assessment of materials [5] and the CDC (Centers for Disease Control and Prevention) Clear Communication Index [6]. However, understanding the material alone is insufficient; a separate evaluation is necessary to determine whether audience can translate the material's content into actionable behavior.

The Patient Education Materials Assessment Tool (PEMAT) is a reliable and validated tool to evaluate and compare the understandability and actionability of patient education materials [7,8]. Understandability refers to the likelihood that the reader or viewer will be able to understand and explain the material's key messages. Actionability refers to the likelihood that the reader or viewer will know how to act on the information presented in the material. The PEMAT calculates a material's understandability and actionability scores as a percentage. There are 2 types of PEMAT: PEMAT-P for printable materials and PEMAT-A/V for audiovisual materials. The PEMAT consists of 26 items in total. For PEMAT-P, items 1-12 and 15-19 assess understandability, while items 20-26 evaluate actionability. For PEMAT-A/V, understandability is assessed using items 1, 3-5, 8-14, and 18-19, while actionability is evaluated with items 20-22 and 25. On the practical side, the PEMAT visualizes the challenges of materials to find the most understandable and actionable materials among the many available. It also supports experts in improving their materials. The original version of the PEMAT was developed in 2013 [7], and as of 2024, Brazilian Portuguese [9], Bahasa-Malay [10,11], Japanese [12], Chinese [13], and Turkish [14] versions are available. The PEMAT has been used to analyze materials for patients of various cultural and linguistic backgrounds, allowing quality comparisons of materials across clinical fields and nations. For example, our study on internet-based materials for Japanese patients with chronic kidney disease found that, unlike trends in English-speaking countries, materials published by for-profit companies were easier to understand and act upon than those published by public organizations [15].

Despite the large number of PEMAT analyses, to date, previous studies have not systematically integrated and compared the findings obtained by the PEMAT. In addition, scoping reviews have comprehensively introduced indicators for assessing the quality of health care information [16-18]; however, no systematic reviews have assessed the understandability and actionability of patient education materials using the PEMAT. This study reviews how the quality of materials has been assessed using the PEMAT in previous patient education materials. We pose the following research questions: "in which areas (eg, clinical areas, types of media, and target populations) have patient-education material quality assessment studies been conducted using the PEMAT?" "what is the degree of understandability and actionability of materials based on the PEMAT in previous studies?" and "what gaps in research and practice should be filled in the future? (eg, in which areas should understandability and actionability of materials be examined and in which areas should understandability and actionability be improved?).

Methods

Study Design and Registration

We designed the study protocol following the PRISMA-P (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols) guidelines [19]. A PRISMA-P checklist is available as Multimedia Appendix 1. Once this protocol is accepted for publication in a peer-reviewed journal and fixed, it will be registered with the International Prospective Register of Systematic Reviews (PROSPERO). We plan to begin the literature search on September 1, 2024, and complete the analysis by late 2024.

Literature Search

We will search the following databases: PubMed, MEDLINE, Cumulative Index to Nursing and Allied Health Literature (CINAHL), APA PsycInfo, and Web of Science Core Collection. We will search abstracts and titles using a combination of keywords related to previous studies: (PEMAT) OR (Patient Education Materials Assessment Tool) OR (understandability) OR (actionability) OR (comprehensibility). Since the development study of the original version of the PEMAT was published in September 2014, the inclusion period will be limited to September 2014 through September 2024. Details of search queries in each database are shown in Table 1. We will import all search results into Rayyan QCRI software to ensure a systematic literature selection process [20]. We will include all publications covered from the time the database search is initiated to the time of the final search. We will search the reference lists of identified eligible studies to supplement the database searches and identify any additional potentially eligible literature.

Table 1. List of search queries.

Database	Interface	Search queries
PubMed	NLM	("PEMAT"[All fields] OR "patient education materials assessment tool"[Title/Abstract] OR "understandability"[Title/Abstract] OR "actionability"[Title/Abstract] OR "comprehensibility"[Title/Abstract]) AND (2014/9/1:2024/6/30[pdat])
MEDLINE	Web of Science	(pemat) OR (AB patient education materials assessment tool) OR (AB understandability) OR (AB actionability) OR (AB comprehensibility) Limit - Publication date: 20140901-20240631
Web of Science	Web of Science	(ALL= (PEMAT))) OR AB=(patient education materials assessment tool)) OR AB=(understandability)) OR AB=(actionability)) OR AB=(comprehensibility)) Timespan: 2014-09-01 to 2024-06-30
CINAHL	EBSCOhost	(pemat) OR (AB patient education materials assessment tool) OR (AB understandability) OR (AB actionability) OR (AB comprehensibility) Limit - Publication date:20140901-20240631
APA PsycInfo	EBSCOhost	(pemat) OR (AB patient education materials assessment tool) OR (AB understandability) OR (AB actionability) OR (AB comprehensibility) Limit - Publication date:20140901-20240631

Inclusion and Exclusion Criteria

This proposed systematic review covers studies that analyzed health and medical information by the PEMAT. The inclusion and exclusion criteria are as follows (Textbox 1):

Textbox 1. Inclusion and exclusion criteria.

Inclusion criteria

Evaluating patient education materials or decision aids (brochures, website, videos, apps, social networking posts, and artificial intelligence tool responses).

Using the Patient Education Materials Assessment Tool (PEMAT) as an evaluation tool.

Published in peer-reviewed scientific journals.

Exclusion criteria

Intervention studies using PEMAT or brush up on existing educational materials by PEMAT.

Articles on the development of original and translated versions of PEMAT.

Systematic review or meta-analysis.

Patient education material itself.

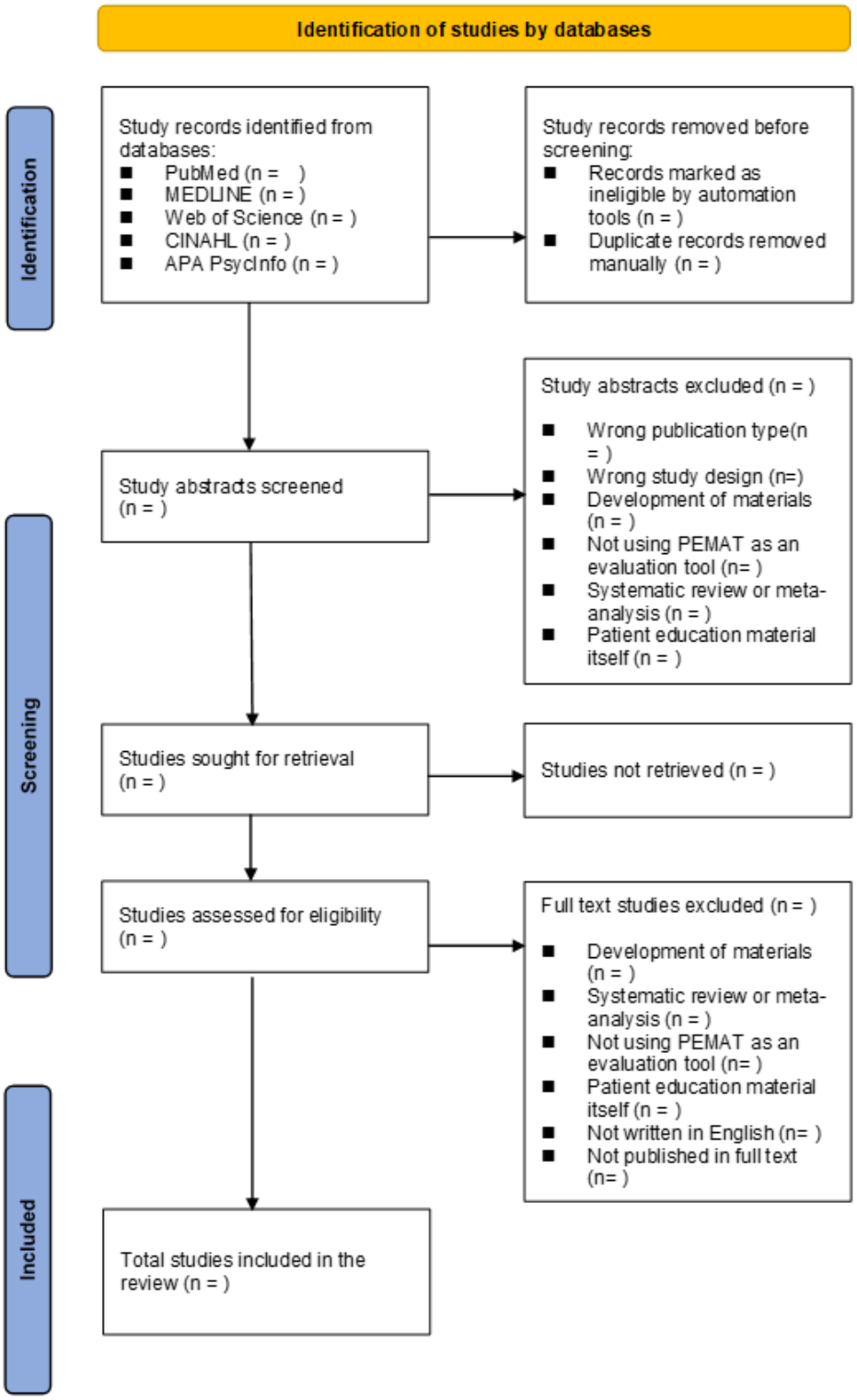
Non-English articles.

Not published in full text.

Screening of Studies

We will conduct study selection using Rayyan QCRI software [20]. Two independent reviewers [EF and ML] will screen the titles and abstracts of all studies initially identified according to the eligibility criteria. Disagreements will be resolved by consensus; the opinion of a third reviewer [HO] will be sought when necessary. A PRISMA-P flow diagram will outline the number of included and excluded studies in each stage of the study (Figure 1 [19]).

Figure 1. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram of the studies.



Data Extraction

The extracted data will include study characteristics (eg, author, year of publication, country, type of publication, and study design), material characteristics (eg, intended audience, language, number, media [eg, text, audio, and video], clinical field, and type of source), evaluation methods (eg, evaluation tools or indicators alongside the PEMAT, the evaluators' expertise, and material evaluation by the audience [if any]), and main results of the evaluation (eg, PEMAT scores, scores of other tools or indicators, quantitative or qualitative material evaluation by audience [if any]), and a summary of the characteristics of contributing studies will be tabulated in the above order.

Data Synthesis

The numerical summary will describe the characteristics of the included studies. We will summarize the findings in tables and

synthesize them in a descriptive, narrative review, using the framework to answer the research questions. We will use descriptive statistics (means, SDs, and proportions) to summarize the characteristics of the retrieved studies. PEMAT scores are expressed as 0%-100% and therefore, considered continuous variables. We will express the estimate of the PEMAT score as the mean difference with 95% CI.

We will conduct subgroup analyses based on material type, clinical field, and type of source as these group comparisons are essential to explore the determinants of material quality. We perform a test of normality when integrating the data. When data are normally distributed, we will use ANOVA for subgroup analysis. If significant differences are found, we will use Tukey multiple comparisons. When data are not normally distributed, we will use the Kruskal-Wallis test. For a post hoc comparison, a 2-arm comparison using the Mann-Whitney U test will be performed with Bonferroni adjustment. We will conduct all statistical analysis using R software (version 4.4.0; R Foundation for Statistical Computing).

For each study, we will assess heterogeneity using a tool for assessing Risk Of Bias due to Missing Evidence in a synthesis (ROB-ME) [21]. ROB-ME provides a systematic method for evaluating the risk of bias when particular methods or results within studies are missing from a meta-analysis due to the *P* value, magnitude, or direction of the study results. Although the studies included in this view are not systematic reviews in a strict sense, their authors have included multiple materials and conducted “reviews” based on certain indicators. The ROB-ME can be used to evaluate the appropriateness of the inclusion criteria and consistency of the description of the results in the included studies. The risk of bias will then be integrated with ROBVIS, a risk-of-bias assessment summary table [22].

Ethical Considerations

This study will be exempted from the Research Ethics Committee of The University of Tokyo Graduate School of Medicine and Faculty of Medicine as the studies under review are publicly accessible and do not involve patient records.

Results

The results will be included in the full systematic review, which started in December 2024 and be completed to be submitted for publication by early 2025.

Discussion

Principal Findings

Since the development of the PEMAT a decade ago, evidence of studies that have evaluated materials using the PEMAT has accumulated. This review is the first to systematically evaluate and analyze studies that have reviewed materials with the PEMAT, providing deeper insight into the potential of existing materials to support action for patients and the general public.

Limitations

This systematic review has several potential limitations. First, the limitations of the PEMAT itself include the fact that it is based on expert evaluation and therefore does not fully reflect the patient’s perspective. Second, the studies used different methods for measuring materials, with differences observed in the assessment approaches used alongside the PEMAT and in the methods for group comparisons. As such, they may have a high degree of heterogeneity. In addition, comprehensiveness may not be fully ensured as we exclude studies written in languages other than English. Despite these limitations, this review will present implications for improving the quality of health information targeted at patients and the general public.

Conclusions

We will carry out a systematic review to examine how the understandability and actionability of existing materials have been assessed using the PEMAT.

Acknowledgments

This work is supported by the Japan Society for the Promotion of Science KAKENHI (grant number 24K23676). We used generative AI, Grammarly, in a limited way, to clarify topic sentences and improve grammar, punctuation, and concision. We have reviewed each suggestion before adopting it. For additional quality control, we discussed professional proofreaders in Forte [23].

Data Availability

The datasets generated during and analyzed during this study will be available from the corresponding author on reasonable request.

Authors' Contributions

EF contributed to conceptualization, methodology, investigation, writing – original draft, and funding acquisition. TO handled methodology, writing – original draft, and writing – review and editing. ML managed investigation and writing – review and editing. HO performed investigation and writing – review and editing. TK contributed to writing – review and editing, resources, and supervision. All authors read and approved the final manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
PRISMA-P (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols) checklist.
[DOCX File , 35 KB - resprot_v14i1e63489_app1.docx]

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Abbreviations

CDC: Centers for Disease Control and Prevention
CINAHL: Cumulative Index to Nursing and Allied Health Literature
PEMAT: The Patient Education Materials Assessment Tool
PRISMA-P: Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols
PROSPERO: International Prospective Register of Systematic Reviews
ROB-ME: Risk Of Bias due to Missing Evidence in a synthesis

Edited by T Leung; submitted 26.06.24; peer-reviewed by Y Shan, JG Lee; comments to author 28.11.24; revised version received 02.12.24; accepted 05.12.24; published 15.01.25.

Please cite as:
Furukawa E, Okuhara T, Liu M, Okada H, Kiuchi T
Evaluating Online and Offline Health Information With the Patient Education Materials Assessment Tool: Protocol for a Systematic Review
JMIR Res Protoc 2025;14:e63489
URL: https://www.researchprotocols.org/2025/1/e63489
doi:10.2196/63489
PMID:

Protocol

Interventions to Maintain HIV/AIDS, Tuberculosis, and Malaria Service Delivery During Public Health Emergencies in Low- and Middle-Income Countries: Protocol for a Systematic Review

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Abstract

Background: Although existing disease preparedness and response frameworks provide guidance about strengthening emergency response capacity, little attention is paid to health service continuity during emergency responses. During the 2014 Ebola outbreak, there were 11,325 reported deaths due to the Ebola virus and yet disruption in access to care caused more than 10,000 additional deaths due to measles, HIV/AIDS, tuberculosis, and malaria. Low- and middle-income countries account for the largest disease burden due to HIV, tuberculosis, and malaria and yet previous responses to health emergencies showed that HIV, tuberculosis, and malaria service delivery can be significantly disrupted. To date, there has not been a systematic synthesis of interventions implemented to maintain the delivery of these services during emergencies.

Objective: This study aimed to synthesize the interventions implemented to maintain HIV/AIDS, tuberculosis, and malaria services during public health emergencies in low- and middle-income countries.

Methods: The systematic review was registered in the international register for prospective systematic reviews. It will include activities undertaken to improve human health either through preventing the occurrence of HIV, tuberculosis, or malaria, reducing the severity among patients, or promoting the restoration of functioning lost as a result of experiencing HIV, tuberculosis, or malaria during health emergencies. These will include policy-level (eg, development of guidelines), health facility–level (eg, service rescheduling), and community-level interventions (eg, community drug distribution). Service delivery will be in terms of improving access, availability, use, and coverage. We will report on any interventions to maintain services along the care cascade for HIV, tuberculosis, or malaria. Peer-reviewed study databases including MEDLINE, Web of Science, Embase, Cochrane, and Global Index Medicus will be searched. Reference lists from global reports on HIV/AIDS, tuberculosis, or malaria will also be searched. We will use the GRADE-CERQual (Grading of Recommendations Assessment, Development, and Evaluation—Confidence in Evidence from Reviews of Qualitative Research) approach to report on the quality of evidence in each paper. The information from the studies will be synthesized at the disease or condition level (HIV/AIDS, tuberculosis, and malaria), implementation level (policy, health facility, and community), and outcomes (improving access, availability, use, or coverage). We will use the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) checklist to report findings and discuss implications for strengthening preparedness and response, as well as strengthening health systems in low- and middle-income countries.

Results: The initial search for published literature was conducted between January 2023 and March 2023 and yielded 8119 studies. At the time of publication, synthesis and interpretation of results were being concluded. Final results will be published in 2025.

Conclusions: The findings will inform the development of national and global guidance to minimize disruption of services for patients with HIV/AIDS, tuberculosis, and malaria during public health emergencies.

Trial Registration: PROSPERO CRD42023408967; https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=408967

International Registered Report Identifier (IRRID): PRR1-10.2196/64316

(JMIR Res Protoc 2025;14:e64316) doi:10.2196/64316

KEYWORDS

service availability; emergencies; tuberculosis; malaria; systematic reviews; health services; emergencies; HIV; AIDS; public health emergency; low- and middle-income countries; qualitative reviews; qualitative; policies; communities; health facilities; emergency; implement; implementation

Introduction

Background

The effective management of disasters requires deliberate investment across the phases of the disaster management cycle including mitigation or prevention, preparedness, response, and recovery [1]. In public health disaster management, several frameworks have been developed to provide a blueprint for investments to improve capacities for preparedness, response, and control of public health emergencies. The most widely applied framework is the World Health Organization (WHO) Joint External Evaluation of the International Health Regulations core capacities [2]. Others include the Global Health Security Index [3], the Health System Resilience Index [4], and the Epidemic Preparedness Index [5]. Taken together, the frameworks are comprehensive insofar as prescribing the mechanics or the hardware of a country's capacity to respond to and control health emergencies. For example, investment in building diagnostic capacity, establishing emergency operations centers, investing in health workers, and having a coordination structure are all critical for both preparedness and response to emergencies. However, little attention is paid to issues such as leadership and trust [6], gender and equity [7], and continuity of other services [8]. Health service maintenance during public health emergencies is critical to minimize preventable disease mortality and morbidity. During the 2014 Ebola outbreak in West Africa, there were 11,325 reported deaths due to the Ebola virus [9] and yet the disruption in access to care also caused more than 10,000 additional preventable deaths due to measles, HIV/AIDS, tuberculosis, and malaria [10]. The 2009 H1N1 pandemic increased the risk of adverse neonatal outcomes among pregnant women [11] and increased emergency department visits [12]. The COVID-19 pandemic also reduced overall health care use across 20 countries by about a third [13]. Furthermore, a systematic review of the effects of the COVID-19 pandemic on service delivery and treatment outcomes of people living with HIV [14] noted that there were challenges in accessing services in health facilities, loss of adherence to drugs, and increase in mortality due to COVID-19–related complications. And yet, several modeling studies [15,16] predicted that even brief interruptions to services such as antiretroviral therapy (ART) and condoms could increase HIV/AIDS–related morbidity and mortality in both the short and long term. Previous researchers have described this failure as the "tyranny of the urgent" [7,17] where the response to the public health emergency is prioritized over other health system functions like routine service delivery. In fact, prior to the COVID-19 pandemic, service continuity was not part of the standard operations of an emergency response [18], and the WHO monitoring and evaluation framework for assessing the effectiveness of a response did not have indicators for monitoring continuity of delivery of other services [19]. Our aim is not to contend that services are delivered during the emergency in the exact same way as in normal settings but to recognize the need for modifications and adaptations to service delivery to maintain demand for and continued access to services. Since the WHO International Health Regulations (2005) governing framework for global health security was established [20], the events that have been declared public health emergencies of international concern include the H1N1 pandemic influenza of 2009, Ebola outbreak in West Africa (2013-2015), Ebola outbreak in the Democratic Republic of Congo (2018-2020), Zika virus outbreak (2016), poliomyelitis (2014 to present), the COVID-19 pandemic [21], and the monkeypox outbreak (2022-2023). Previous studies have consistently shown the impact these public health emergencies have on access to HIV, tuberculosis, and malaria services [22-26]; in addition to the already high mortality and morbidity due to these diseases in low- and middle-income countries [27]. To date, there has not, to our knowledge, been a systematic synthesis of the interventions implemented to maintain the demand for and delivery of HIV, tuberculosis, and malaria services during emergencies. Recent reviews have primarily focused on the challenges [28] or the interventions [29] for the delivery of maternal and child health services during emergencies. The findings from this review will inform the development of national and global guidance on the maintenance of services for HIV/AIDS, tuberculosis, and malaria during public health emergencies.

Review Question

What interventions have been implemented to maintain the delivery of HIV/AIDS, tuberculosis, and malaria services during public health emergencies in low- and middle-income countries?

Objective

This study aims to identify strategies and interventions used to maintain the delivery of and access to HIV/AIDS, tuberculosis, and malaria services during public health emergencies of international concern including H1N1 2009, Ebola 2014, Zika 2015, and the COVID-19 pandemic in low- and middle-income countries to inform efforts for incorporating essential health services maintenance as a key preparedness and response strategy.

Methods

Study Design

The proposed systematic review will be conducted following the guidance given by the Cochrane Handbook for Systematic Reviews of Interventions [30]. The systematic review has been registered in the International Register for Prospective Systematic Reviews (PROSPERO Registration #CRD42023408967).

Inclusion Criteria

Concept

For purposes of this systematic review, we will define interventions as any strategies or activities undertaken to improve human health either through preventing the occurrence of HIV, tuberculosis, or malaria, reducing the severity of HIV, tuberculosis, or malaria among patients, or promoting the restoration of functioning lost as a result of experiencing HIV, tuberculosis, or malaria [31]. The interventions for the continuity of HIV/AIDS, tuberculosis, and malaria services will include policy-level interventions (eg, development of guidelines), health facility–level interventions (eg, service rescheduling), and community-level interventions (eg, community drug distribution). We will define service delivery in terms of improving access (physical and economic ability to use services), availability (physical presence of services), use (quantity of services used), and coverage (proportion of people who access a needed service) [32].

We will report on any interventions to maintain services along the stages of the HIV care cascade including improving testing, linkage to care, retention in care, ART adherence, and viral suppression [33]. Similarly, we will report any interventions implemented to maintain services along any of the stages of the tuberculosis care cascade including tuberculosis testing, linkage to treatment, retention in treatment, posttreatment survival, and achieving durable cure [34]. For malaria, we will include interventions aimed at prevention (eg, vector control), diagnosis, or treatment according to the WHO malaria guidelines [35]. We will include studies reporting any quantitative assessment of service delivery processes (screening, testing, linkage to care, retention in care, and ART adherence) or outcomes (viral suppression, cure, and case counts).

Context

This systematic review will include studies conducted to maintain delivery of and access to HIV, tuberculosis, and malaria services during public health emergencies of international concern in low- and middle-income countries according to the World Bank classification of countries by income level [36].

Types of Sources

This systematic review will consider both quantitative and qualitative studies that use cross-sectional, case-control, randomized and nonrandomized control trials, or cohort study designs. Other designs such as before and after, interrupted time series, and analytical observational studies will be considered for inclusion. Global disease-specific reports published by the Joint United Nations Programme on HIV/AIDS, WHO, or any other global bodies will be considered for inclusion. Editorials, preprints, abstracts, study protocols, commentaries, webinar papers, or opinion pieces will not be eligible for inclusion in the study. Studies conducted among animals or studies assessing the direct effects of emergencies will also be excluded as the review focuses on the maintenance of services for HIV/AIDS, tuberculosis, and malaria.

Search Strategy

A test search was conducted in PubMed to identify published papers on the maintenance of HIV, tuberculosis, and malaria services during public health emergencies. Thereafter, we developed a full search using words in the titles and abstracts of the papers we identified to be relevant (Multimedia Appendix 1). The search strategy will be used to identify relevant papers in each of the other databases. We will include only studies published in English. In addition, we will restrict the search to studies published between 2009 (when the H1N1 pandemic happened) and the end of March 2023.

Peer-reviewed study databases including MEDLINE, Web of Science, Embase, Cochrane, and Global Index Medicus will be searched. Two experienced librarians at Karolinska Institutet's University Library provided guidance about the choice of article databases that would provide the most relevant studies related to the research question. In addition, we will review reference lists of eligible studies, specific journals, and Google Scholar for relevant studies. Reference lists from Global Reports for HIV/AIDS, tuberculosis, or malaria will also be searched for relevant papers. The search will be guided by 2 experienced librarians from Karolinska Institutet's University Library. We anticipate that this search will be completed by the end of May 2023.

After the search is completed, the citations of all identified studies will be exported to Endnote X7 (Clarivate) and screened to remove any duplicates. Thereafter, the search will then be exported to Rayyan [37]—a web-based software that was developed by the Qatar Computing Research Institute and uses semiautomation to expedite the process of screening studies. Two reviewers will independently apply the inclusion and exclusion criteria and select studies based on the title and abstract. Disagreements between the individual judgments of the reviewers will be resolved through a discussion. After consensus building on studies based on titles and abstracts, additional studies may be excluded at full-text review.

Data Extraction

A data abstraction form will be used to obtain information from each of the relevant studies (Multimedia Appendix 2). The data to be extracted from each paper includes the year of publication, first author, year of study, journal or other publication source, country or countries, title, study design, target population, circumstance or outbreak, disease category (HIV/AIDS, tuberculosis, malaria, or a combination of these), list of measures implemented to maintain services, and limitations and strengths. The other information to be extracted about the interventions include the implementer (facility health workers and community health workers), the level at which the intervention is implemented (facility and community), the measure of assessment of the intervention (eg, number of people initiated on ART, number of people tested, and viral load coverage), and the type of indicator (process: number receiving drugs or outcome: number virally suppressed). The number of variables and the order in which they are presented will be adjusted depending on the amount of relevant information we find in the identified studies.

Risk of Bias or Quality Assessment

We will use several strategies to ensure the quality of studies included in the systematic review. First, we will involve 2 reviewers to screen the studies that will be included in the review. The reviewers will have experience in research related to HIV/AIDS, tuberculosis, and malaria service delivery as well as response and control of public health emergencies. In addition, since we do not anticipate quantitatively combining the relevant studies, we will use the GRADE-CERQual (Grading of Recommendations Assessment, Development, and Evaluation—Confidence in Evidence from Reviews of Qualitative Research) approach [38] to assess the quality of each paper. Each study will be assessed for quality in terms of the methodological quality, coherence, adequacy, and quality of the data collected and the relevance of results in line with the review question. The overall assessment of the quality of each study will be graded as either high, moderate, low, or very low.

Data Synthesis and Presentation

Findings from the systematic review will be presented using the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) checklist and flow diagram [39]. The data extracted for the review studies will be summarized and presented in tabular or graphic form as appropriate. The synthesis of the data will be conducted at various levels. These will include at disease or condition level (HIV/AIDS, tuberculosis, malaria, or a combination of these), at the implementation level (policy, health facility, and community), and outcomes (improving access, availability, use, or coverage of services)

Results

The initial search for published literature yielded 8119 studies from web-based databases. This search was conducted between January 2023 and March 2023. At the time of publication, synthesis and interpretation of results were being concluded. Final results will be published in 2025.

Discussion

Expected Findings

We will discuss the findings and their implications for strengthening both preparedness and response, as well as strengthening health systems in low- and middle-income countries. Specifically, we will discuss interventions that are common to the 3 disease programs and how such interventions can support the response to a public health emergency but also be scaled up to strengthen service delivery beyond the emergency. We will also discuss how the interventions have been assessed by comparing process indicators (such as number of people tested) and outcome indicators (such as number of people with viral suppression).

Previous literature has tried to synthesize the challenges [28] and interventions [29] for the delivery of specific service delivery programs like delivery of maternal and child health services during emergencies. However, the scope of essential health services is broad and includes services for noncommunicable diseases like diabetes and hypertension, services for older adults as well as health promotion and referral services. This protocol will provide a structure and framework for the synthesis of the literature for the continuity of essential health services more broadly beyond HIV/AIDS, tuberculosis, and malaria.

Limitations

The main limitation of the review will be the exclusion of studies conducted in languages other than English. In addition, the review will include only studies publishing information about interventions implemented during public health emergencies of international concern. However, a public health emergency need not be declared to be of international concern to cause disruption of access and delivery of HIV, tuberculosis, and malaria services. Nonetheless, the identified interventions will be transferrable to contexts in which an emergency is local and does not pose a threat to the international community. In addition, the development of the protocol followed the PRISMA-P (Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols) checklist (Multimedia Appendix 3).

Conclusions

The findings will inform the development of national and global guidance to minimize disruption of services for patients with HIV/AIDS, tuberculosis, and malaria during public health emergencies. The protocol will also inform studies conducted to synthesize interventions to maintain other health programs beyond HIV/AIDS, tuberculosis, and malaria.

Acknowledgments

The authors are grateful to Emma-Lotta Säätelä and Love Strandberg at Karolinska Institutet's University Library for the technical and administrative support during the process of conducting and refining the literature search from the various databases.

Authors' Contributions

SNK, RKW, and TA were involved in idea conceptualization. RKW, HL, NR, JMS, and TA were involved in the review of technical content and supervision. SNK wrote the first draft of the manuscript. All authors reviewed and approved the final version of the manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Search strategy.
[PDF File (Adobe PDF File), 209 KB - resprot_v14i1e64316_app1.pdf]

Multimedia Appendix 2
Data Abstraction Form.
[DOCX File , 31 KB - resprot_v14i1e64316_app2.docx]

Multimedia Appendix 3
Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols (PRISMA-P) checklist.
[PDF File (Adobe PDF File), 131 KB - resprot_v14i1e64316_app3.pdf]

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Abbreviations

ART: antiretroviral therapy
CERQual: Confidence in Evidence from Reviews of Qualitative Research
GRADE: Grading of Recommendations Assessment, Development, and Evaluation
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-analyses
PRISMA-P: Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols
PROSPERO: International Register for Prospective Systematic Reviews
WHO: World Health Organization

Edited by A Schwartz; submitted 15.07.24; peer-reviewed by HM Chun, N Ryan; comments to author 08.08.24; revised version received 20.08.24; accepted 12.12.24; published 15.01.25.

Please cite as:
Kabwama SN, Wanyenze RK, Lindgren H, Razaz N, Ssenkusu JM, Alfvén T
Interventions to Maintain HIV/AIDS, Tuberculosis, and Malaria Service Delivery During Public Health Emergencies in Low- and Middle-Income Countries: Protocol for a Systematic Review
JMIR Res Protoc 2025;14:e64316
URL: https://www.researchprotocols.org/2025/1/e64316
doi:10.2196/64316
PMID:

Protocol

Strategies to Improve Health Care Provider Prescription of and Patient Adherence to Guideline-Recommended Cardiovascular Medications for Atherosclerotic Occlusive Disease: Protocol for Two Systematic Reviews and Meta-Analyses of Randomized Controlled Trials

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Abstract

Background: In patients with atherosclerotic occlusive diseases, systematic reviews and meta-analyses of randomized controlled trials (RCTs) report that antiplatelets, statins, and antihypertensives reduce the risk of major adverse cardiac events, need for revascularization procedures, mortality, and health care resource use. However, evidence suggests that these patients are not prescribed these medications adequately or do not adhere to them once prescribed.

Objective: We aim to systematically review and meta-analyze RCTs examining the effectiveness of implementation or adherence-supporting strategies for improving health care provider prescription of, or patient adherence to, guideline-recommended cardiovascular medications in patients with atherosclerotic occlusive disease.

Methods: We designed and reported the protocol according to the PRISMA-P (Preferred Reporting Items for Systematic Review and Meta-Analysis-Protocols) statement. We will search MEDLINE, Embase, The Cochrane Central Register of Controlled Trials, PsycINFO, and CINAHL from their inception. RCTs examining implementation or adherence-supporting strategies for improving prescription of, or adherence to, guideline-recommended cardiovascular medications in adults with cerebrovascular disease, coronary artery disease, peripheral artery disease, or polyvascular disease (>1 of these diseases) will be included. Two investigators will independently review identified titles/abstracts and full-text studies, extract data, assess the risk of bias (using the Cochrane tool), and classify implementation or adherence-supporting strategies using the refined Cochrane Effective Practice and Organization of Care (EPOC) taxonomy (for strategies aimed at improving prescription) and Behavior Change Wheel (BCW; for adherence-supporting strategies). We will narratively synthesize data describing which implementation or adherence-supporting strategies have been evaluated across RCTs, and their reported effectiveness at improving prescription of, or adherence to, guideline-recommended cardiovascular medications (primary outcomes) and patient-important outcomes and health care resource use (secondary outcomes) within refined EPOC taxonomy levels and BCW interventions and policies. Where limited clinical

heterogeneity exists between RCTs, estimates describing the effectiveness of implementation or adherence-supporting strategies within different refined EPOC taxonomy levels and BCW interventions and policies will be pooled using random-effects models. Stratified meta-analyses and meta-regressions will assess if strategy effectiveness varies by recruited patient populations, prescriber types, clinical practice settings, and study design characteristics. GRADE (Grading of Recommendations, Assessment, Development, and Evaluation) will be used to communicate evidence certainty.

Results: The search was completed on June 6, 2023. Database searches and the PubMed "related articles" feature identified 4319 unique citations for title/abstract screening. We are currently screening titles/abstracts.

Conclusions: These studies will identify which implementation and adherence-supporting strategies are being used (and in which combinations) across RCTs for improving the prescription of, or adherence to, guideline-recommended cardiovascular medications in adults with atherosclerotic occlusive diseases. They will also determine the effectiveness of currently trialed implementation and adherence-supporting strategies, and whether effectiveness varies by patient, prescriber, or clinical practice setting traits.

Trial Registration: PROSPERO CRD42023461317; https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=461317; PROSPERO CRD42023461299; https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=461299

(JMIR Res Protoc 2025;14:e60326) doi:10.2196/60326

KEYWORDS

coronary artery disease; cerebrovascular disease; peripheral artery disease; polyvascular disease; underprescription; nonadherence; implementation strategy; adherence-supporting strategy; statins; antiplatelets; antihypertensives; guideline-recommended medications; implementation; atherosclerosis; patient adherence; RCT; randomized controlled trials; PRISMA

Introduction

Background

Atherosclerotic occlusive disease is common worldwide, increasing in global prevalence, and characterized by arterial stenosis (narrowing) and occlusion secondary to the buildup of lipid-rich plaque within arterial walls [1]. This disease may be further categorized by anatomic location, with atherosclerotic plaque buildup within the arteries of the extracranial and intracranial circulation, heart, and peripheral arteries being referred to as cerebrovascular disease (CVD), coronary artery disease (CAD), and peripheral artery disease (PAD), respectively [1]. An estimated 101 million [2], 197 million [3], and 113 million [4] individuals have CVD, CAD, and PAD worldwide, respectively. CVD, CAD, and PAD are associated with a significantly increased risk of hospitalization; need for coronary, carotid, or lower limb revascularization; major adverse cardiac events (MACEs) and major adverse limb events (MALEs); stroke; and cardiovascular and all-cause mortality [5,6].

International, evidence-based clinical practice guidelines strongly and consistently recommend that adults with CVD, CAD, PAD, and polyvascular disease be prescribed and take antiplatelets and statins (ie, hydroxymethylglutaryl-CoA reductase inhibitors) [7-11]. They also recommend antihypertensives for those patients with concurrent hypertension [7-11]. These recommendations are based on high-quality data from randomized controlled trials (RCTs) and systematic reviews and meta-analyses of RCTs that reported a significantly lower risk of MACE; MALE; need for coronary, carotid, and lower limb revascularization procedures; cardiovascular and all-cause mortality; and health care resource use when these patients are prescribed these medications [12-14].

Despite this, evidence suggests that many patients with atherosclerotic occlusive disease are not prescribed these medications adequately or do not adhere to them after prescription [15-18]. More specifically, only approximately 40% to 90% of patients with any form of atherosclerotic occlusive disease are prescribed any antiplatelet, 30% to 60% any statin, 40% to 60% any antihypertensive, and 10% to 40% all three guideline-recommended cardiovascular medications [15,16]. Studies also report that patient adherence percentages to these medications range from ~70% to 80% for antiplatelets, ~50% to 60% for statins, ~40% to 70% for antihypertensives, and ~20% to 40% for all three guideline-recommended cardiovascular medications [17,18]. Those with PAD are also significantly less likely to be prescribed these medications and adhere to them compared to those with CVD and CAD [19]. The increased frequency at which patients with PAD are underprescribed and nonadherent to guideline-recommended cardiovascular medications may partially explain why studies demonstrate persistently higher risks of cardiovascular-related hospitalization (eg, for atherothrombotic events), MACE, stroke, and cardiovascular mortality in patients with PAD compared to those with CVD or CAD [20].

To improve the use of guideline-recommended cardiovascular medications among patients with atherosclerotic occlusive disease, RCTs [21-48] have evaluated implementation strategies (interventions directed at the health system and health care providers) and adherence-supporting strategies (interventions aimed at patients directly) [49] to improve health care provider prescription of and patient adherence to guideline-recommended cardiovascular medications, respectively. However, the design [21-24], length of follow-up [24,27,31], setting [21,24-26], and implementation or adherence-supporting strategies examined [21,26,27,30-32,36,40-48] varies considerably across published trials. Existing RCTs have also examined implementation and adherence-supporting strategies aimed at improving prescription of or adherence to different medication classes (antiplatelets [25,28,29], statins [27-29], antihypertensives [25,28,42], or all guideline-recommended medications [27,29,43,44]) among patients with different diagnoses (CVD [31-33], CAD

[24,26,27], PAD [34,35], and polyvascular disease [36,37]). Further, the implementation and adherence-supporting strategies examined within published trials target different types of health care providers (ie, cardiovascular specialists [38,39] or noncardiovascular specialists [21,23]) and health care provider behaviors [31,33,38,40]. Given this interstudy heterogeneity, evidence-synthesis efforts are needed to interpret the results of the above RCTs collectively.

Rationale

Two updated, comprehensive, and methodologically rigorous systematic reviews and meta-analyses are needed to determine the effectiveness of implementation and adherence-supporting strategies for improving health care provider prescription of, and patient adherence to, guideline-recommended cardiovascular medications for atherosclerotic occlusive diseases. All forms of atherosclerotic occlusive disease (CVD, CAD, PAD, and polyvascular disease) will be examined within both systematic reviews as the underlying pathophysiology [50-52], and guideline-recommended cardiovascular medications for medical management of these diseases [7-11] are nearly identical. Further, patients with these atherosclerotic occlusive diseases tend to have similar demographics (ie, frequently past or current smokers, often male, and typically over 65 years of age) and comorbidities [53-55]. Finally, these diseases often coexist together [56,57], and similar prescribers are involved in their medical management [58-60]. The results of these systematic reviews will help identify promising implementation and adherence-supporting strategies for each and all classes of cardiovascular medications recommended for patients with atherosclerotic occlusive diseases. The systematic reviews will facilitate an effective comparison of implementation and adherence-supporting strategies by classifying them according to established taxonomies [61,62].

Objectives

The primary objectives of the two systematic reviews are to synthesize the effectiveness of implementation and adherence-supporting strategies for improving health care provider prescription of, and patient adherence to, guideline-recommended cardiovascular medications among patients with atherosclerotic occlusive disease, including CVD, CAD, PAD, or polyvascular disease. We conceptualized the desired behavior changes for our primary objectives and key actors involved in bringing about these desired behavior changes using the Action, Actor, Context, Target, Time (AACTT) framework [63] (see Table 1 for the underprescription systematic review AACTT framework and Table 2 for the nonadherence systematic review AACTT framework).

Table 1. AACTT[a] behavior specification framework [63] for the systematic review of implementation strategies for improving health care provider prescription of guideline-recommended cardiovascular medications to adults with atherosclerotic occlusive disease.

AACTT domains	Examples among the systematic review of implementation strategies for improving health care provider prescription of cardiovascular medications
Action	Prescription of guideline-recommended cardiovascular medications (antiplatelets, statins, or antihypertensives)
Actor	Health care providers responsible for managing patients with atherosclerotic occlusive disease
Context	Any setting where prescribers are responsible for prescribing medication to patients with atherosclerotic occlusive diseases (eg, primary care practices, tertiary academic hospitals, or pharmacies)
Target	Patients with an atherosclerotic occlusive disease (cerebrovascular disease, coronary artery disease, peripheral artery disease, or polyvascular disease) in whom one or more guideline-recommended cardiovascular medications is indicated
Time	During encounters between prescribers and patients with atherosclerotic occlusive disease

[a]AACTT: Action, Actor, Context, Target, Time.

Table 2. AACTT[a] behavior specification framework [63] for the systematic review of adherence-supporting strategies for improving patient adherence to guideline-recommended cardiovascular medications in adults with atherosclerotic occlusive disease.

AACTT domains	Examples among the systematic review of adherence-supporting strategies for improving patient adherence to cardiovascular medications
Action	Adherence to guideline-recommended cardiovascular medications for atherosclerotic occlusive disease (antiplatelets, statins, or antihypertensives)
Actor	Patients with a diagnosed atherosclerotic occlusive disease (cerebrovascular disease, coronary artery disease, peripheral artery disease, or polyvascular disease)
Context	Any setting in which patients (or their caregivers) are responsible for managing their own medications
Target	Patients who have been prescribed one or more guideline-recommended cardiovascular medications for management of their atherosclerotic occlusive disease by a health care professional
Time	Following prescription of guideline-recommended cardiovascular medications by a health care professional

[a]AACTT: Action, Actor, Context, Target, Time.

The AACTT framework [63] was developed to describe the action (ie, the behavior to change), actor (ie, who is involved in performing the behavior), context (ie, the physical, social, or emotional settings where the behavior is performed), target (ie, the person or people for or with whom the behavior is performed), and time (ie, when the behavior is performed) of

behaviors targeted for change in clinical practice. Describing desired behavior changes using the five elements of the AACTT framework [63] provides a concise overview of which individuals at what organizational levels need to do what differently to ensure the effective implementation of desired best practices. Secondary objectives are to determine whether (1) the effectiveness of implementation or adherence-supporting strategies at improving health care provider prescription of or increasing patient adherence to guideline-recommended cardiovascular medications for atherosclerotic occlusive disease varies by patient characteristics, prescriber traits, medication classes, atherosclerotic occlusive disease diagnoses, or clinical settings; and (2) improved health care provider prescription of or patient adherence to guideline-recommended cardiovascular medications improves patient outcomes and reduces health care resource use.

Methods

Registration and Reporting

This protocol was created following recommendations from the PRISMA-P (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols) statement [64] (a completed PRISMA-P checklist is provided in Multimedia Appendix 1). The protocols for the systematic reviews of implementation and adherence-supporting strategies for improving health care provider prescription and patient adherence were registered separately on PROSPERO (underprescription systematic review: CRD42023461317; nonadherence systematic review: CRD42023461299). We chose to create a single protocol paper describing the methods of the two planned systematic reviews and meta-analyses as we felt that their background, rationale, and methods overlap significantly. However, as scout searches suggested that one systematic review may include over 100 RCTs, we plan to report their results separately to summarize the results of these evidence syntheses in sufficient detail.

Eligibility Criteria

Eligibility criteria for the two systematic reviews were created according to the Population, Intervention, Comparison, Outcome, and Design framework [65]. Their specific inclusion and exclusion criteria are presented in Table 3 (underprescription systematic review) and Table 4 (nonadherence systematic review).

Table 3. Inclusion and exclusion criteria for systematic review examining implementation strategies for improving health care provider prescription of guideline-recommended cardiovascular medications to patients with atherosclerotic occlusive disease.

PICOD[a] framework domain	Inclusion criteria[b]	Exclusion criteria[c]
Population	• Prescribers (ie, physicians, nurse practitioners, or pharmacists) involved in the management of adults (≥18 years of age) with atherosclerotic occlusive disease (defined as cerebrovascular disease, coronary artery disease, peripheral artery disease, or polyvascular disease).	• >20% of the patient population had nonatherosclerotic cardiovascular disease (eg, aneurysmal disease). This 20% threshold was selected based on prior literature [66]. • Studies examining the prescription of nonguideline-recommended medications. • Prescribers involved in the management of people exclusively <18 years of age.
Intervention	• Any implementation strategy aimed at increasing health care provider prescription of guideline-recommended cardiovascular medications to patients with atherosclerotic occlusive disease. An implementation strategy will be defined as any "method or technique to enhance the adoption, implementation, and sustainability of a clinical program or practice" [49].	• Studies examining implementation strategies directed exclusively at patients.
Comparison	• Health care providers prescribing guideline-recommended cardiovascular medications to patients with atherosclerotic occlusive disease without the use of an implementation strategy, patients receiving the same implementation strategy at a lower intensity or shorter duration than the intervention group, or patients receiving a different implementation strategy than the intervention group.	• Studies examining implementation strategies directed exclusively at patients.
Outcomes	• Primary[d]: Effect estimates (or data required to calculate) describing differences in health care provider prescription between implementation strategy and control arms of each (ie, antiplatelets, statins, or antihypertensives) or all classes of guideline-recommended cardiovascular medications. • Secondary[d]: Effect estimates (or data required to calculate these) describing differences between patients in the implementation strategy and control arms regarding adverse clinical outcomes (eg, major adverse cardiac events, revascularization procedures, amputations, cardiovascular mortality, or all-cause mortality) and health care resource use outcomes (eg, emergency department visits, hospital admission or readmission, or length of hospitalization).	• Studies not reporting effect estimates (or data required to calculate) describing differences in guideline-recommended cardiovascular medication prescription between prescribers in the implementation strategy and control arms.
Design	• Study designs will include RCTs[e] and cluster-RCTs.	• Nonrandomized studies (eg, prospective cohort studies). • Studies published in abstract form only and unpublished studies (ie, gray literature).

[a]PICOD: Population, Intervention, Comparison, Outcome, and Design.

[b]Inclusion criteria formulated according to the Population, Intervention, Comparison, Outcome, and Design framework for posing clinical questions [65].

[c]Studies meeting one or more of the following criteria will be excluded.

[d]Effect estimates (and measures of variation, such as 95% CIs) will be extracted as reported and may include weighted mean differences or standardized mean differences for continuous outcomes; odds ratios, relative risks, and risk differences for binary outcomes; and hazard ratios for time-to-event data.

[e]RCT: randomized controlled trial.

Table 4. Inclusion and exclusion criteria for systematic review examining adherence-supporting strategies for improving patient adherence to guideline-recommended cardiovascular medications in patients with atherosclerotic occlusive disease.

PICOD[a] framework domain	Inclusion criteria[b]	Exclusion criteria[c]
Population	• Adults (≥18 years of age) with atherosclerotic occlusive disease (cerebrovascular disease, coronary artery disease, peripheral artery disease, or polyvascular disease) prescribed one or more guideline-recommended cardiovascular medications (eg, statins, antihypertensives, or antiplatelets).	• >20% of patients had nonatherosclerotic cardiovascular disease (eg, aneurysmal disease). This threshold was selected based on prior literature [66]. • Studies where ≥20% of patients were pediatrics (<18 years of age). • Studies examining adherence to medications not recommended within relevant clinical practice guidelines.
Intervention	• Any adherence-supporting strategy aimed at increasing adherence to guideline-recommended cardiovascular medication in patients with atherosclerotic occlusive disease. An adherence-supporting strategy will be defined as any "method or technique to enhance the adoption, implementation, and sustainability of a clinical program or practice" [49].	• Studies examining adherence-supporting strategies directed at health care providers or the health care system without components directed toward patients.
Comparison	• Patients taking guideline-recommended cardiovascular medications for atherosclerotic occlusive disease management without a concurrent adherence-supporting strategy, patients receiving a different adherence-supporting strategy than the intervention group, or patients receiving the same adherence-supporting strategy at a lower intensity or shorter duration than the intervention group.	• Studies examining adherence-supporting strategies directed at health care providers or the health care system without components directed toward patients.
Outcomes	• Primary[d]: Effect estimates (or data required to calculate) describing differences in medication adherence between adherence-supporting strategy and control arms of each (eg, antiplatelets, statins, or antihypertensives) or all classes of guideline-recommended cardiovascular medications. • Secondary[d]: Effect estimates (or data required to calculate these) describing differences between patients in the adherence-supporting strategy and control arms regarding adverse clinical outcomes (eg, major adverse cardiac events, revascularization procedures, amputations, cardiovascular mortality, or all-cause mortality) and health care resource use outcomes (eg, emergency department visits, hospital admission or readmission, or length of hospitalization).	• Studies not reporting effect estimates (or data required to calculate) describing differences in medication adherence between patients in the intervention and control arms.
Design	• RCTs[e] and cluster-RCTs.	• Nonrandomized studies (eg, case-control studies). • Unpublished studies (ie, gray literature) and studies published in abstract form only.

[a]PICOD: Population, Intervention, Comparison, Outcome, and Design.

[b]Inclusion criteria formulated according to the Population, Intervention, Comparison, Outcome, and Design framework for posing clinical questions [65].

[c]Studies meeting one or more of the following criteria will be excluded.

[d]Effect estimates (and measures of variation, such as 95% CIs) will be extracted as reported and may include weighted mean differences or standardized mean differences for continuous outcomes; odds ratios, relative risks, and risk differences for binary outcomes; and hazard ratios for time-to-event data.

[e]RCT: randomized controlled trial.

Guideline-recommended cardiovascular medications will be defined as any medications recommended within evidence-based clinical practice guidelines cited within the included studies. In studies where evidence-based clinical practice guidelines are not cited, guideline-recommended cardiovascular medications will be defined as antiplatelets (eg, aspirin or clopidogrel), statins, and antihypertensives (eg, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, β-blockers, calcium-channel blockers, or thiazide diuretics), as these medications are consistently recommended for individuals with CVD, CAD, PAD, and polyvascular disease across multiple evidence-based clinical practice guidelines [7-11].

Clinical Questions

Primary Clinical Questions

The primary clinical questions are as follows:

1. What is the effectiveness of different implementation strategies for improving health care provider prescription of guideline-recommended cardiovascular medications to

adults (≥18 years of age) with atherosclerotic occlusive disease, including CVD, CAD, PAD, or polyvascular disease?
2. What is the effectiveness of adherence-supporting strategies for increasing adherence to guideline-recommended cardiovascular medications among adults with atherosclerotic occlusive disease?

Secondary Clinical Questions

The secondary clinical questions are as follows:

1. Does the effectiveness of implementation and adherence-supporting strategies for improving health care provider prescription of and patient adherence to guideline-recommended cardiovascular medications to adults with atherosclerotic occlusive diseases vary by study design, prescriber characteristics, patient characteristics, atherosclerotic occlusive disease diagnosis, or clinical practice setting?
2. Does the use of implementation or adherence-supporting strategies aimed at improving health care provider prescription of or patient adherence to guideline-recommended cardiovascular medications to adults with atherosclerotic occlusive disease improve patient outcomes or reduce health care resource use?

Information Sources

We will search MEDLINE, Embase, The Cochrane Central Register of Controlled Trials, PsycINFO, and CINAHL from their inception. We will also use the PubMed "related articles" feature and manually search reference lists of included studies and relevant reviews identified during the search.

Search Strategy

Our electronic search strategy was designed in consultation with an information scientist. Using combinations of Medical Subject Headings (National Library of Medicine) or Emtree (Elsevier) terms and keywords, we constructed search filters covering the themes "atherosclerotic occlusive disease" and "medication prescription or adherence." These search filters were then combined with a validated RCT search filter from the Cochrane Handbook for Systematic Reviews of Interventions [67]. The search strategy was subsequently piloted and refined by adding additional thesaurus or indexing terms to the nonsearch filter themes when new, relevant citations were located during iterative pilot searches. The penultimate search strategies were peer-reviewed by another medical librarian in accordance with the Peer Review of Electronic Search Strategies framework [68] (see Multimedia Appendix 2 for final search strategies).

Study Selection and Management

Titles and abstracts of identified citations will be reviewed by two independent reviewers using Rayyan Systematic Review Software [69]. Citations deemed potentially relevant by either reviewer during title/abstract screening will be subject to independent full-text review using relevant inclusion and exclusion criteria (see Tables 3 and 4). Disagreements regarding study inclusion will be resolved by consensus.

Outcomes

The primary outcome for the underprescription systematic review will be the health care provider's prescription of each (eg, antiplatelets, statins, or antihypertensives) or all classes of guideline-recommended cardiovascular medications between the implementation strategy and control arms. The primary outcome of the nonadherence systematic review will be the patient adherence to each (eg, antiplatelets, statins, or antihypertensives) or all classes of guideline-recommended cardiovascular medications between the adherence-supporting strategy and control arms. Secondary outcomes for both systematic reviews will be differences in patient outcomes and health care resource use between the implementation or adherence-supporting strategy and control arms. Patient outcomes will include MACE [70] (defined as nonfatal myocardial infarction, stroke, or cardiovascular mortality), MALE [70] (defined as limb ischemia requiring revascularization or above-ankle lower limb amputation), stroke, revascularization procedures, amputations, patient-reported outcome measures, cardiovascular mortality, all-cause mortality, and any other patient-important outcomes reported by study authors. Health care resource use outcomes will include emergency department visits, hospital admission or readmission, length of hospitalization, and any other health care resource use outcomes reported by study authors.

Data Items and Selection Process

Two investigators will independently extract data using a predesigned electronic data extraction spreadsheet (see Tables 5 and 6 for data items to be extracted from the underprescription and nonadherence systematic reviews, respectively).

When potentially relevant articles published in languages other than English are identified, translators will be recruited to review the full texts and extract data if identified studies meet inclusion criteria. Effect estimates and their 95% CIs (or data required to calculate these measures) describing associations between implementation or adherence-supporting strategy use and primary and secondary outcomes will be extracted as reported in studies and may include weighted mean differences or standardized mean differences for continuous outcomes; odds ratios (ORs), relative risks (RRs), and risk differences for binary outcomes; and hazard ratios (HRs) for time-to-event data. Where studies do not provide effect estimates and their 95% CIs (or data required to calculate these measures) within the text or summary tables but summarize this information within figures, data will be extracted independently by two investigators using ImageJ software (National Institutes of Health) [72] and then their results will be averaged across investigators. Where data are not provided in the text, summary tables, or figures, these data will be sought from the supplementary materials of included trials or from trial registration repositories. In cases where data cannot be found using the above methods, study authors will be contacted in a final attempt to obtain all relevant study data. Discrepancies between investigators regarding data extraction will be resolved by consensus.

Table 5. Data items to be extracted from included studies when reported for systematic review examining implementation strategies for improving health care provider prescription of guideline-recommended cardiovascular medications to adults with atherosclerotic occlusive disease.

Data item theme	Items to be extracted
Study design	• Country of origin • Recruitment period • Study design (eg, RCT[a] or cluster-RCT) • Setting (eg, primary, secondary, or tertiary) • Number of health care providers, patients, or clusters • Follow-up duration • Clinical practice guidelines followed (eg, 2016 American College of Cardiology/American Heart Association PAD[b] guidelines [7])
Prescriber characteristics	• Health care provider specialty (cardiovascular specialist or noncardiovascular specialist) • Health care provider subspecialty (eg, family medicine, general internal medicine, cardiology, or vascular surgery) • Number of female health care providers • Mean years of health care provider practice
Patient characteristics	• Number of patients with different atherosclerotic occlusive diseases (cerebrovascular disease, coronary artery disease, PAD, or polyvascular disease) • Mean or median patient age • Mean or median patient BMI • Number of female patients • Number of non-White patients • Number of patients with low socioeconomic status[c] • Number of past or current smokers • Whether patients were inpatients, outpatients, or long-term care residents • Number of patients who are overweight[d] or obese[e] • Number of patients residing in rural areas • Number of patients with specific comorbidities (dyslipidemia, diabetes mellitus, hypertension, congestive heart failure, chronic kidney disease, or chronic obstructive pulmonary disease)
Guideline-recommended medications	• Classes of guideline-recommended medications examined (antiplatelets, statins, antihypertensives, or all medications) • Types of guideline-recommended medications examined (eg, clopidogrel, simvastatin, or β-blockers)
Implementation strategies	• Implementation strategy classification according to refined Effective Practice and Organization of Care taxonomy [61]
Effect measures	• Effect measures (eg, weighted mean differences, standardized mean differences, odds ratios, relative risks, risk differences, or hazard ratios) and measures of variability (eg, 95% CIs) describing the effect of implementation strategies on primary and secondary outcomes
Risk of bias	• Risk of bias for the 7 domains of the Cochrane risk of bias tool [71]

[a]RCT: randomized controlled trial.

[b]PAD: peripheral artery disease.

[c]As defined by study authors.

[d]Defined as a BMI ≥25 kg/m^2.

[e]Defined as a BMI ≥30 kg/m^2.

Table 6. Data items to be extracted from included studies when reported for systematic review examining adherence-supporting strategies for improving patient adherence to guideline-recommended cardiovascular medications in adults with atherosclerotic occlusive disease.

Data item theme	Items to be extracted
Study design	• Country of origin • Study design (eg, RCT[a] or cluster-RCT) • Setting (eg, primary, secondary, or tertiary) • Recruitment period • Number of patients, prescribers, or clusters • Clinical practice guidelines followed (eg, 2022 Canadian Cardiovascular Society PAD[b] guidelines [9]) • Duration of follow-up
Patient characteristics	• Atherosclerotic occlusive disease diagnoses (cerebrovascular disease, coronary artery disease, PAD, or polyvascular disease) • Whether patients were inpatients, outpatients, or long-term care residents • Mean or median age • Mean or median BMI • Number of patients with low socioeconomic status[c] • Number of female patients • Number of non-White patients • Number of past or current smokers • Number of patients who are overweight[d] or obese[e] • Number of patients residing in rural areas • Number of patients with specific medical comorbidities (dyslipidemia, diabetes mellitus, hypertension, congestive heart failure, chronic kidney disease, or chronic obstructive pulmonary disease)
Prescriber characteristics	• Specialty of health care providers (cardiovascular specialist or noncardiovascular specialist) • Subspecialty of health care providers (eg, family medicine, general internal medicine, cardiology, or vascular surgery) • Mean or median years of health care provider practice • Number of female health care providers
Guideline-recommended medications	• Classes of guideline-recommended medications examined (statins, antiplatelets, antihypertensives, or all guideline-recommended medications) • Types of guideline-recommended medications examined (eg, aspirin, rosuvastatin, or angiotensin-converting enzyme inhibitors)
Adherence-supporting strategies	• Adherence-supporting strategy classification according to the Behavior Change Wheel [62]
Effect measures	• Effect measures (eg, weighted mean differences, standardized mean differences, odds ratios, relative risks, risk differences, or hazard ratios) and applicable variation measures (eg, 95% CIs) describing the effect of adherence-supporting strategies on primary and secondary outcomes
Risk of bias	• Risk of bias for 7 domains of the Cochrane risk of bias tool [71]

[a]RCT: randomized controlled trial.

[b]PAD: peripheral artery disease.

[c]As defined by study authors.

[d]Defined as a BMI ≥25 kg/m^2.

[e]Defined as a BMI ≥30 kg/m^2.

Risk of Bias

Two independent investigators will assess the risk of bias for all included trials using the Cochrane risk of bias tool [71]. Discrepancies between investigators regarding risk of bias assessment will be resolved by consensus.

Data Synthesis

Qualitative

Before considering meta-analyses, we will first perform thematic clustering [73] of all included studies. We will classify implementation or adherence-supporting strategies used within both the intervention and comparator arms of identified trials based on (1) the levels and categories of the refined Effective Practice and Organization of Care (EPOC) taxonomy [61] (for implementation strategies for improving health care provider prescription); or (2) the nine intervention functions (education, persuasion, incentivization, coercion, training, restriction, environmental restructuring, modelling, and enablement) and seven policy categories (communication or marketing, guidelines, fiscal, regulation, legislation, environmental or social planning, and service provision) of the Behavior Change Wheel (BCW) [62] (for adherence-supporting strategies for improving patient adherence). The refined EPOC taxonomy was selected

because it was designed to assist reviewers in selecting papers for inclusion in systematic reviews of implementation strategies [61]. It has also been used in systematic reviews examining RCTs of implementation strategies for patients with other chronic conditions [74,75] and allows for an adequate description of complex and multiple implementation strategies [61]. The BCW was selected because it was constructed by behavior change experts through systematic analysis and synthesis of 19 previously existing adherence-supporting strategy classification frameworks [62]. The BCW also satisfies three usefulness criteria not completely satisfied by any of the 19 individual frameworks on which it is built (comprehensiveness, coherence, and links to an overarching model of behavior) and can classify every adherence-supporting strategy that has been developed [62]. Further, linkage to an overarching model of behavior (the capability, opportunity, and motivation model) may allow for the selection of adherence-supporting strategies more likely to achieve the desired behavior change [62]. The BCW has also been shown to be reliable for classifying adherence-supporting strategies across a wide range of clinical contexts [62]. Implementation and adherence-supporting strategies will be classified by 2 independent investigators. Disagreements regarding implementation or adherence-supporting strategy classification will be resolved through consultation with a health psychologist.

Following implementation and adherence-supporting strategy classification, we will tabulate studies [73] based on the implementation strategies contained within their intervention and comparator arms. This will allow us to narratively summarize [73] how the implementation or adherence-supporting strategies used within the intervention and comparator arms of included studies differ regarding (1) the type and number of implementation or adherence-supporting strategies used; or (2) the intensity and duration of implementation or adherence-supporting strategy use. It will also allow us to describe which and how frequently specific implementation or adherence-supporting strategies are used in combination (ie, how frequently they co-occur together in complex implementation or adherence-supporting strategies). Studies will also be tabulated [73] by the classes of guideline-recommended cardiovascular medications that their implementation or adherence-supporting strategies are designed to improve the prescription of or adherence to, the predominant diagnoses of the patients included in this study (CVD, CAD, PAD, and polyvascular disease), and whether their implementation strategy was aimed at cardiovascular or noncardiovascular specialists (for implementation strategies for improving health care provider prescription).

Quantitative

Descriptive data will be summarized using weighted means and SDs, medians and IQRs, or counts and percentages where appropriate. Where minimal clinical interstudy heterogeneity exists [76], DerSimonian and Laird [77] random effects models will be used to pool effect estimates whenever two or more studies report on the effect of implementation or adherence-supporting strategies of the same type (according to the refined EPOC taxonomy [61] [underprescription systematic review] or the BCW [62] [nonadherence systematic review]) on similar outcomes. We will preferentially summarize the pooled effects of implementation or adherence-supporting strategies on the primary and secondary outcomes using RRs for dichotomous outcomes, weighted mean differences for continuous outcomes, and HRs for time-to-event outcomes (along with their 95% CIs). Where substantial interstudy clinical heterogeneity exists [76], we will summarize the results of included studies narratively [73] by reporting effect estimates (along with their 95% CIs) describing the effectiveness of implementation or adherence-supporting strategies at improving primary or secondary outcomes.

Where studies report effect measures other than RRs (ie, ORs or HRs), we will use corresponding raw data describing the cumulative incidence of underprescription or nonadherence or secondary outcomes to calculate RRs from ORs or HRs using validated methods [78,79] as has been done previously [80,81].

For included cluster-RCTs, we will calculate a design effect (DE) for each study using an established formula ($DE = 1+ [n - 1] \times \rho$) [82,83]. This DE will then be used to reduce the total sample size to an "effective sample size" (*effective sample size = n/DE*) to account for clustering effects [82]. If an interclass correlation coefficient (ICC; ρ) is not reported in one or more of the included studies, a single conservative ICC value will be used [84]. The value of this single conservative ICC will be based on ICCs from similar studies [84] and will be imputed separately for RCTs examining provider-level or health care system-level strategies (ie, those targeting underprescription) and patient-level strategies (ie, those targeting nonadherence) [85].

Interstudy heterogeneity will be assessed by inspecting forest plots and calculating I^2 statistics [86]. We will consider I^2 statistics >25%, >50%, and >75% to represent low, moderate, and high degrees of heterogeneity, respectively [86]. We will also conduct stratified meta-analyses and meta-regressions using several prespecified risk factors for underprescription and nonadherence selected based on the findings of related systematic reviews [87-92] and methodological considerations [15,16,93-103]. The following risk factors will be used within these analyses to determine whether they may be effect modifiers: (1) whether the predominant atherosclerotic occlusive disease was CAD or another atherosclerotic occlusive disease (CVD, PAD, or polyvascular disease) [15,16]; (2) whether most prescribers were cardiovascular specialists (eg, cardiologists or vascular surgeons) or noncardiovascular specialists (eg, family physicians, general internal medicine physicians, pharmacists, or nurse practitioners) [96-98]; (3) whether studies originated from high or low-middle income countries [99,100] (according to the list provided by the World Bank in 2023) [93]; (4) the proportion of female [101-103], non-White [101-103], and low socioeconomic status [101-103] patients; (5) whether the mean age of patients was ≥65 years of age instead of <65 years of age (or whether ≥50% of the population was aged ≥65 years versus <50% of the population was aged ≥65 years) [101-103]; (6) study setting (primary care versus tertiary care) [101-103]; (7) whether participants were predominantly inpatients, outpatients, or long-term care residents (nonadherence systematic review only) [101,102]; (8) whether there was a high or unclear versus lower risk of bias related to random sequence generation,

allocation concealment, and blinding of outcome assessors [73]; and (9) whether information regarding medication adherence was obtained using objective methods (eg, biochemical assays [94,95], electronic pill bottle openings [94,95]) or participant self-report [94] (eg, Morisky Medication Adherence Scale [104], Medication Adherence Report Scale [105] [nonadherence systematic review only]).

Publication Bias and Small-Study Effects

The presence of publication bias will be evaluated using the Egger test and by visually inspected produced funnel plots from primary outcomes [106].

Statistical Software

All analyses will be conducted using Stata Standard Edition (version 17.0; Stata Corp). Risk-of-bias graphics will be generated using Review Manager Systematic Review Software (version 5.4; The Cochrane Collaboration).

Certainty in the Cumulative Evidence

We will use the GRADE (Grading of Recommendations, Assessment, Development, and Evaluation) [107] to rate certainty in outcome estimates. First, we will assess the risk of bias, imprecision, inconsistency, indirectness, and publication bias in outcome estimates [107]. The overall certainty in these estimates will then be judged as high ("further research is very unlikely to change our certainty in the estimate"), moderate ("further research is likely to have an important impact on our certainty in the estimate and may change the estimate"), or low ("further research is very likely to have an important impact on our certainty in the estimate and is likely to change the estimate") [107].

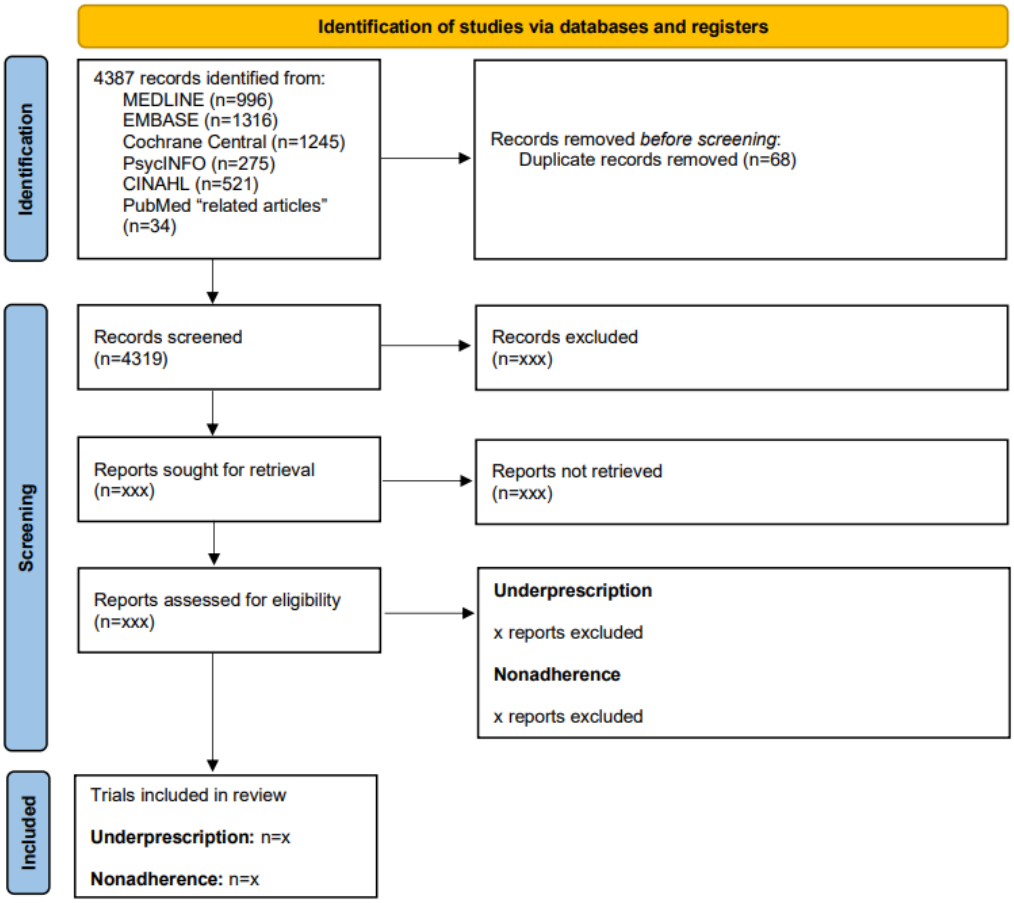
Ethical Considerations

These systematic reviews will examine previously published data and are therefore exempt from ethics approval at our institution.

Results

We conducted the database and PubMed "related articles" search on June 6, 2023. Database searches identified 4353 total citations (n=996 from MEDLINE; n=1316 from Embase; n=1245 from Cochrane Central; n=275 from PsycINFO; and n=521 from CINAHL). The PubMed "related articles" feature identified another 34 citations. After removing duplicates, 4319 unique citations remain for title/abstract screening (see Figure 1 for our PRISMA [Preferred Reporting Items for Systematic Review and Meta-Analysis] flow diagram). We are currently in the process of performing title/abstract screening. We hope to complete analyses for the two systematic reviews by mid-2025.

Figure 1. PRISMA flow diagram describing the flow of articles through the systematic reviews. PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses.



Discussion

Future Directions and Anticipated Principal Results

Our systematic reviews will assess all RCTs examining the effectiveness of implementation and adherence-supporting strategies for improving health care provider prescription of, and patient adherence to, guideline-recommended cardiovascular medications among adults with atherosclerotic occlusive diseases. We also aim to determine the effectiveness of implementation strategies at improving medication prescription across different classes of health care providers working across different clinical practice settings. We anticipate that clinician education may be a particularly effective strategy for improving prescription among those working in primary care settings, given that these types of practitioners may have relatively reduced awareness of guideline recommendations for the management of patients with atherosclerotic occlusive disease relative to cardiovascular specialists [108]. As patients treated at tertiary medical centers tend to have complex electronic medical records [109], we anticipate that a facilitated relay of information to clinicians may be particularly effective for improving medication prescription among cardiovascular specialists and clinicians working in tertiary academic centers. Strategies anticipated to be promising for improving guideline-recommended cardiovascular medication prescription across different health care provider types and clinical practice settings include audit and feedback, provider reminder systems, and organizational changes given the promise these interventions have demonstrated for improving medication prescription among patients with varied cardiovascular diseases [87,88].

We will also examine whether the effectiveness of adherence-supporting strategies varies across patients with different types of atherosclerotic occlusive diseases (CVD, CAD, PAD, and polyvascular disease). In particular, identifying promising adherence-supporting strategies for improving medication adherence among patients with PAD is of crucial importance given that research has shown that those with PAD are less likely to be prescribed guideline-recommended medications compared to those with CVD or CAD [19]. As patients with PAD tend to have worse awareness of their condition and relevant secondary medical prevention options compared to those with other atherosclerotic occlusive diseases [110], we anticipate that patient education may be a particularly promising strategy for improving medication adherence among patients with PAD. Adherence-supporting strategies involving fiscal components (eg, medication copayment) may also be a particularly promising strategy for improving medication adherence among patients with PAD given the high costs of guideline-recommended cardiovascular medications [111]. Further, as patients with atherosclerotic occlusive disease tend to be older [53-55], strategies that remind patients to take their prescribed medications may serve as promising adherence-supporting strategies across patients with atherosclerotic occlusive disease in general.

Comparison With Previous Work

Although systematic reviews have examined the effectiveness of implementation and adherence-supporting strategies for improving health care provider prescription of [87,88], and patient adherence to [89-92], guideline-recommended cardiovascular medications for atherosclerotic occlusive diseases, they have important limitations. One systematic review of implementation strategies for improving health care provider prescription [87] characterized its implementation strategies according to the EPOC taxonomy [112], which was developed to help authors classify implementation strategies in systematic reviews. However, it aggregated implementation strategies together to assess whether they collectively increased health care provider prescription of guideline-recommended medications instead of examining whether strategy effectiveness varied within different EPOC taxonomy [112] levels (ie, professional, organizational, financial, and regulatory). This systematic review [87] also only examined patients with CAD. Although a second systematic review [88] on the effectiveness of implementation strategies for improving health care provider prescription also characterized implementation strategies using the EPOC taxonomy [112], it examined the effectiveness of improving physician adherence to "guideline-recommended care" (eg, use of cardiovascular risk assessment tools or following guidelines for cardiovascular disease screening) in addition to medication prescription [88]. It also included patients with nonatherosclerotic cardiovascular diseases. Limitations of the existing systematic reviews of adherence-supporting strategies for improving patient adherence is that many include patients "at risk" of developing an atherosclerotic occlusive disease or with nonatherosclerotic cardiovascular diseases (eg, hypertension or congestive heart failure) [91,92]. Further, many only examine specific adherence-supporting strategies (eg, polypills, text-message reminders, or patient education) [89,90,92] or adherence to specific cardiovascular medications among patients with CVD or CAD [89-92]. Many also did not categorize their adherence-supporting strategies according to an established taxonomy [91]. Finally, many relevant RCTs have been completed since the publication of prior underprescription [87,88] and nonadherence [89-92] systematic reviews.

Strengths and Limitations

Our proposed systematic review has potential limitations. First, we anticipate that it may be difficult to pool the results of some studies due to interstudy heterogeneity [113]. We anticipate that many relevant RCTs [21-48] may have reported different primary and secondary outcomes at different time points and using different outcome measurement scales. Should we be unable to pool our quantitative results, we will summarize our results narratively instead of using the methods outlined above [73]. Second, it may be argued that including patients with all forms of atherosclerotic occlusive disease in our study population may introduce clinical heterogeneity due to small differences in underlying disease pathophysiology [50-52] and epidemiology [53-55]. Nevertheless, the patient populations in our proposed systematic reviews are more similar regarding disease pathology, epidemiology, and medication requirements than others in previously published systematic reviews [87-92]. Further, these conditions commonly coexist within patients [56,57] and similar prescribers are involved in their medical management [58-60]. Finally, although the use of self-reported

data to quantify medication adherence introduces the possibility of outcome misclassification bias [94], we plan on performing stratified meta-analysis and meta-regression to determine whether observed differences in medication adherence vary by whether studies quantified medication adherence using objective methods versus participant self-report.

Conclusions

In conclusion, we will perform systematic reviews and meta-analyses of RCTs examining implementation and adherence-supporting strategies designed to improve health care provider prescription of, and patient adherence to, guideline-recommended cardiovascular medications among patients with atherosclerotic occlusive diseases. These systematic reviews will also determine the effect of these interventions on patient-important outcomes and health care resource use. Finally, they will determine whether effectiveness varies by patient characteristics, prescriber traits, and clinical practice setting.

Acknowledgments

The authors would like to thank RS and her colleagues for their help in designing, peer-reviewing, and executing the electronic literature search strategies. This research is supported by a 2024 Vanier Canada Graduate Scholarship (awarded to AMK and supervised by DJR). DJR's research program is also supported by funding from the Physician Services Incorporated foundation; The Ottawa Hospital Academic Medical Organization; and the Division of Vascular and Endovascular Surgery, and the Department of Surgery, University of Ottawa. This study's sponsor (University of Ottawa) played no role in the design of this study or drafting of this study's protocol.

Data Availability

Data from the systematic review will be provided by study authors upon reasonable request.

Authors' Contributions

AMK and DJR conceived this study, and AMK, DJR, DAF, JP, and DIM developed this study. AMK, RS, and DJR designed the search strategy and the qualitative and quantitative data synthesis plan, which DAF, JP, and DIM further refined. AMK wrote the initial draft of the protocol, which was critically reviewed by DAF, JP, DIM, and DJR. AMK submitted the protocol to PROSPERO. All of this study's authors have critically read and approved the final version of this protocol.

Conflicts of Interest

None declared.

Multimedia Appendix 1
PRISMA-*P* 2015 checklist. PRISMA-P: Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols.
[DOCX File , 24 KB - resprot_v14i1e60326_app1.docx]

Multimedia Appendix 2
Database search strategies (June 6, 2023). MeSH: Medical Subject Heading.
[DOCX File , 17 KB - resprot_v14i1e60326_app2.docx]

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Abbreviations

AACTT: action, actor, context, target, time
BCW: Behavior Change Wheel
CAD: coronary artery disease
CVD: cerebrovascular disease
DE: design effect
EPOC: Effective Practice and Organization of Care
GRADE: Grading of Recommendations, Assessment, Development, and Evaluation
HR: hazard ratio
ICC: interclass correlation coefficient
MACE: major adverse cardiac event
MALE: major adverse limb event
OR: odds ratio
PAD: peripheral artery disease
PRISMA: Preferred Reporting Items for Systematic Review and Meta-Analysis
PRISMA-P: Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols
RCT: randomized controlled trial
RR: relative risk

Edited by A Schwartz; submitted 07.05.24; peer-reviewed by M Wright; comments to author 15.10.24; revised version received 07.11.24; accepted 14.11.24; published 16.01.25.

Please cite as:
Kirkham AM, Fergusson DA, Presseau J, McIsaac DI, Shorr R, Roberts DJ
Strategies to Improve Health Care Provider Prescription of and Patient Adherence to Guideline-Recommended Cardiovascular Medications for Atherosclerotic Occlusive Disease: Protocol for Two Systematic Reviews and Meta-Analyses of Randomized Controlled Trials
JMIR Res Protoc 2025;14:e60326
URL: https://www.researchprotocols.org/2025/1/e60326
doi:10.2196/60326
PMID:

Protocol

Applications of Natural Language Processing and Large Language Models for Social Determinants of Health: Protocol for a Systematic Review

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Abstract

Background: In recent years, the intersection of natural language processing (NLP) and public health has opened innovative pathways for investigating social determinants of health (SDOH) in textual datasets. Despite the promise of NLP in the SDOH domain, the literature is dispersed across various disciplines, and there is a need to consolidate existing knowledge, identify knowledge gaps in the literature, and inform future research directions in this emerging field.

Objective: This research protocol describes a systematic review to identify and highlight NLP techniques, including large language models, used for SDOH-related studies.

Methods: A search strategy will be executed across PubMed, Web of Science, IEEE Xplore, Scopus, PsycINFO, HealthSource: Academic Nursing, and ACL Anthology to find studies published in English between 2014 and 2024. Three reviewers (SR, ZZ, and YC) will independently screen the studies to avoid voting bias, and two (AS and YX) additional reviewers will resolve any conflicts during the screening process. We will further screen studies that cited the included studies (forward search). Following the title abstract and full-text screening, the characteristics and main findings of the included studies and resources will be tabulated, visualized, and summarized.

Results: The search strategy was formulated and run across the 7 databases in August 2024. We expect the results to be submitted for peer review publication in early 2025. As of December 2024, the title and abstract screening was underway.

Conclusions: This systematic review aims to provide a comprehensive study of existing research on the application of NLP for various SDOH tasks across multiple textual datasets. By rigorously evaluating the methodologies, tools, and outcomes of eligible studies, the review will identify gaps in current knowledge and suggest directions for future research in the form of specific research questions. The findings will be instrumental in developing more effective NLP models for SDOH, ultimately contributing to improved health outcomes and a better understanding of social determinants in diverse populations.

International Registered Report Identifier (IRRID): DERR1-10.2196/66094

(JMIR Res Protoc 2025;14:e66094) doi:10.2196/66094

KEYWORDS

social determinants of health; SDOH; natural language processing; NLP; systematic review protocol; large language models; LLM

Introduction

Rationale

Social Determinants of Health

Social determinants of health (SDOH) are the nonmedical conditions in which people are born, grow, live, work, and age [1]. These circumstances are shaped by the distribution of money, power, and resources at global, national, and local levels, and are primarily responsible for health inequities—the unfair and avoidable differences in health status seen within and between countries. As a result, one of Healthy People 2030's five overarching goals is specifically related to SDOH: "Create social, physical, and economic environments that promote attaining the full potential for health and well-being for all" [2]. Studies have shown that SDOH has powerful influences on health [3] and well-being at the individual and population levels [4]; therefore, it is important to capture them. Such information is valuable to a range of stakeholders including patients, health care providers, policymakers, and insurance companies. For instance, clinicians might modify a patient's medication regimen if they learn that the patient has difficulty affording their prescriptions or lacks reliable transportation to the pharmacy. It is important to note here that SDOH concepts are often described using a variety of synonyms, paraphrases, or language variations [5], which makes it difficult for simple keyword-based methods to capture all relevant instances. Moreover, many SDOH indicators are not directly stated but implied through context.

Natural Language Processing

Natural language processing (NLP) is a subfield of artificial intelligence and computer science that enables computers to understand, interpret, and generate human language in a way that is both meaningful and useful. NLP encompasses a wide range of tasks, including but not limited to language translation, sentiment analysis, speech recognition, text summarization, and information extraction. NLP offers a promising tool to systematically analyze vast amounts of unstructured text data, including electronic health records (EHRs), social media, public health reports, and others [6]. Such tools and techniques can, therefore, be used to extract socioeconomic factors, environmental conditions, and personal lifestyles that significantly impact an individual's health outcomes. NLP models trained on labeled datasets can learn to recognize these patterns, which can improve extraction accuracy. SDOH information is often embedded within patient narratives or longer descriptions. NLP can assist in parsing and understanding context, coreferences, and the relationships between text parts. Unlike a manual review (time-consuming, labor-intensive, and prone to human error), NLP enables the rapid and scalable analysis of large datasets with greater accuracy and consistency [7,8].

NLP for SDOH

Multiple studies exist that showcase the application of NLP to various SDOH-related tasks in addressing health disparities. One key application is the identification and extraction of SDOH factors from EHRs, where NLP techniques have been used to classify and analyze clinical notes for social needs, behavioral factors, and other determinants that influence patient outcomes [9-12]. In the context of public health, NLP has been used to explore the impact of external events (eg, the COVID-19 pandemic) on marginalized communities by analyzing social media data [13]. Additionally, NLP has been leveraged to identify SDOH in specific populations, such as pediatric patients [14,15], patients living with Alzheimer disease [11], and individuals with lower back pain [16]. Advanced models such as the recent GPT and transformer-based models have further refined the extraction of SDOH from patient records and contributed to more precise and scalable analyses [17,18]. Moreover, NLP has been used to find out the underlying social factors in clinical social work notes [19] and emergency medical services records [20] that further enhance the understanding of how social determinants influence health care delivery.

Despite the promise of NLP in the SDOH domain, the literature is dispersed across various disciplines. Hence, a systematic review is necessary to consolidate existing knowledge, identify knowledge gaps in the literature, and inform future research directions in this emerging field. Our systematic review will focus on studies from 2014 onwards which is well-supported by the significant advancements in NLP techniques and the conceptual evolution of SDOH research that have occurred during this period. The development and introduction of Word2Vec [21] and the subsequent introduction of transformer models [22] marked a point of great improvement in NLP research. In addition, the rise in popularity of large language models (LLMs) such as BERT [23] and GPT [24] has driven substantial progress in the field of NLP. By limiting the review to this decade, the systematic review will capture the evolution of NLP approaches and their application in SDOH tasks, thereby providing a comprehensive and up-to-date study of the literature.

Objectives

This systematic review has two major objectives. First, to identify and highlight distinct NLP techniques, including LLMs (commercial, as well as open-sourced), which are used for tasks including but not limited to augmentation, organization, annotation, prediction, trend analysis, detection, identification, extraction, or classification of SDOH in a given dataset. The NLP model can be used in conjunction with other techniques, but at minimum, the NLP element should be there. The second objective is to report the effectiveness of such techniques or models, identify potential knowledge gaps, and design research questions for future studies.

Methods

Protocol and Registration

The study has been registered in PROSPERO (CRD42024578082) and will be carried out under PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines [25]. This protocol was developed using the 2015 PRISMA-P recommended checklist (Multimedia Appendix 1) for systematic review protocols [26]. However, we omit items 16 (meta-biases) and 17 (confidence in cumulative evidence), given we will not synthesize the outcomes of studies. The review team is composed of researchers across disciplines with diverse backgrounds.

Eligibility Criteria

The eligible publications for this review are restricted to peer-reviewed published literature (observational studies, algorithm validation studies, computational model evaluations, experimental, and qualitative), including journal studies and full conference papers such as ACL anthology. The study must be written in English, although the language of the textual dataset used can vary. The publication period of the included studies was restricted to the last decade, that is, from 2014 to 2024. To be included, a study should answer a research question on the design, development, and application of NLP in health data analysis for SDOH and have used (1) a dataset containing health care data including but not limited to EHRs, social media posts, and clinical notes or narratives, and (2) NLP techniques or models or LLMs (commercial, as well as open source) for tasks including but not limited to augmentation, organization, annotation, prediction, trend analysis, detection, identification, extraction, or classification of SDOH in a given dataset. The NLP model can be used in conjunction with other techniques, but at least the NLP element should be there. Comparisons will be performed against studies included in the review.

For this review, we focused primarily on peer-reviewed literature to ensure the reliability of quantitative information. However, as part of the final systematic review, we will incorporate relevant preprints published between the last search query and up to one month before publication. This approach balances the inclusion of recent advancements while maintaining methodological rigor.

Information Sources

We conducted a systematic search of the following databases from January 1, 2014, to August 9, 2024, across 7 databases: PubMed, Scopus, Health Source: Nursing/Academic, PsycINFO, Web of Science, ACL Anthology, and IEEE EXPLORE. Preprints (arXiv/bioRxiv), forewords, prefaces, table of contents, programs, schedules, indexes, call for papers or participation, lists of reviewers, lists of tutorial abstracts, invited talks, appendices, session information, obituaries, book reviews, newsletters, lists of proceedings, lifetime achievement awards, erratum, systematic reviews, scoping reviews, and notes will be excluded. We will screen relevant review studies based on eligibility criteria. We will further screen studies that cited the included studies (forward search). We will perform hand searches.

Search Strategy

The database search strategies were developed by a health sciences librarian (HR) with expertise in literature searches. Known relevant studies collected by the authors were analyzed to select keywords for the search query. The initial search strategy in PubMed was then iteratively developed by adding or removing additional keywords until all known relevant studies were retrieved by the search query. Textbox 1 shows a draft of the search strategy to be used for the PubMed database, including planned limits. The full search strategies for all information sources are provided in Multimedia Appendix 2.

Textbox 1. Search strategy on PubMed.

Query

("Natural Language Processing"[Mesh] OR "natural language"[tw] OR NLP[tw] OR "large LM*"[tw] OR LLM[tw] OR LLMs[tw] OR "large language model*"[tw] or ChatGPT*[tw] OR "Chat GPT*"[tw] OR GPT4*[tw] OR GPT-4*[tw] OR GPT3*[tw] OR GPR-3*[tw] OR "Generative Pre-trained Transformer*"[tw] OR LLAMA[tw] OR "Claude 3"[tw] OR Mistral[tw] OR MedPaLM*[tw] OR Med-PaLM*[tw] OR "text mining"[tw] OR "text process*"[tw] OR "information retrieval"[tw] OR "information extract*"[tw])

AND

("Social Determinants of Health"[Mesh] OR SDOH[tw] OR SDH[tw] OR SBDH*[tw] OR "determinants of health"[tw] OR "health determina*"[tw] OR "life events"[tw] OR "social determinant*"[tw] OR "socioeconomic determinant*"[tw] OR "socioeconomic factor*"[tw] OR "social determinate*"[tw] OR "social factor*"[tw] OR "social need*"[tw] OR "social prescribing"[tw] OR "social determining factor*"[tw] OR "social risk*"[tw])

Filters

- Manuscript language: English
- Publication years: 2014-2024
- Other: exclude preprints

In addition, a refreshed search strategy will be implemented to ensure that the systematic review includes the most up-to-date and relevant studies. If a significant amount of time has elapsed between the initial literature search and the subsequent stages of citation screening or paper preparation, a secondary search will be conducted. This refreshed search will follow the same search strategy as the initial one, using the same databases, search terms, and inclusion or exclusion criteria. Any newly

identified studies will undergo the same rigorous screening process as those identified in the original search to ensure their relevance and quality before inclusion in the final analysis.

Study Records

Data Management

Potentially relevant citations will first be imported into EndNote (Clarivate) and then exported as an XML file to Covidence (Veritas Health Innovation Ltd), which will identify and remove duplicate records.

Selection Process

Three reviewers (SR, ZZ, and YC) will independently screen each study for eligibility by marking it as a "yes" (for inclusion), "no" (for exclusion), or "maybe" (in case of uncertainty about relevance) in the Covidence platform. Two senior reviewers (AS and YX) will resolve potential discrepancies during any screening step. All voting is blinded, meaning the colleagues cannot see votes until they have cast their own, and vice versa. In the first stage, the reviewers will screen the titles and abstracts of each study as identified in the databases by our search strategies. In the second stage of screening, the team will obtain and screen the full-text papers as per the eligibility criteria. Studies that do not meet the eligibility criteria will be moved to an exclusion folder. The final corpus of selected studies will be then approved by the consensus of all reviewers involved in this study and sent to an expert consultant for potential suggestions. The selection process will be displayed in a PRISMA flowchart.

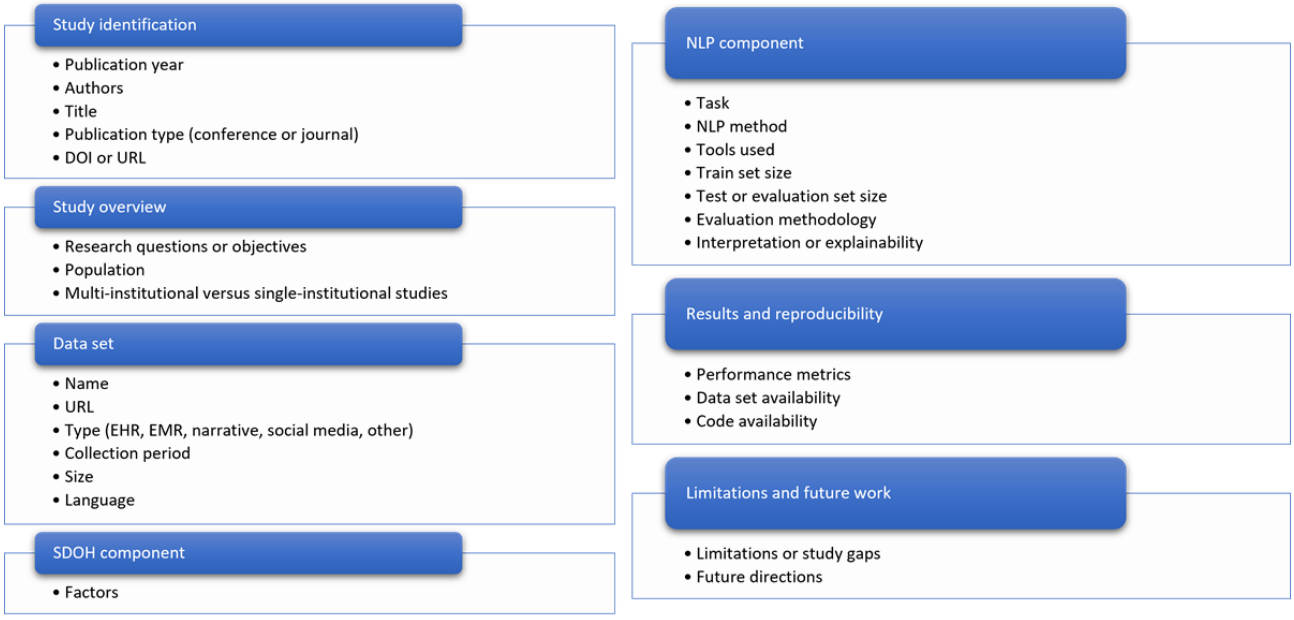
Data Collection Process

Two independent researchers (SR and ZZ) will extract data from the final included full texts. Before formal data extraction, one reviewer (SR) will pilot the data extraction form with a sample of five papers to identify and address any issues in the form to ensure it is comprehensive. The data extraction will then be conducted independently by both reviewers using the finalized form. Any disagreements between the two reviewers will be discussed and resolved through consensus. If consensus cannot be reached, a third reviewer will mediate. In cases where data is incomplete or unclear, the original study authors may be contacted to request additional information or clarification. All data will be managed using Covidence or via a shared Excel (Microsoft Corp) sheet to ensure consistency throughout the process.

Data Items

Figure 1 outlines a preliminary list of variables for which data will be collected, including study identifications (eg, year of publication and type), dataset details (eg, sample size and type), intervention specifics (eg, type of NLP technique and SDOH task), and outcomes (eg, accuracy and precision). Each variable is defined to ensure consistency across studies. During the data extraction process, any assumptions made (such as imputing missing values or converting data into a common format) will be documented and justified. If necessary, modifications to the list of variables will be made during the review, and these changes will be detailed in the final systematic review report.

Figure 1. The data to be extracted. EHR: electronic health record; EMR: emergency medical services; NLP: natural language processing; SDOH: social determinants of health.



Outcomes and Prioritization

We will focus on evaluating the effectiveness and accuracy of various NLP techniques and models applied to SDOH tasks. The primary outcomes of interest will include key performance metrics such as precision, recall, F_1-score, and others, as these are critical indicators of the success of NLP models. Secondary outcomes will involve assessing the integration of NLP techniques with other computational models, such as machine learning and deep learning approaches, to determine their combined impact on model performance. In cases where metrics are not reported, the review will include a qualitative assessment of the study's findings, focusing on the reported outcomes and their relevance to the SDOH task.

Risk of Bias Assessment

We anticipate that the studies included in the review may vary significantly. For instance, some may use complex NLP algorithms while others rely on rule-based systems. Hence, it is challenging to name one specific tool for assessing bias at this stage. We will prioritize assessing key factors that could introduce bias, such as the quality of the datasets, the transparency in reporting the models' performance, and the robustness of the evaluation metrics such as precision and recall.

In addition to assessing general risks of bias, this review will evaluate potential algorithmic bias across individual studies. Algorithmic bias can arise from imbalanced datasets, where certain populations or social determinants are underrepresented, leading to biased predictions. We will examine whether studies report efforts to mitigate such biases.

Data Synthesis

For this systematic review, a narrative synthesis approach will be used. Data from the included studies will be analyzed by two reviewers, with any disagreements resolved through discussion or consultation with a third reviewer if necessary. Given the diverse methods used in the selected studies, the synthesis will focus on identifying and describing common patterns, trends, and knowledge gaps. The analysis will be divided into the following parts:

- Characteristics of the studies (such as the number of studies, types of datasets, NLP techniques, outcomes, and potential biases).
- Contributions of these studies to the development and application of NLP models for SDOH. As this review is intended to be qualitative, no (or minimum) statistical tools will be applied.

Ethical Considerations

No ethical approval is required for this protocol and proposed systematic review, as we will only use data from previously published papers that have received ethics clearance and used proper informed consent procedures. The systematic review's results will be disseminated through publication in a peer-reviewed journal and shared on a publicly accessible GitHub repository [27].

Results

As of December 2024, the systematic review is in progress (SR, ZZ, and YC started screening studies) and is expected to be finished by March 2025. Our final paper is expected to be submitted to peer-reviewed journals by spring 2025.

Discussion

Anticipated Principal Findings

This systematic review is expected to reveal valuable insights into the current state of NLP applications in SDOH tasks. We anticipate identifying the most effective NLP techniques and models across various types of health care data, as well as the common challenges and limitations associated with these approaches. Specifically, we expect to find that the integration of NLP with other computational models, such as machine learning and deep learning, often enhances performance and results in more robust outcomes. We also anticipate that the review will reveal significant variability in model performance based on the type of data used (eg, EHRs vs social media posts) and the specific SDOH being targeted (eg, socioeconomic status vs housing stability). It is important to investigate these factors separately because the challenges in data processing and model effectiveness can vary significantly across different contexts. Investigating these subgroups will provide insights into which NLP techniques are most effective for specific types of data and SDOH, which will enable a more targeted approach in future model development and application. We anticipate that the GitHub repository will offer a platform where researchers can contribute new studies and insights, facilitating ongoing dialogue and collaboration in the field of NLP for SDOH.

Limitations

One limitation of this study is the selection of studies published between 2014 and 2024. Although this timeframe is chosen to focus on recent advancements, it may limit the historical context. We focus on peer-reviewed papers to ensure the inclusion of high-quality and rigorously evaluated studies. While this approach emphasizes established research, it may mean that some recent studies (such as preprints) will not be captured. By prioritizing peer-reviewed literature, we base our findings on research that has undergone thorough scrutiny.

Acknowledgments

We are grateful to the anonymous reviewers at JMIR Research Protocols for their helpful feedback. YX is supported by the National Institute of Mental Health (RF1MH134649), the American Foundation for Suicide Prevention (YIG-2-133-22), the Mental Health Research Network, Google, and the National Institutes of Health (1OT2OD032581-02-259). AS is supported by the National Institute on Drug Abuse (R01DA057599).

Data Availability

All data generated or analyzed during this study will be included in the final systematic review publication and its supplementary information files.

Authors' Contributions

SR developed the study concept and methodology, conducted the investigation, wrote the original manuscript, and created Figure 1. ZZ reviewed the papers, did a literature review, and wrote the manuscript. YC reviewed the papers and wrote the manuscript. HR provided data for Textbox 1 and handled search query curation. AS and YX conceptualized the study, resolved study review conflicts, and provided overall supervision and project administration. All authors reviewed the final manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
PRISMA-P 2015 checklist: recommended items to address in a systematic review protocol.
[PDF File (Adobe PDF File), 132 KB - resprot_v14i1e66094_app1.pdf]

Multimedia Appendix 2
Search strategies and the number of results.
[PDF File (Adobe PDF File), 1643 KB - resprot_v14i1e66094_app2.pdf]

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Abbreviations

EHR: electronic health record
LLM: large language model
NLP: natural language processing
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRISMA-P: Preferred Reporting Items for Systematic Reviews and Meta-Analyses—Protocols
SDOH: social determinants of health

Edited by T Leung; submitted 03.09.24; peer-reviewed by JA Yaun, L Chinthala, W Wu; comments to author 27.11.24; revised version received 04.12.24; accepted 26.12.24; published 21.01.25.

Please cite as:
Rajwal S, Zhang Z, Chen Y, Rogers H, Sarker A, Xiao Y
Applications of Natural Language Processing and Large Language Models for Social Determinants of Health: Protocol for a Systematic Review
JMIR Res Protoc 2025;14:e66094
URL: https://www.researchprotocols.org/2025/1/e66094
doi:10.2196/66094
PMID:

Protocol

Sign Language Recognition System for Deaf Patients: Protocol for a Systematic Review

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Abstract

Background: Individuals with hearing impairments may face hindrances in health care assistance, which may significantly impact the prognosis and the incidence of complications and iatrogenic events. Therefore, the development of automatic communication systems to assist the interaction between this population and health care workers is paramount.

Objective: This study aims to systematically review the evidence on communication systems using human-computer interaction techniques developed for deaf people who communicate through sign language that are already in use or proposed for use in health care contexts and have been tested with human users or videos of human users.

Methods: A systematic review will be performed based on a literature search in MEDLINE, Web of Science, ACM, and IEEE Xplore as well as top-tiered conferences in the area to identify relevant studies. The inclusion criteria are the description of the development of a sign language recognition system in a health care context and the testing with human users. Independent investigators (LFRO, LRV, and LMMSR) will screen eligible studies, and disagreements will be solved by a senior researcher (MSM). The included papers will undergo full-text screening. A PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) flow diagram will be presented to visually summarize the screening process, ensuring clarity and transparency in presenting the results. Additionally, a comprehensive chart table will be constructed to consolidate essential data related to the key variables extracted from the studies. These results will be meticulously analyzed and presented descriptively, offering insightful interpretations of the information encapsulated within the table.

Results: A preliminary search was performed in April 2024. Researchers concluded the study selection by July 2024. Data extraction, synthesis, report, and recommendations are expected to be finished by February 2025.

Conclusions: This systematic review will identify human-machine systems that enable communication in health services involving deaf patients, presenting the framework that includes usability and application in human contexts. We will present a comprehensive panel of findings, highlighting systems used to tackle communication barriers and offer a narrative comparison of current implementation practices.

International Registered Report Identifier (IRRID): PRR1-10.2196/55427

(JMIR Res Protoc 2025;14:e55427) doi:10.2196/55427

KEYWORDS

computer neural networks; artificial intelligence; biomedical technology; communication aids for disabled; computer vision; sign language; hearing loss; deaf people; communication barriers; gestures

Introduction

The term “disabling hearing loss” refers to any type of hearing problem that is considered to be at least moderate (greater than 40 dB), including deafness, and that requires some type of health device to allow adequate communication with the individual [1]. According to the World Health Organization, approximately 430 million people, which accounts for over 5% of the world’s population, have some disabling hearing loss [2]. It is estimated that by 2050, over 700 million people will have some hearing impairment [2].

The scientific literature highlights numerous inequalities faced by the deaf community regarding access to health care services [3-5]. A qualitative study involving 93 deaf adults primarily communicating in American Sign Language revealed that most participants struggled with understanding medical instructions due to communication challenges [6]. Despite often being accompanied by family members during medical appointments, participants expressed dissatisfaction with their effectiveness as communication facilitators. They reported feeling excluded from conversations and expressed privacy concerns when using interpreters [6], a pertinent issue regarding the confidentiality of medical interactions.

In this context, it becomes evident that individuals with hearing impairment are more likely to experience preventable health issues, including adverse problems in acute care and chronic diseases, such as obesity, hypertension, cardiovascular disease, diabetes, smoking, and alcoholism [7,8]. A scoping review of 2022 revealed a gap in the interpretation of sign language for health care and showed that this area is underresearched [9]. Thus, several studies have been committed to the development of assistive technologies, using artificial intelligence techniques, aiming to mitigate the inequalities related to health accessibility experienced by the deaf community. Among these technologies, it is important to highlight that the creation of communication systems that allow translation between sign language and written text, has shown to be very promising [10]. However, despite all the progress attained, the current literature has also shown a huge gap regarding the use of these strategies with deaf people, especially in health care contexts. For this reason, it seems obvious that the creation and implementation of communication systems to enable better interaction between the deaf population and health care workers are paramount. This study aims to systematically review the evidence on communication systems using human-computer interaction techniques developed for deaf individuals who communicate through sign language that are already in use or proposed for use in health care contexts and have been tested with human users or videos of human users.

Methods

Study Design

This is a systematic review protocol. The study design is a systematic search of the medical and other technical literature followed by a narrative synthesis of the results. The research protocol was registered in the Open Science Framework (OSF) [11]. It followed guidance from the Cochrane Guidelines and the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) statement [12]. The PRISMA-P (PRISMA Protocols) checklist can be seen in Multimedia Appendix 1.

A multidisciplinary team comprising researchers from health and computing domains, along with linguistic specialists in sign language, will collaboratively conduct the systematic review. Two members (ELAB and RAAC) of the team are linguistic specialists and sign language researchers, of whom one is deaf (RAAC). Both of them revised the terminology used in this review and revised the methodology critically to ensure that the needs of deaf people have been taken into account.

Strategy for Preparing the Research

Phases of this review are as follows: (0) identification of the need for a review, (1) preparation of a proposal for a review, (2) development of a review protocol, (3) protocol registration in OSF, (4) identification of research, (5) selection of studies, (6) study quality assessment, (7) data extraction, (8) data synthesis, and (9) report and recommendations.

Research Question

The primary research question is as follows: What technologies have been developed and tested in real-world settings to translate sign and oral languages, facilitating communication between deaf patients who primarily use sign language and health care workers?

The specific questions are as follows:

- Question 1: In which context of health care have these technologies been used?
- Question 2: Which languages (sign and oral) can these technologies translate?
- Question 3: Which technologies are required
in loco
for it to be used?
- Question 4: How were they developed?
- Question 5: How were they deployed and tested?
- Question 6: How has the communication between health care workers and deaf people been improved by using these technologies?
- Question 7: How was the efficacy of these technologies evaluated?
- Question 8: Is the system or technology “bidirectional”?

Search Strategy

The search process will commence following registration on the OSF [10]. Independent reviewers will meticulously search the following databases: Web of Science, MEDLINE, IEEE Xplore, ACM, and Google Scholar.

A draft of the search strategy was developed by 5 of the authors (MSM, LFRO, LRV, ROP, and ZSNR), using Medical Subject Headings (MeSH), and text words related to the topic of interest were defined. The proposed search strategy is shown in Multimedia Appendix 2.

Studies published from the inception of the database onward will be inclusively considered, without imposing restrictions on the time frame or publication date, as well as language. Searches will be rerun before the final analysis to ensure comprehensiveness. Additionally, in the event of unpublished studies, authors will be contacted. Reference lists of eligible studies will be thoroughly explored to identify additional eligible studies.

Detailed search data for the identified studies and information for each phase will be presented in a flowchart, accessible in Multimedia Appendix 3, following the guidelines outlined in the PRISMA method [12].

Eligibility Criteria

To be included in the systematic review protocol, a study must be prospective, retrospective, or descriptive; describe the development of communication systems applied to deaf people who communicate through sign language in a health care encounter context; and include testing with human users or videos of human users. The human users of the identified technologies should encompass individuals of any age who are deaf and primarily communicate through sign language.

Correspondences, short communications, and conference abstracts will also be included. Studies that do not align with the research questions specified earlier, fail to report use within health care encounters, do not involve testing with human users, or lack videos of human users will be excluded from the review.

Outcome Definition

The primary anticipated outcome will consist of a compilation of reports detailing technologies using human-computer approaches aimed at facilitating communication for deaf patients during health care encounters. Secondary outcomes will involve conducting a narrative comparison of the identified technologies.

Study Selection

In the screening phase, studies will be selected based on the predetermined inclusion and exclusion criteria after reviewing their titles, abstracts, and full texts. Researchers will independently screen titles and abstracts, with full-text review conducted if uncertainty arises from the abstract. Papers deemed potentially eligible based on title and abstract will undergo full-text screening for final eligibility determination. Eligible papers will be included in the study. Any disagreements regarding eligibility will be resolved by a senior member (MSM) of the team (MSM). The study selection process is represented using the PRISMA flow diagram, which can be found in Multimedia Appendix 3. Included studies will subsequently be selected for qualitative and quantitative analysis during the inclusion phase.

Risk of Bias and Methodological Quality Analysis

The review will conduct a descriptive analysis. There is no specific risk of bias tool for the type of study we expect to find. If applicable, we use the mobile health evidence reporting and assessment checklist in the individual studies [13].

Data Extraction and Data Synthesis

Independent reviewers (LFRO, LRV, and LMMSR) will extract data from the full text of eligible manuscripts using a predefined model. Any uncertainties or divergences will be resolved by a senior researcher (MSM). The following data items will be extracted from each publication: first author, journal and year of publication, country, the aim of the study, whether it was a multidisciplinary study team, corpus of terms used to develop the communication system, corpus examples, communication system development, intervention and testing, languages involved (oral and sign), evaluation or use in a real context, sample size (number of users), preconditions to use the technology and technology needed (hardware or software), development technology (artificial intelligence, imaging processing, etc), which health context (eg, general, emergency, and teleconsultation), technology readiness level (development and testing or if it is being marketed), testing: human users or video of human users, accuracy measures, metrics for evaluating communication effectiveness and parameters to assess to what extent innovation is addressing the communication needs of deaf persons, and ethical and software security issues. These data are detailed in Multimedia Appendix 4. Whenever possible, we will also seek to infer systems' characteristics of flexibility and scalability in various health care settings. Additionally, the research team will email researchers from all individual studies included in the systematic review to update the current status of their systems and to ensure the accuracy and relevance of the information presented in the systematic review. A qualitative analysis of the usability results will be performed for the review.

Results will be presented in a PRISMA flow diagram and a descriptive format (using tables and diagrams, if necessary) aligned with the objective and scope of the review. Results will be presented to carry out a descriptive analysis of the information in the table. For each variable extracted, a narrative summary will be provided, describing how the results relate to the review's objective.

Data Management

The abstracts and full text of manuscripts identified from the search will be uploaded to Rayyan software from Qatar Computing the Research Institute, a software developed specifically to expedite the screening of titles, abstracts, and manuscripts using a process of semiautomation [14]. After uploading the search results, duplicates will be removed in the Rayyan environment [15]. A data extraction form will be developed in Microsoft Excel and piloted before use.

Description of Statistical Methods and Software Used

If feasible, we intend to conduct statistical analysis to aggregate accuracy measures. However, we anticipate that this approach may not be sufficient. In such instances, the systematic review will proceed with a narrative review of the evidence, providing a qualitative synthesis of the findings.

Ethical Considerations

The systematic review does not require ethics approval, as all data used will be provided from published documents. The authors are committed to reporting any outcomes, even the unexpected ones, to ensure transparency and responsibility.

Results

A preliminary search was performed in April 2024. Researchers concluded the study selection by July 2024. Data extraction, synthesis, report, and recommendations are expected to be finished by February 2025. The review timeline is shown in Multimedia Appendix 5.

Discussion

Expected Findings

Communication barriers persist for deaf individuals in health care, urging solutions. In this context, this review aims to summarize the current literature on communication systems using human-computer interaction techniques for sign language users, in a health care context. As the main finding, we aim to reveal the current state of communication systems dedicated to improving health care interactions with deaf people and using a variety of advanced models to enhance accuracy and usability. Additionally, we seek to identify existing gaps in the development of these systems. We anticipate that the predominant focus on technical aspects or innovations may lead to a scarcity of manuscripts addressing communication outcomes, which should ideally be the primary focus, as it determines the effectiveness of communication.

Strengths

Sign language recognition is often considered less advanced compared to other recognition systems like facial or speech recognition. Several characteristics are important to enhance communication with deaf people using systems and devices, such as adequate screens, stable internet connection, qualified and trained professionals, interoperability of the system, safety for the patient and professional, and extensive testing [9]. Research in this field must focus on models that improve the accuracy of recognition systems and, more importantly, communication. To investigate these factors, a multidisciplinary staff including health, linguistic, and technology teams will participate in the search process, conducting and validating its progress. This would strengthen the results, as it broadens the results landscape. Another important strength to highlight is that the systems assessed in this review will not depend on a translator, as is the case for video remote interpretation. We believe that, if proven effective, these systems could enhance the autonomy of deaf individuals in managing their health care. Furthermore, these systems have the potential to surmount barriers related to patient privacy concerns and communication challenges. With the escalating integration of artificial intelligence techniques in health care, there is growing recognition that capturing signs or gestures and converting them into audio or written language, and vice versa, can significantly enhance accessibility to health care services, ranging from primary care facilities to emergency departments. Identifying information regarding the availability, usability, and implementation specifics of such systems stands as a crucial outcome to be unearthed.

In response to this urgent demand, our research group is diligently conducting a comprehensive and high-caliber systematic review. While the ultimate goal must consider context and innovation, it is paramount to prioritize meeting the needs of the ultimate end users: individuals who are deaf.

To identify and delineate these systems, along with associated contextual possibilities, use methods, required equipment, and technological development and testing, we will present a comprehensive findings panel and conduct a narrative comparison. This approach aims to facilitate a comprehensive overview and deeper understanding of the current state of the art. Our results are poised to offer valuable insights into the landscape of systems and the evolution of human-computer–assistive technologies used in aiding deaf patients.

In emergency care units, timely access to information is crucial for defining patient routes, conducting necessary examinations, and providing critical interventions and advice. Previous studies have shown that preventable adverse events are more likely to occur in cases with communication problems, particularly in emergency situations [7]. Despite the pressing need for studies in this area, testing interventions in emergency contexts is more complex, leading us to anticipate fewer analyses in this critical domain.

Limitations and Future Directions

This systematic review, while intended to be comprehensive, may encounter limitations impacting its conclusions. First, the diversity of sign language dialects, and the specificity of their use, might limit the generalizability of the findings across different cultural contexts. Additionally, the rapid evolution of technology in the field of sign language recognition systems may also mean that some of the reviewed technologies quickly become outdated.

With the results of this review, we expect to advocate future directions for the creation of more adaptive and inclusive communication systems, capable of learning from a broader spectrum of sign language dialects and styles. However, it specifically targets individuals who use sign language. This approach may not represent the entire deaf community, as some individuals may prefer lip reading, writing, or other forms of communication due to unfamiliarity with or reluctance to use sign language. Further studies should explore technologies aimed at enhancing communication for individuals with varying degrees of hearing impairment and differing abilities in sign language proficiency. Expanding research in this direction can

contribute significantly to addressing the diverse communication needs within the deaf and hard-of-hearing community.

Our team plans to disseminate the protocol and findings of this research in forums with public authorities, academies, and the population to present solutions for improving effective communication in health services, especially involving the most vulnerable populations. In addition, as social media has a relevant impact on our society, all the results will be posted on social media as well to be available to the population.

Acknowledgments

This study was funded in part by the National Institute of Science and Technology for Health Technology Assessment (*Instituto de Avaliação de Tecnologias em Saúde*)/National Council for Scientific and Technological Development (*Conselho Nacional de Desenvolvimento Científico e Tecnológico*; grant 465518/2014-1), *Financiadora de Estudos e Projetos* (grant 01.21.0097.00), and SignumWeb Comunicação Inclusiva Ltda, as part of the project "*Captar-Libras: Sistema de Comunicação por vídeos para surdos aplicado ao pré-atendimento médico*." MSM, MFMC, and LRV were supported in part by *Conselho Nacional de Desenvolvimento Científico e Tecnológico* (grant 310561/2021-3, grant 316841/2021-8, and grant 134878/2023-0, respectively). The funding sources had no role in the design of this study and will not have any role during its execution, analyses, interpretation of the data, or decision.

Data Availability

All data generated or analyzed during this study are included in this published paper and its supplementary information files.

Authors' Contributions

MSM, LFRO, LRV, ROP, and ZSNR developed a draft of the literature search, which was executed by LFRO and LRV. MSM, ROP, ZSNR, TBCS, and MFMC guided the construction of the protocol, and MSM is a guarantor of the review. MSM, LFRO, LRV, and LMMSR drafted the manuscript; all the other authors performed critical revisions. ELAB is a linguistic professor who is a specialist in sign language. She has revised the whole manuscript to ensure that language complies with disability and deaf literature. All authors read and approved the final manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
PRISMA-P (Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols) checklist.
[DOCX File , 38 KB - resprot_v14i1e55427_app1.docx]

Multimedia Appendix 2
Search strategy.
[DOCX File , 14 KB - resprot_v14i1e55427_app2.docx]

Multimedia Appendix 3
PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) flowchart.
[DOCX File , 65 KB - resprot_v14i1e55427_app3.docx]

Multimedia Appendix 4
The variables analyzed in the systematic review.
[DOCX File , 196 KB - resprot_v14i1e55427_app4.docx]

Multimedia Appendix 5
Gantt chart for the project timetable.
[DOCX File , 20 KB - resprot_v14i1e55427_app5.docx]

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Abbreviations

OSF: Open Science Framework
MeSH: Medical Subject Headings
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analysis
PRISMA-P: Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols

Edited by S Ma; submitted 12.12.23; peer-reviewed by MC Velarde, Y Chu; comments to author 20.02.24; revised version received 11.03.24; accepted 12.06.24; published 23.01.25.

Please cite as:
Marcolino MS, Oliveira LFR, Valle LR, Rosa LMMS, Reis ZSN, Soares TBDC, Bernardino ELA, Cordeiro RAA, Prates RO, Campos MFM
Sign Language Recognition System for Deaf Patients: Protocol for a Systematic Review
JMIR Res Protoc 2025;14:e55427
URL: https://www.researchprotocols.org/2025/1/e55427
doi:10.2196/55427
PMID:39847417

Protocol

Role of Injectable Platelet-Rich Fibrin in the Management of Soft and Hard Tissue Periodontal Regeneration in Dentistry: Protocol for a Systematic Review

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Abstract

Background: Injectable platelet-rich fibrin (i-PRF) has the capacity to release great amounts of several growth factors, as well as to stimulate increased fibroblast migration and the expression of collagen, transforming growth factor β, and platelet-derived growth factor. Consequently, i-PRF can be used as a bioactive agent to promote periodontal tissue regeneration.

Objective: We aim to compare and evaluate the effectiveness of i-PRF in periodontal tissue regeneration.

Methods: We will conduct an electronic search in the following databases: PubMed, Cochrane Library, Google Scholar, Semantic Scholar, Scopus, and Web of Science. Papers will be restricted to those in English and to those that are randomized controlled trials comparing PRF or any other biomaterial with i-PRF for periodontal regeneration during dental treatment. The included papers in this review and the reference lists of pertinent reviews will be manually searched. The selection of studies, data extraction, and assessment will be carried out separately by 2 reviewers using the Risk of Bias 2 tool for the included research.

Results: The success of i-PRF will be evaluated by comparing the mean difference in periodontal regeneration of soft and hard tissues in terms of gingival recession, probing pocket depth, clinical attachment level, bone gain, and gingival width. The combined effect size measurements and the associated 95% CIs will be estimated using a random-effects model. The synthesis or work for this systematic review started in October 2023 and will last until December 2025.

Conclusions: i-PRF may play a role in dentistry and could enhance soft and hard tissue regeneration.

Trial Registration: PROSPERO CRD42023464250; https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=464250

International Registered Report Identifier (IRRID): PRR1-10.2196/65137

(JMIR Res Protoc 2025;14:e65137) doi:10.2196/65137

KEYWORDS

injectable platelet-rich fibrin; pulp regeneration; periodontal regeneration; periodontium; tissue engineering

Introduction

Rationale

A leucocyte-enriched platelet-rich concentrate called injectable platelet-rich fibrin (i-PRF) has recently been researched and developed to help in wound healing and increase the success of periodontal tissue regeneration [1,2]. The objective of developing an i-PRF formulation is to provide specialists with a platelet concentration in liquid form that is simple to administer and may be mixed with various biomaterials or used alone [3-6]. By adopting slower and shorter centrifugation rates, i-PRF yields significantly more regenerated cells and higher concentrations of growth factors than prior PRF formulations that used faster centrifugation speeds [7]. i-PRF has been shown

to produce more fibroblast migration and have higher levels of growth factor production, as well as superior antibacterial adhesive action against a range of periodontal disease pathogens [8].

i-PRF is a novel platelet-rich concentrate that enhances periodontal tissue regeneration due to its "supraphysiological" growth factors and cell concentrations [1]. The slow release of growth factors is possible due to the dynamic fibrin liquid gel that i-PRF delivers, which embeds platelets rich in leucocytes, collagen type I, osteocalcin, and growth factors even in their liquid phase. i-PRF can improve intrinsic tissue regeneration by generating human mesenchymal stem cells (MSCs) and starting osteogenic differentiation in MSCs [9]. By allowing the inclusion of grafts without the need for additives or anticoagulants, i-PRF creates a well-agglutinated "sticky bone graft" [1].

The applicability of i-PRF as a promising regenerative adjuvant in periodontal tissue regeneration has been validated by clinical research [2]. Liquid PRF permits other alterations, like incorporating different biomaterials, in an injectable form [10]. One of the components that makes up i-PRF is fibronectin, which is an extracellular glycoprotein with a high molecular weight (approximately 440 kDa) [4,6,11]. It has been demonstrated that i-PRF centrifugation at a horizontal angle is far more effective than traditional fixed-angle centrifugation at accumulating more cells and growth factors. The physician can construct customized clotted PRF membranes (biografts) by manipulating i-PRF before clotting, which can then be combined with different regenerating agents [9].

Objective

This systematic review will determine the effect of i-PRF in the management of soft and hard tissue periodontal defects in the context of periodontal tissue regeneration. The review will highlight the use of i-PRF as a bioactive agent capable of stimulating periodontal tissue regeneration.

Methods

Overview

We aim to ascertain whether i-PRF is effective in soft and hard tissue regeneration in periodontics by conducting a systematic review of the literature.

Eligibility Criteria

We will examine eligible studies and describe how i-PRF is used for the treatment of pulp and periodontal tissue regeneration. The publications that qualify will be limited to those published in English. There will be no restrictions on publication date. We will search the identified publications' reference lists for more papers that might meet the eligibility requirements. This review will cover the research designs of clinical randomized controlled trials (RCTs).

Information Sources

We will search the following electronic databases for papers that fit the review's eligibility requirements: PubMed, Cochrane Library, Google Scholar, Semantic Scholar, Scopus, and Web of Science.

Search Strategy

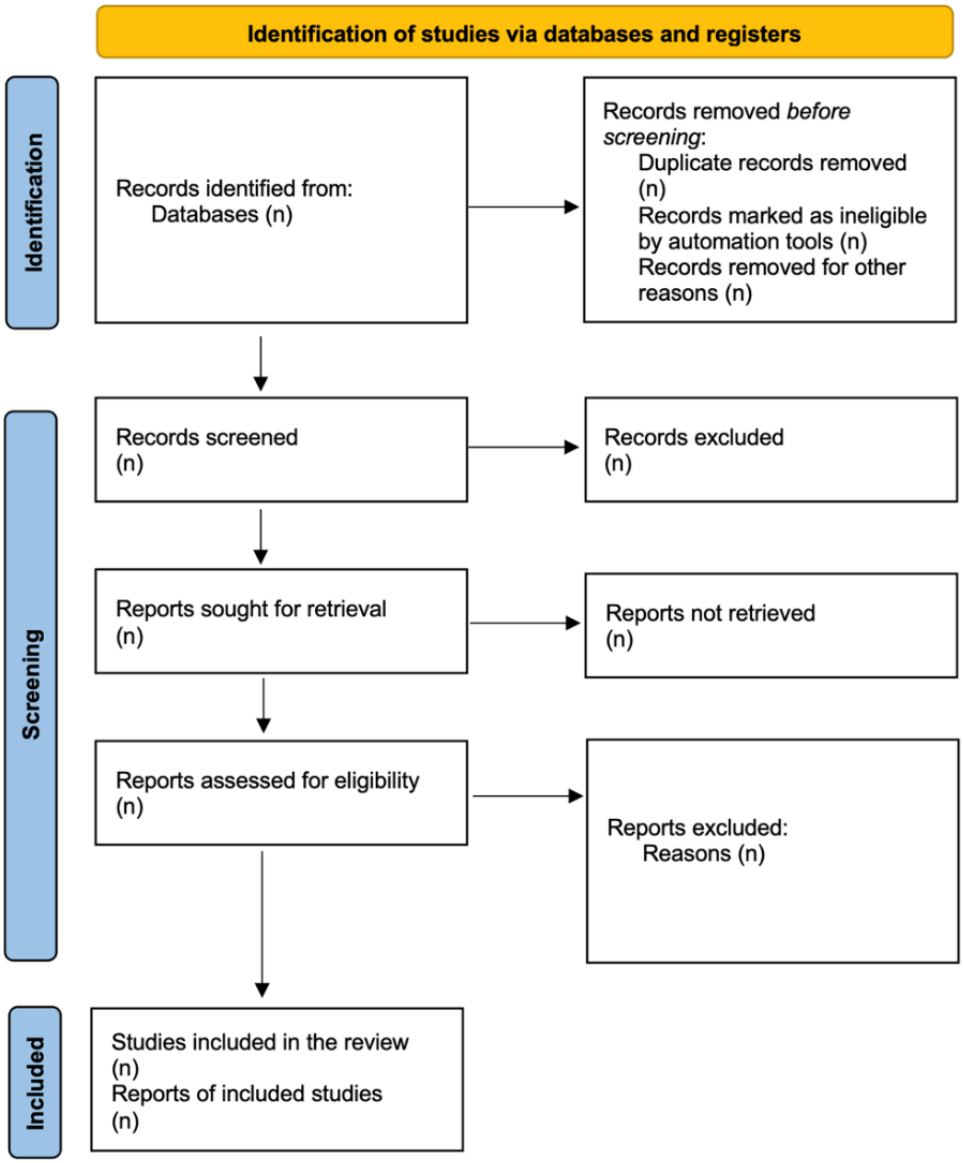
First, a restricted search of MEDLINE was carried out to find applicable papers. A comprehensive search method was developed using words found in the titles, abstracts, and keywords.

Study Selection, Data Management, and Data Collection Process

When choosing which studies to include, the 3 reviewers (US, PB, and MW) will refer to the eligibility criteria. Records management and duplicate removal will be facilitated by the recording of selections. Blind screening of studies will be used, and differences will be settled through discussion. Two researchers will load the retrieved studies and perform title and abstract screening. Two authors will conduct a full-text review, and any disagreements will be settled by discussion or, if necessary, a third reviewer. A summary of the study selection procedure is given in Figure 1.

Reviewers will be guided by a data extraction tool applied to the included articles. Systemically healthy patients and patients receiving periodontal or pulp regenerative therapy will be included in the RCTs. Patients with a history of systemic illness, as well as pregnant women, will be excluded. A narrative summary of the results from the included research will be provided. We will assess methodological, statistical, and clinical heterogeneity. If there is enough homogeneity among the included studies, a quantitative synthesis, or meta-analysis, will be carried out.

Figure 1. Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) flowchart.



Data Items

Two separate, blinded reviewers (US and PB) will each record the extracted data in duplicate. The extracted data, which will include publication details, the research study's setting, the regeneration agent, adjunctive treatment, and the defect type, will be entered into a Microsoft Excel spreadsheet. Clinical determinants will include periodontal clinical parameters, osseous defect fill, and soft tissue parameters.

Outcomes and Prioritization

The primary outcome is to determine the role of i-PRF in soft and hard periodontal tissue regeneration in dentistry. The secondary outcomes will be whether i-PRF improves probing pocket depth reduction, gain in clinical attachment loss, and osseous fill in periodontal osseous defects.

Risk of Bias

The Risk of Bias 2 (RoB 2) tool will be used to evaluate the risk of bias in included studies and to verify the methodological quality of the reviews. The assessments will be completed by 2 different reviewers (US and MW), with the 2 other reviewers (PB and MP) acting as arbiters to settle any disputes. The entire process will be concealed from the reviewers.

Data Synthesis and Assessment of Heterogeneity

Statistical heterogeneity will be assessed with a random-effects model. If there is enough homogeneity among the included studies, a quantitative synthesis, or meta-analysis, will be carried out. The goal is, if at all feasible, to carry out a subgroup analysis based on the effects of various i-PRF preparation protocols on the regeneration of hard and soft tissues by varying centrifugation force, revolutions per minute, and time. Using statistical software, the results will be aggregated and computed according to the statistical guidelines cited in the most recent edition of the *Cochrane Handbook for Systematic Reviews of Interventions*.

Results

This study is to be completed from October 2023 to December 2025. Each stage of the procedure will involve the blinding of

2 reviewers. To resolve disagreements or conflicts between the reviewers, regular team meetings will be convened. This will help to improve the review process's transparency. Every conversation will be documented. The systematic review will be submitted for publication as soon as it is finished. The planned review has been registered with PROSPERO (CRD42023464250) and will be carried out in compliance with the guidelines provided in the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) checklist.

Discussion

Anticipated Findings

i-PRF in the periodontal regenerative process offers hope for improved patient outcomes and enhanced therapeutic interventions [12,13]. It might help to provide improved healing and periodontal tissue reconstitution in the context of improvement in osseous fill or bone gain, as well as soft tissue fill, by reducing probing pocket depth and increasing clinical attachment loss. i-PRF might potentially act as a bioactive agent capable of inducing tissue regeneration. Wang et al [14] contrasted i-PRF to conventional platelet-rich plasma (PRP) and examined the osteoblast behavior of a unique therapeutic i-PRF that was 100% natural and additive-free. They found a noticeable increase in the messenger RNA levels of osteocalcin, Runx2, alkaline phosphatase, and immunofluorescent staining of osteocalcin when comparing an i-PRF group to a PRP group. The results of that study favored the use of naturally formulated i-PRF in conjunction with anticoagulants over PRP [14].

Varela et al [15] investigated the blood cell composition, morphological characteristics, type I collagen gene expression, and growth factor release of i-PRF. Blood samples from 15 people were used to create i-PRF samples. The study found that i-PRF was a potentially effective treatment option for the healing of soft and mineralized tissues because it promoted the development of a 3D fibrin network comprising platelets, leukocytes, type I collagen, osteocalcin, and growth factors. Indeed, given its flowable mixing capabilities with other biomaterials and simplified procedures, i-PRF may be used in various dental applications [15]. Iozon et al [4] investigated how human gingiva–derived mesenchymal stem cells (MSCs) proliferated and underwent osteo-differentiation in response to i-PRF; they concluded that gingiva-derived MSC proliferation was promoted by 5% i-PRF, but that an overabundance of i-PRF may hamper osteogenic induction [4].

Strengths and Limitations

To the best of our knowledge, this is the first systematic review to focus on whether i-PRF aids in tissue regeneration. The integration of qualitative as well as quantitative data synthesis in this study will help in promoting oral and periodontal health.

Limitations of this systematic review may include variations in the study design, sample size, and methodological quality of the included studies, as well as potential bias in reporting outcomes related to the use of i-PRF for periodontal tissue regeneration. Additionally, heterogeneity in treatment protocols, variations in PRF preparation methods, and differences in follow-up duration may influence the generalizability of findings. Publication bias and the exclusion of non–English language studies could further affect the comprehensiveness of the review.

Conclusion and Directions for Dissemination

This study aims to assess whether i-PRF has the potential for regeneration of periodontal structures. If we find that the intervention has an effect, the results will aid in tissue engineering, maintaining and promoting osseous defect gain by osseous fill, and hastening healing. Results from this study will be published in national and international academic journals. This protocol follows the PRISMA-P guidelines (Multimedia Appendix 1).

Acknowledgments

The authors acknowledge the help from the Datta Meghe Institute of Higher Education and Research, as well as the databases and resources that are needed for the data synthesis. All authors declared that they had insufficient funding to support open access publication of this manuscript, including from affiliated organizations or institutions, funding agencies, or other organizations. JMIR Publications provided article processing fee (APF) support for the publication of this article.

Data Availability

Data sharing is not applicable to this article as no data sets were generated or analyzed during this study.

Authors' Contributions

All authors contributed to the drafting and writing of the manuscript. US and PB conceptualized and registered the work. MW and MP worked on drafting the initial manuscript and on study design. Final study design and manuscript writing were done by US. All authors checked and finalized the manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1

Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) checklist.
[DOCX File , 33 KB - resprot_v14i1e65137_app1.docx]

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Abbreviations

i-PRF: injectable platelet-rich fibrin
MSC: mesenchymal stem cell
PDGF: platelet-derived growth factor
PRISMA-P: Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols
PRP: platelet-rich plasma
RCT: randomized controlled trial
RoB 2: Risk of Bias 2

Edited by T Leung; submitted 06.08.24; peer-reviewed by A Elfana, S Bernardi, K Xiu; comments to author 11.10.24; revised version received 13.10.24; accepted 26.12.24; published 23.01.25.

Please cite as:
Shirbhate U, Bajaj P, Wanjari M, Patil M
Role of Injectable Platelet-Rich Fibrin in the Management of Soft and Hard Tissue Periodontal Regeneration in Dentistry: Protocol for a Systematic Review
JMIR Res Protoc 2025;14:e65137
URL: https://www.researchprotocols.org/2025/1/e65137
doi:10.2196/65137
PMID:

Protocol

Effectiveness of Gastric Cancer Endoscopic Screening in Intermediate-Risk Countries: Protocol for a Systematic Review and Meta-Analysis

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Abstract

Background: Gastric cancer (GC) is the fifth most prevalent neoplasm worldwide and the fourth with the highest mortality, and its geographical distribution is not homogeneous with high-risk, intermediate-risk (IR), and low-risk areas. Advanced stages at diagnosis are related to high mortality, but early detection greatly increases the chances of survival. Upper endoscopy with biopsy is the gold standard for GC diagnosis. Several studies have investigated the relevance of endoscopic screening and how to implemente it in IR countries. However, most Western societies recommend screening only in selected populations with high-risk factors for GC. No systematic reviews on GC endoscopic screening in IR countries exist.

Objective: We aimed to determine the effectiveness of endoscopic GC screening in IR countries.

Methods: We will include randomized and nonrandomized controlled trials, cohort studies, case-control studies, cross-sectional studies, and economic studies focusing on endoscopic screening of GC in the asymptomatic population of IR countries. The search will be conducted in MEDLINE, SCOPUS, Embase, and Web of Science. Other gray literature sources will be additionally searched. Studies published in English, Portuguese, or Spanish until September 2024 will be included. Two independent reviewers will screen the titles and abstracts of all search results. The selected studies will then be fully analyzed, and the data will be collected and coded in a database. To minimize the risk of bias, the included studies will undergo a quality analysis according to Cochrane risk of bias tools, RoB 2 of randomized trials and ROBINS-I for nonrandomized trials; Newcastle-Ottawa Quality Assessment Scale for case-control and cohort studies; and National Heart, Lung and Blood Institute study quality assessment tools for cross-sectional studies. The data collected will be cataloged in 2 categories: efficacy or effectiveness data and economic data, and separate meta-analyses will be performed for each category if appropriate.

Results: This study is expected to provide results on the efficacy, effectiveness, and cost-effectiveness of endoscopic screening in an IR population. To date, 969 studies were screened for title and abstract, 75 were selected for full-text screening, and 44 were retained for data analysis. Additionally, 2 studies were selected from our manual search. Currently, the study is in the early stages of data extraction and risk of bias assessment and is expected to be published in the first quarter of 2025.

Conclusions: To our knowledge, this review will be the first to provide evidence on the effectiveness of endoscopic GC screening in IR countries. In doing so, we believe we will help guide future research, inform health care decisions and assist policy makers in this area, and support future decisions to implement GC screening programs in this type of population.

Trial Registration: PROSPERO CRD42024502174; https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=502174
International Registered Report Identifier (IRRID): DERR1-10.2196/56791

(JMIR Res Protoc 2025;14:e56791) doi:10.2196/56791

KEYWORDS

gastric cancers; endoscopic screening; intermediate-risk countries; neoplasia; early detection; diagnosis; cancer screening; survival; meta-analysis; gastrointestinal cancers

Introduction

Gastric adenocarcinoma, also known as gastric cancer (GC), is a malignant neoplasm resulting from anarchic growth of gastric mucosal gland cells [1]. It is a heterogeneous disease with multiple clinical, histological, and molecular variables that influence its presentation [1,2].

According to data from The Global Cancer Observatory 2022, GC is the fifth most common and the fifth most lethal neoplasm worldwide [3]. Its geographical distribution is not homogeneous: there are high-risk areas with incidence 20 and more (age-standardized rate measured per 100,000 people-year; eg, Japan, South Korea, or Mongolia); intermediate-risk (IR) areas with age-standardized rate 10 and more and less than 20 (eg, Portugal or China); and low-risk areas with age-standardized rate 10 or less (United States, United Kingdom, Switzerland, or Germany) [2,3].

Diagnosis at an advanced stage and the aggressiveness of the disease result in a 5-year survival rate of between 20% and 40% [4]. In contrast, early-stage GC has an excellent prognosis, with a 5-year survival rate of greater than 90%, and can often be treated with minimally invasive and organ-sparing techniques such as endoscopic resection [5]. Therefore, early detection of cancer greatly increases the chances of successful treatment. The 2 components of cancer screening are early diagnosis and screening. The former focuses on detecting symptomatic patients as early as possible, while the latter involves testing healthy individuals to identify those with the disease before symptoms occur [6]. The symptoms of stomach cancer are nonspecific and usually develop late, meaning that detection based on symptoms would not detect the disease in its early stages. On the other hand, screening programs should be implemented when: their effectiveness has been demonstrated; the resources needed to implement them are sufficient to cover the target population; there are facilities to confirm the diagnosis, treatment, and follow-up of those with positive results; and the prevalence of the disease is high enough to justify the effort and cost of the screening program [6]. Therefore, the decision to implement the screening program requires that these conditions are met. Several methods have been proposed to screen for GC, namely serological markers, biomarkers, molecular or genetic tests, or more invasive techniques such as upper gastrointestinal endoscopy [7]. The latter, which allows direct visualization of the gastric mucosa and collection of biopsies for histological examination, is considered the gold standard technique for definitive diagnosis of GC [8].

In some high-risk countries, such as Japan and South Korea, GC screening programs have been in place for several years and have been shown to reduce mortality and increase early detection and 5-year survival rates [9-11]. The same has been demonstrated in screening programs developed in China [12,13].

In Western IR countries, several studies have been developed to determine the relevance of screening and how it might be developed. Of particular importance was the study developed by Areia et al [14], which showed that endoscopic screening for GC in IR countries can be cost-effective when combined with endoscopic screening for colorectal cancer. This has been included in the recommendations of the United European Gastroenterology and the European Society of Gastrointestinal Endoscopy [14-16]. Despite this evidence and the recommendations, most Western Societies continue to recommend screening only in selected populations with high-risk factors for GC [16,17]. Furthermore, and to the best of our knowledge, there are no systematic reviews on GC endoscopic screening in IR countries. With this systematic literature review, we aim to analyze the scientific evidence published until September 2024 on the cost-effectiveness of endoscopic screening for GC in IR countries.

This study aims to determine the effectiveness and economic viability of endoscopic GC screening in IR countries**,** which will answer the research question, “What is the effectiveness of endoscopic screening for GC in IR countries?”

These objectives are defined according to the Population, Intervention, Comparison, Outcome and Study Design (PICOS) framework (Textbox 1).

Textbox 1. Population, Intervention, Comparison, Outcome and Study Design (PICOS) framework for the systematic review and meta-analysis.

PICOS question: What is the effectiveness of endoscopic screening for gastric cancer (GC) in intermediate-risk countries?

- Population:

  Asymptomatic population of intermediated-risk countries (countries with incidence age-standardized rate 10-20 per 100.000 person/years: Tajikistan, Iran, Azerbaijan, Kyrgyzstan, Bhutan, Belarus, Peru, Mali, Chile, Costa Rica, Democratic People Republic of Korea, China, Kazakhstan, Russian Federation, Viet Nam, Estonia, Colombia, Portugal, Ecuador, Albania, Guadeloupe [France], Guatemala, Latvia, Armenia, Turkmenistan, Myanmar, Samoa, Turkey, Lithuania, Lao People's Democratic Republic, Sao Tome and Principe, Afghanistan, Martinique [France], Brunei Darussalam, Zimbabwe, and Uzbekistan), between 40 and 80 years of age, without diagnostic of GC or precancerous lesions.
- Intervention: Endoscopic screening for GC.
- Comparison: No screening for GC.
- Outcome: The effectiveness of endoscopic screening of GC is defined as the detection rate of Helicobacter pylori; detection rate of precancer lesions; detection rate of GC; detection rate of early GC; stage at diagnosis; mortality rate of GC of screened versus nonscreened patients; 5-year survival rate of GC screened; and costs of screening program.
- Study designs: Randomized controlled trials, nonrandomized controlled trials, cohort studies, case-control studies, cross-sectional studies, and cost-effectiveness studies.

Methods

This study will follow the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [18] and PICOS criteria for comprehensive assessment.

Eligibility Criteria

The inclusion criteria include studies published as free full papers in English, Portuguese, or Spanish until September 2024, from countries with an IR for GC (countries with incidence age-standardized rate 10-20 per 100,000 person/years: Tajikistan, Iran, Azerbaijan, Kyrgyzstan, Bhutan, Belarus, Peru, Mali, Chile, Costa Rica, Democratic People Republic of Korea, China, Kazakhstan, Russian Federation, Viet Nam, Estonia, Colombia, Portugal, Ecuador, Albania, Guadeloupe [France], Guatemala, Latvia, Armenia, Turkmenistan, Myanmar, Samoa, Turkey, Lithuania, Lao People's Democratic Republic, Sao Tome and Principe, Afghanistan, Martinique [France], Brunei Darussalam, Zimbabwe, Uzbekistan); eligible study designs are randomized controlled trials, nonrandomized controlled trials, cohort studies, case-control studies, cross-sectional studies, and cost-effectiveness studies; and no filters or restrictions related to year of publication or publication status, will be applied.

The exclusion criteria include systematic reviews and other types of reviews, meta-analyses, case series, case reports, and other publication types such as editorials, commentaries, notes, letters, and opinions.

Information Sources

The information sources for this systematic review are electronic databases (MEDLINE, SCOPUS, Embase, and Web of Science). To capture additional studies (gray literature), manual searches will include published abstracts from the most relevant international gastroenterology and endoscopy conferences, clinical trial registries for ongoing studies, reference lists of included studies or other published reviews or meta-analyses. Authors of unpublished studies or published studies in which data are missing will be contacted to confirm eligibility.

Search Strategy

The search strategy follows the Peer Review of Electronic Search Strategies (PRESS) guidelines [19]. The search will be conducted in MEDLINE, SCOPUS, Embase, and Web of Science and the search strategy will be tailored to each database using database-specific search terms (Multimedia Appendix 1).

Selection Process

The references, including the abstract of studies retrieved after searching each database, will be imported to Rayyan (Rayyan Systems, Inc), an open-source software that allows several reviewers to blindly access the inclusion or exclusion of studies in literature reviews registering the entire process. This software will analyze and merge the potential duplicates, under operator validation. The initial selection process will be carried out by 2 independent reviewers (MBM and NP) based on the title and abstract. Studies will be classified as "included," "excluded," or "maybe." The selection process will be blinded and supervised by 2 other independent authors (FT and ABP). Conflicts and "maybe" assessments will be resolved between the 2 reviewers with the support of 2 authors (FT and ABP). After the final list of included studies is obtained, the full texts are retrieved. The full text of each study will be analyzed by 3 independent reviewers (MBM, NP, and ABP), and a decision taken on inclusion or exclusion. The list of items included is exported to a Microsoft Excel database where the data to be analyzed are entered.

The agreement rate will be calculated using Cohen κ, Egger regression, and Begg regression and will be reported at all stages of the selection process (title screening, abstract screening, and full-text screening).

Data Collection Process

Data from included studies will be collected by 2 reviewers (MBM and NP) and inserted into a Microsoft Excel database with data coding. The data collected will be cataloged in 2 categories: efficacy or effectiveness data and economic data, and separate meta-analyses will be performed for each of these categories.

For the statistical analyses and meta-analysis of the data collected, the authors will use SPSS (version 29.0.2.0; IBM Corp) and Jamovi (version 2.5; The jamovi Project). Bibliographic references will be managed in Zotero (Corporation for Digital Scholarship) software. Artificial intelligence tools may be used to extract and analyze data.

Data Items

The data collection form will include the items or variables defined in outcomes (Table 1) and other variables (Table 2).

Table 1. Variables related to outcomes of screening and cost-efficiency.

Variable	Definition or domain
Endoscopic screening	Number of individuals screened by endoscopy.
Frequency of screening	Frequency of endoscopic screening in years.
Age range covered by screening	Age at start and end of screening.
Screening adherence rate	Percentage of invited individuals that did the screening.
Number of biopsies	Total number of biopsies performed in the study.
Helicobacter pylori diagnosis rate	Percentage of individual screened that were diagnosed with *Helicobacter pylori*.
Detection rate of premalignant lesions	Number of premalignant lesions (atrophic gastritis, intestinal metaplasia and low-grade intraepithelial neoplasia, formerly low-grade dysplasia) / total number of upper endoscopies performed.
Gastric cancer detection rate	Number of gastric cancers diagnosed by screening endoscopy / total number of screening upper endoscopies performed.
Early gastric cancer detection rate	Number of early gastric cancers (high-grade intraepithelial neoplasia and mucosal adenocarcinoma) detected by endoscopic screening / total number of gastric cancers detected by endoscopic screening.
Lethality rate	Number of people who died from gastric cancer diagnosed by endoscopic screening / population at risk during the study period.
5-year survival rate in patients diagnosed with gastric cancer at screening	Percentage of patients diagnosed with stomach cancer at screening who live at least 5 years after diagnosis.
Incremental cost-effectiveness ratio	Value (in euro) of implementing the upper endoscopy screening program (or adding it to other existing screening programs, eg, endoscopic screening for colorectal cancer).

Table 2. Other variables

Variable	Domain
Study Bibliographic Reference	• Reference
Country or countries of origin of the study	• Country
Study design	• Randomized controlled trial • Nonrandomized controlled trial • Cohort • Case-control • Cross-sectional • Cost-effectiveness
Population or sample	• Base population potentially to be screened by upper endoscopy
Participants	• Age • Sex distribution

Risk of Bias in Individual Studies

To minimize the risk of bias, the included studies will undergo a quality analysis according to Cochrane risk of bias tools, RoB 2 of randomized trials and ROBINS-I, for nonrandomized trials; Newcastle-Ottawa Quality Assessment Scale [20] for case-control and cohort studies; and National Heart, Lung and Blood Institute study quality assessment tools [21] for cross-sectional studies. The Consensus on Health Economic Criteria (CHEC) list [22] will be used for the assessment of the methodological quality of cost-effectiveness studies.

Studies with low quality or high risk of bias will be reported and not be used for meta-analysis.

Data Synthesis

If it is possible to collect quantitative data from the selected studies, we will perform 2 separate meta-analysis: one to report the effect size of 5 outcomes in studies reporting efficacy or

effectiveness of endoscopic screening for GC (detection rate of premalignant lesions, detection rate of GC, detection rate of early GC, and 5-year survival rate and mortality of GC diagnosed in screening programs); other to report the effect size of cost-effectiveness of endoscopic screening for GC in IR countries.

If appropriate (at least 2 studies per outcome) [23], pooled rates and odds ratio along with 95% CIs will be calculated for GC detection, early GC detection, adherence to the screening program, and GC mortality using random-effects model, using SPSS, Jamovi, and Meta-Essentials for Microsoft Excel (Erasmus Research Institute of Management). The I^2 homogeneity will also be performed to check the need for subgroup analysis (moderation analysis).

If it is not possible to carry out a meta-analysis due to insufficient data, an executive summary is prepared that summarizes the data from the studies included in the systematic review.

Meta-Bias(es)

After evaluating the biases of individual studies and ensuring that all studies that may be of interest for their conclusions are integrated into the review, a summary of the risks of bias in the meta-analysis or meta-synthesis will be presented.

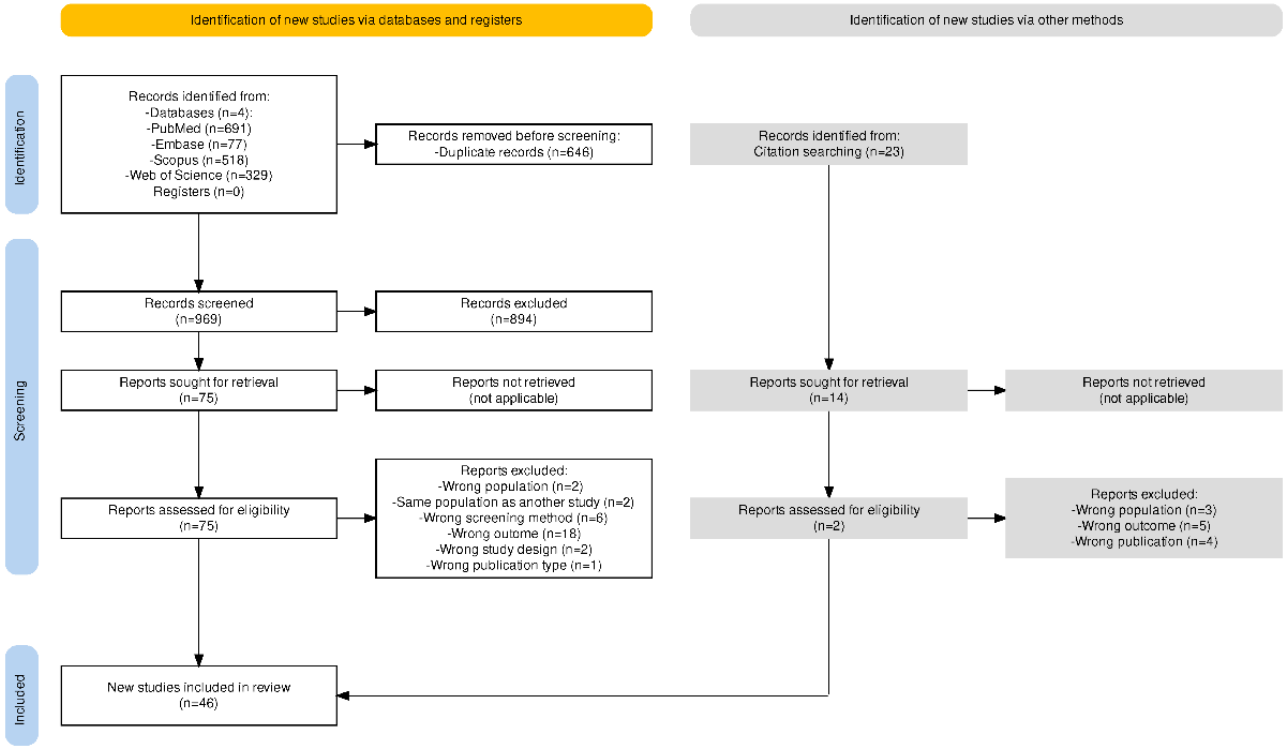
Confidence in Cumulative Evidence

The strength of the body of evidence will be assessed with Grading of Recommendations, Assessment, Development and Evaluation (GRADE) [24].

Results

Our initial search of the 4 electronic databases, using descriptors adapted for each database, identified 1615 studies of potential interest (Figure 1). After excluding duplicates, 969 studies were screened for title and abstract. Of these, 75 were selected for full-text screening. We retained 44 studies for data analysis and the remaining 31 studies were excluded for the following reasons: wrong population (n=2), same population as another study (n=2), wrong screening method (n=6), wrong outcome (n=18), wrong study design (n=2), and wrong publication type (n=1). In addition, our manual search identified 23 publications of potential interest, of which 2 were selected for the data extraction phase. Currently, the study is in the early stages of data extraction and risk of bias assessment and is expected to be published in the first quarter of 2025.

Figure 1. Flowchart of PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses). NA: not applicable.



Discussion

This protocol outlines the methods for a systematic literature review and meta-analysis of published primary scientific studies on the effectiveness of endoscopic GC screening in IR countries.

This study will provide results on the following outcomes: frequency of screening, age range covered by screening, screening adherence rate, number of biopsies, *Helicobacter pylori* diagnosis rate, detection rate of premalignant lesions, GC detection rate, early GC detection rate, lethality rate, 5-year survival rate in patients diagnosed with GC at screening, and incremental cost-effectiveness ratio.

To the best of our knowledge, this is the first systematic review of the effectiveness of endoscopic screening for GC in IR countries and it is expected that the presentation of these results will shed light on the relevance of endoscopic GC screening in these populations. The benefit of performing screening upper endoscopy for asymptomatic individuals for GC remains

controversial [25]. Due to the high burden of GC, countries in East Asia such as Japan and Korea have implemented nationwide population-based GC screening strategies to reduce incidence and mortality [9,26]. Other studies have shown that endoscopic screening for GC is cost-effective in the IR to high-risk population [14,27]. However, to date, we have not found a systematic review that synthesizes the results of all studies conducted in IR countries, and for this reason, our systematic review is of particular interest to inform health policy makers in IR countries about the effectiveness of endoscopic screening for GC in this type of population.

An extensive search of databases and gray literature will be conducted to identify all relevant studies. However, this review may have some important limitations. First, it is important to bear in mind that the majority of IR countries, especially Western countries, do not yet have population-based screening for this pathology, which may make it difficult to obtain primary studies on this topic from these countries. Second, although China is an IR country with endoscopic screening for GC, some studies reporting the results of these screening programs are written in Chinese and cannot be included in our review. Nevertheless, we will conduct an intensive search of the databases to ensure that we obtain studies written in English, Portuguese, or Spanish that report the results of these screening programs. Third, on the other hand, the Chinese territory is so large that risk varies greatly between different areas of the country, which may introduce a significant bias if some included studies are based only on results of high-risk areas, as this type of population may have different characteristics from those observed in other areas of China or other IR countries. These limitations will be reported in the final paper of the systematic review so that our results can be interpreted rigorously and truthfully. The final paper of the systematic review and meta-analysis will be published in the first quarter of 2025.

With this systematic review and meta-analysis, we hope to contribute to the design of GC screening strategies in IR countries, with the primary goal of reducing mortality from this disease. In the future, it may be necessary to update this systematic review as a new consortium. Towards Gastric Cancer Screening Implementation in the European Union [28] has recently been established in Europe to study and implement GC screening in this area.

Acknowledgments

The protocol and systematic review publication are supported by the main author and her company TrueConnection Lda. The company's mission is to train health care professionals, provide medical services, and conduct clinical research. We are grateful to Master Ricardo Serra and Dr Ricardo Bagina for their collaboration at various stages of the revision of this manuscript. No artificial intelligence support was used in the creation of this manuscript, except for grammar and style corrections.

Data Availability

All data generated or analyzed during this study are included in this published article (and its supplementary information files).

Authors' Contributions

MBM was responsible for designing and writing the protocol. NP provided assistance with protocol design and writing. AB was responsible for reviewing the writing of the manuscript. FT provided assistance with protocol design. RC was responsible for designing the search expression in the various databases. IF and MA were involved in protocol design and manuscript review. RD was responsible for the revision of the manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Search strategy.
[PDF File (Adobe PDF File), 27 KB - resprot_v14i1e56791_app1.pdf]

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Abbreviations

CHEC: Consensus on Health Economic Criteria
GC: gastric cancer
GRADE: Grading of Recommendations, Assessment, Development and Evaluation
IR: intermediate-risk
PICOS: Population, Intervention, Comparison, Outcome and Study Design
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRESS: Peer Review of Electronic Search Strategies

Edited by A Schwartz; submitted 27.01.24; peer-reviewed by A Hassan, G Esposito; comments to author 16.09.24; revised version received 26.09.24; accepted 14.11.24; published 03.02.25.

Please cite as:
Mourato MB, Pratas N, Branco Pereira A, Taré F, Chança R, Fronteira I, Dinis R, Areia M
Effectiveness of Gastric Cancer Endoscopic Screening in Intermediate-Risk Countries: Protocol for a Systematic Review and Meta-Analysis
JMIR Res Protoc 2025;14:e56791
URL: https://www.researchprotocols.org/2025/1/e56791
doi:10.2196/56791
PMID:39545590

Protocol

Mesenchymal Stem Cell Therapy for Acute Myocardial Infarction: Protocol for a Systematic Review and Meta-Analysis

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Abstract

Background: Medical therapy and interventional approaches have improved outcomes in patients with acute myocardial infarction (MI). However, these strategies are inadequate for replacing cells lost during tissue ischemia, thereby leaving behind noncontractile scar tissue. The anti-inflammatory and immune modulating properties of mesenchymal stem cells (MSCs) may prove useful in inducing functional cardiac regeneration following acute MI.

Objective: This is a protocol for systematic review and meta-analysis that will aggregate and synthesize high-level clinical data on the effects of MSC therapy for acute MI. The findings of this study may serve as evidence for clinicians and researchers in guiding the use of MSC therapy as an adjunct to reperfusion and optimal medical therapy in patients with acute MI.

Methods: The proposed systematic review is registered with PROSPERO (International Prospective Register of Systematic Reviews). A systematic search of bibliographical databases, including Embase, PubMed, and Cochrane was conducted from inception to June 2023 to identify English-language human studies with adult patients receiving MSC therapy and optimal medical therapy for acute MI in comparison with respective controls. Article screening was performed using PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. Data on functional cardiac outcomes and major adverse cardiac events were extracted and analyzed as primary outcomes.

Results: Literature search and article screening commenced in June 2023. Data extraction and analysis will be completed by October 2024. The findings will be synthesized and reported by the end of November 2024.

Conclusions: This systematic review and meta-analysis will summarize the best available updated evidence from published randomized controlled trials on the effects of MSC therapy for the treatment of acute MI. The findings of this systematic review and meta-analysis may shed light on the efficacy of MSC therapy in improving cardiac functional and structural parameters and reducing adverse cardiac events following acute MI.

Trial Registration: PROSPERO CRD42024522398; https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=522398

International Registered Report Identifier (IRRID): DERR1-10.2196/60591

(JMIR Res Protoc 2025;14:e60591) doi:10.2196/60591

KEYWORDS

mesenchymal stem cells; mesenchymal stromal cells; progenitor cells; acute myocardial infarction; outcomes; stem cell; myocardial; protocol; systematic review; meta-analysis; medical therapy; therapy; cardiac; efficacy

Introduction

Background

Acute myocardial infarction (MI) remains a significant cause of morbidity and mortality globally, with nearly 3 million people experiencing an acute MI annually worldwide [1]. During acute MI, blood flow to the myocardium is reduced, resulting in tissue hypoxia, ischemia, and eventual cell death, which in turn, may result in adverse consequences, including left ventricular (LV) dysfunction, heart failure, arrhythmias, cardiogenic shock, and death. Myocardial reperfusion with percutaneous coronary intervention is a standard treatment for acute MI. Time to reperfusion is directly correlated with prognosis; therefore, prompt revascularization should be pursued [2]. After reperfusion, patients receive optimal medical therapy, which has significantly improved outcomes since its advent [3]. However, reperfusion and medications are unable to replenish necrotic cardiac myocytes, and many patients still experience significant morbidity and mortality following acute MI [4]. Following significant tissue infarction, large areas of the myocardium are scarred and rendered nonfunctional, leading to the adoption of regenerative therapies as a possible solution.

Accordingly, regenerative therapies that aim to restore functional cardiac tissue continue to be a topic of clinical research interest. Recent evidence suggests that stem cells may be useful as a method of repairing damaged myocardial tissue [5,6]. In animal models, studies have shown the potential of Mesenchymal stem cells (MSCs) to differentiate into cardiac myocytes, to participate in regenerative signaling through immunomodulation, and paracrine actions [7-9]. So far, human clinical trials have yielded mixed results. Several randomized control trials (RCTs) in patients with acute MI have demonstrated improvement in LV ejection fraction (LVEF), remodeling, myocardial viability, and reduction in hospitalization rates following treatment with MSCs [10-13]. Conversely, other RCTs have shown no difference in LVEF between MSC-treated patients and the standard-of-care [14,15]. Concerns for safety has arisen with the novelty of regenerative therapy, and the evaluation of major adverse cardiac events (MACE) has been the hallmark for safety [10-15]. Particularly, mortality rates (periprocedurally and long-term), malignant arrhythmias, recurrent MI, cerebral vascular accident, and revascularization are among the most common evaluated adverse events [10-15]. Although with no significant difference was noted in previous RCTs, our meta-analysis aims to evaluate the safety of MSC therapy through the evaluation of MACE. There may be added benefit to decreasing MACE outcomes through the use of MSC therapy, which will also be evaluated.

While many clinical trials have examined the efficacy of MSCs in acute MI treatment, the data collection methods, timing of MSC administration, route of MSC administration, and evaluated end points have been heterogeneous. Several articles representing long-term follow-up of original studies have recently been published, which collectively provide additional insights. Aggregation and analysis of the updated data are needed to gain a better understanding of the effects of MSC administration in patients with acute MI.

Objectives

Several previous meta-analyses have been published on the outcomes of stem cell therapy for acute MI, however, these were based on studies with a heterogeneous mixture of stem cells, not exclusively MSCs. In addition, the existing meta-analyses included only original RCTs without the follow-up studies, thereby obscuring insights related to longer-term outcomes. The current systematic review aims to provide the most comprehensive and updated evidence regarding MSC transplantation solely for the treatment of acute MI, along with a meta-analysis focused specifically on RCTs, including follow-up RCTs to evaluate long-term outcomes of MSC therapy. The meta-analysis will compare the effects of MSC injection and standard therapy on LVEF, LV end-systolic volume (LVESV), LV end-diastolic volume (LVEDV), and MACE as primary end points. Secondary end points will include, but not limited to, myocardial viability, myocardial perfusion defect, and stroke volume.

Methods

Review Question

This study aimed to answer the following question: “What are the short-term and long-term effects of MSC therapy in patients with acute MI?”

Eligibility Criteria

Inclusion and exclusion criteria were initially determined using the PECOS (Population, Exposure, Comparator, Outcome, Study Design) framework. Detailed PECOS criteria for the meta-analysis are denoted in Multimedia Appendix 1.

The initial systematic review included RCTs, single-arm studies, and case series. The meta-analysis included RCTs and secondary reports based on the original studies. English-only original articles published before June 15, 2023, were included; case reports, abstract-only articles, systematic reviews, meta-analyses, animal studies, commentaries, position papers, opinions, and editorials were excluded from the meta-analysis. Studies enrolling adult patients aged 18 years and older with acute MI who received MSC therapy within 1 month of MI were included. Studies using MSCs, mesenchymal stromal cells, and mesenchymal progenitor cells as therapeutic substrates were included. Studies that included patients with recurrent MI in their study were excluded. Studies with other types of stem cells or combinatorial cellular mixtures were excluded. Studies that did not report the outcomes of interest were excluded.

Information Sources and Search Strategy

Bibliographic databases, including PubMed, Cochrane, and Embase were queried from inception to June 2023. The search strategy was guided by 2 librarian experts in medical sciences and was reviewed and devised in accordance with the Peer-Reviewed Electronic Search Strategy guidelines [16].

The original search strategy was formulated for PubMed and used PubMed syntax. Additional searches were modified and optimized for subsequent databases. Given the specificity of the question at hand, the search strategy used key search terms without the use of MeSH (Medical Subject Headings).

The full search strategy, including the development of the final search terms, can be found in Table S1 in the Multimedia Appendix 2. Keywords in the final search strategy included the following: mesenchymal stem cell, progenitor cell, mesenchymal stromal cell, ST-elevation MI, ST-elevation myocardial infarction, and acute MI.

Selection Process

All retrieved articles were reviewed by 2 independent investigators to check for inclusion and exclusion criteria in a stepwise process to include title screening, abstract screening, and full-text screening. Reasons for the exclusion of articles will be addressed in greater detail in the final publication.

Study Records

Data Collection Process and Management

Data extraction from the eligible full-text articles was performed by 2 investigators who independently extracted the data elements of interest to ensure accuracy and completeness. Extracted data and records are maintained in separate Microsoft Excel sheets by the 2 investigators, as well as a combined Microsoft Excel sheet after consensus.

Incongruencies in data extraction were resolved through discussion with a third senior investigator to achieve consensus.

Data Items/Elements

Data extraction elements for both systematic review and meta-analysis are outlined in Table S2, which can be found in Multimedia Appendix 3.

Information that required further clarification and/or required additional data were attempted to be resolved by contacting the corresponding authors of the respective articles; queries that yielded no response were not included in the data extraction or analysis.

Outcomes

The primary outcomes of the meta-analysis included (1) effects of transplantation on LVEF, (2) LVESV, (3) LVEDV, and (4) MACE.

The secondary outcomes that included (1) myocardial viability, (2) myocardial perfusion defect index, (3) coronary flow reserve, (4) adenosine-induced minimal vascular resistance index, and (5) stroke volume.

Quality Analysis

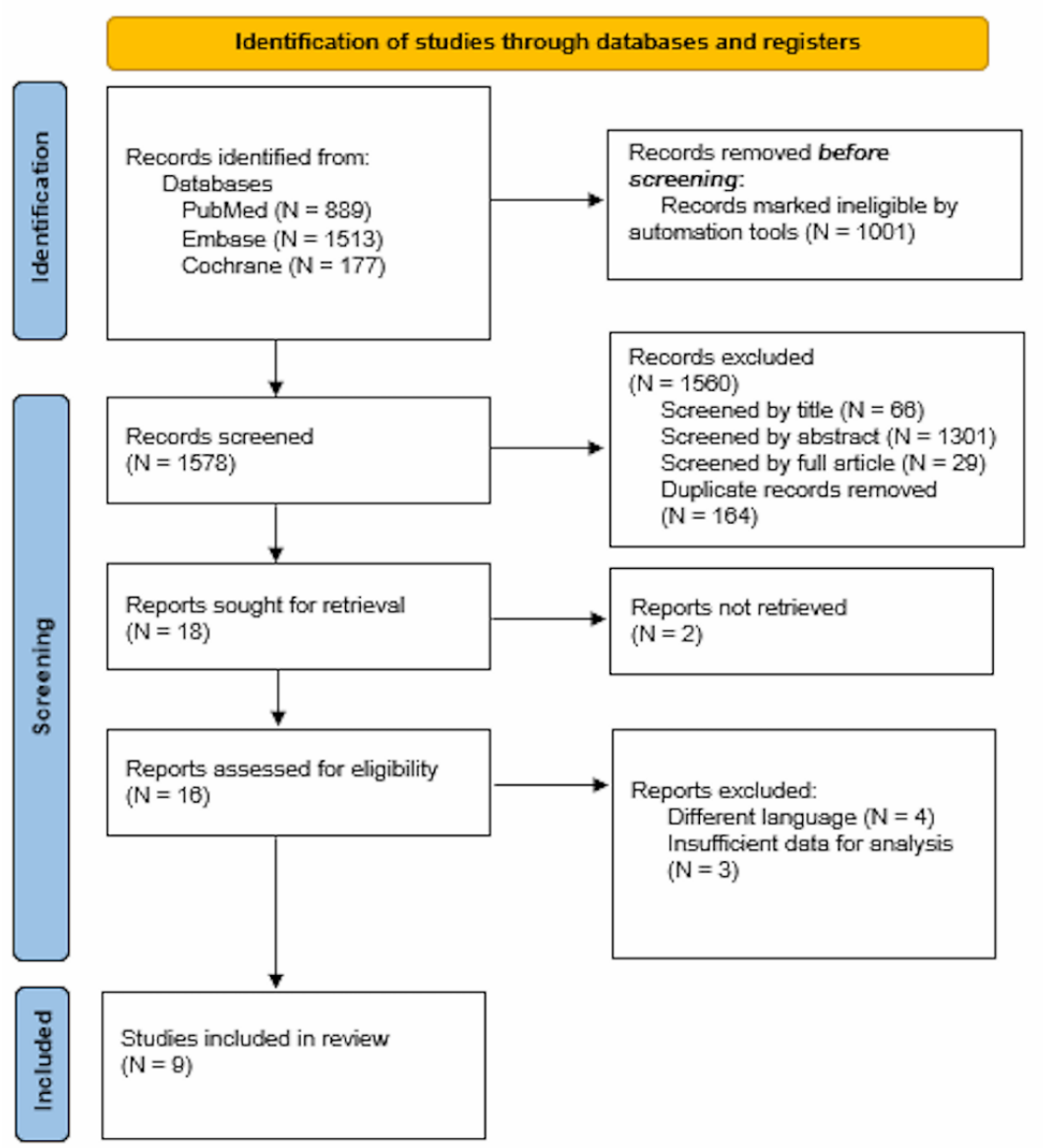
Overview

Quality assessments for strength of the body of evidence of all included studies will be performed using the National Heart, Lung, and Blood Institute (NHLBI) quality assessment tool. A total of 2 investigators will independently screen full texts for quality. Scoring will be performed independently. All essential components of original research studies will be evaluated using the NHLBI scoring checklist (Multimedia Appendix 4). Study quality will model the scoring protocol performed by Elks et al [17].

Risk of Bias Assessment

Within the quality assessment, articles selected for analysis underwent assessment for risk of bias. Bias was assessed by examining randomization and adequacy of randomization, blinding, and attrition. Specific questions are outlined in Figure 1 below. Meta-biases will be assessed as appropriate.

Figure 1. The PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram modified for the current study selection process.



Data Synthesis

First results of all finally included studies will be described succinctly in the form of a summary table. A random-effects model will be used to calculate pooled estimates as this is a more robust estimate regardless of heterogeneity [18]. Cochran Q and I^2 statistics will be used as indicators of heterogeneity. The pooled estimates of the primary end points (eg, LVEF, LVESV, and LVEDV) will be calculated as the weighted mean differences with 95% CIs using the Comprehensive Meta-analysis Package (CMA version 3.0). For dichotomous outcomes, Peto odds ratios will be used as this allows the inclusion of the continuity correction of 0.5 to all 0 cells outcomes and accounts for the expected rarity of events. Sensitivity analysis will be conducted to identify studies that may severely affect the pooled estimates. The Exploratory subgroup analyses by different moderator variables (eg, MSC source, MSC route of administration, location of MI, and duration of follow-up, etc) will also be conducted to examine sources of heterogeneity. A funnel plot and Egger linear regression test will be used to assess publication bias [19]. The significant level will be set as 2-sided and $P<.05$. Forest plots will be used to present the data.

Data Analysis and Presentation

Data will be presented in a tabular form and as a conclusive summary of our analysis. A data extraction form will be developed and agreed upon by all investigators before article analysis occurs. Selected articles will be present in the rows of the table, and variables will be present in the columns of the table. Quantitative analysis of all extracted variables will be performed.

Ethical Considerations

IRB or institutional review was not needed in this systematic review and meta-analysis since this design relies only on the findings from the previously published data and did not involve direct interaction with human participants. However, to adhere to a strict methodology, the protocol of this systematic review

and meta-analysis was registered with PROSPERO (International Prospective Register of Systematic Reviews) registration number CRD42024522398. PROSPERO is an international database of prospectively registered systematic reviews, which provides a unique permanent registration number to the protocol that prevents duplication, thereby reducing reporting bias. In addition, PRISMA-P (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols) checklist was completed during the process to ensure comprehensive and quality results (Figure 2).

Figure 2. PRISMA-P (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) checklist completed for the current study.

Section and topic	Item No	Checklist item	Completed? (Y or N)
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	Y
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	N/A
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	Y
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	Y
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	Y
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	N/A
Support:			
Sources	5a	Indicate sources of financial or other support for the review	N/A
Sponsor	5b	Provide name for the review funder and/or sponsor	N/A
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	N/A
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	Y
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	Y
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	Y
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	Y
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	Y
Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	Y
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	Y
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	Y
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	Y
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	Y
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	Y
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	Y
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	Y
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	Y
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	Y
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	Y
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	Y

Results

The development of the search strategy for this systematic review and meta-analysis began in June 2023. The search strategy underwent peer-reviewed electronic search strategy review with 2 academic librarians in June 2023. The final search strategy was agreed upon by all investigators in July 2023. Databases were queried and articles were screened between September 2023 and October 2023. Data extraction took place between November 2023 and February 2024. Data analysis is currently taking place as of March 2024 with the final analysis anticipated to be completed in October 2024. It is anticipated that findings will be synthesized and reported by the end of November 2024. Findings will be organized, summarized, and submitted for publication in a peer-reviewed journal. The goal of this work is to provide a comprehensive analysis and enhance the understanding of the safety and effectiveness of MSC therapy in acute MI. A timeline is provided in Table 1.

Preliminary searches performed in PubMed, Embase, and Cochrane databases yielded 1578 articles after appropriate filters were applied. A total of 889 articles were returned from PubMed, of which 521 were human studies. A total of 1,513 articles were returned from Embase, of which 880 were human studies. A total of 177 articles were returned from the Cochrane

database, which were all reviews of human studies (Figure 1). A detailed step-by-step outline of our search strategy, including search terms, limit criteria, and results is provided in Table S1 of the Multimedia Appendix 2 (adapted from Page et al [20]).

Table 1. Timeline of project task completion.

Task	Jun 2023	Jul 2023	Aug 2023	Sep 2023	Oct 2023	Nov 2023	Dec 2023	Jan 2024	Feb 2024	Mar 2024	Apr 2024	May 2024	Jun 2024	Jul 2024	Aug 2024	Sep 2024	Oct 2024	Nov 2024
Design search strategy	✔	✔																
Title screening			✔															
Abstract screening				✔														
Full-text screening				✔	✔													
Data extraction						✔	✔	✔	✔									
Synthesis and risk of bias assessment										✔	✔							
Data analysis										✔	✔	✔	✔	✔	✔	✔	✔	
Abstract and manuscript drafting												✔	✔	✔	✔	✔	✔	✔
Data dissemination																		✔

Discussion

Overview

This systematic review and meta-analysis will be a comprehensive review and analysis of the existing relevant literature pertaining to the efficacy of MSC therapy in patients enduring from acute MI. We anticipate that the current findings will be congruent with the previous observations regarding the outcomes and safety of MSC therapy. We also aim to glean insights with regard to changes in LVEF, LVESV, and LVEDV as a result of MSC therapy. In addition, we will examine the pooled event ratio estimates of MACE, including death, recurrent MI, need for revascularization, and stroke, compared with control, to draw conclusions on the safety of MSC therapy.

In an attempt to ensure the comprehensiveness of the assessment of relevant data, a narrative synthesis of studies that lie at relatively lower levels of hierarchical evidence as compared with the gold standard (RCTs) was also performed. These additional qualitative findings allow us to gain a complete understanding of several factors, including timing and route of administration, source of cells, and other variables that may impact the outcomes of MSC therapy.

Significance

We anticipate that our results, by virtue of including data from recently published RCTs, will significantly advance the existing evidence regarding the safety and efficacy of MSC therapy. Previous meta-analyses examining the effects of MSC therapy in ischemic heart diseases often combined with chronic and acute ischemic heart diseases [21,22], whereas we plan to focus on acute MI therapy alone. In addition, previous meta-analyses reviewed a variety of regenerative cells [6] for the treatment of acute MI, whereas our focus specifically on mesenchymal stem and progenitor cells will allow us to comment on the efficacy of a specific cell type in the management of acute MI. Finally, while our meta-analysis examines primary RCTs, we have also included secondary/follow-up RCTs of original studies in our analysis, which will provide additional information regarding the longer-term and additional end points for subgroup analysis.

Limitations

This meta-analysis will have several limitations. First, there will be inherent heterogeneity among included studies due to the variability of research methodologies undertaken by each unique study. We anticipate heterogeneity in several variables, including the timing and route of MSC administration, the tissue source of MSCs, the methods used to measure primary and secondary end points (for example, echocardiogram vs angiography vs cardiac magnetic resonance imaging), and the follow-up period after MSC transplantation. Second, there is a risk that relevant literature will be missed because studies with insignificant findings or low sample size are seldom published, thus leading to publication bias. Finally, there will be inherent reviewer bias when selecting articles during the screening process, which will be mitigated by using an individualized screening process with 2 independent reviewers, along with a

third senior reviewer to resolve disagreements on article selection.

Dissemination Plan

The findings of this systematic review and meta-analysis will be submitted as a manuscript to a peer-reviewed journal by the end of 2024. Derivations of this work will be submitted as abstracts to academic conferences.

Conclusions

This systematic review and meta-analysis will provide a comprehensive review of the safety and efficacy of MSC therapy in patients with acute MI. It will include an analysis of data on clinically relevant primary end points pertaining to functional cardiac parameters, such as LVEF, LVESV, and LVEDV. It will also examine specific safety outcomes by performing a subgroup analysis on MACE. This review will also provide qualitative synthesis of evidence related to MSC therapy, which will generate additional insights toward its potential future clinical applications in a broader spectrum of cardiovascular pathologies.

Acknowledgments

The authors would like to acknowledge the Ana Coral and Aidybert Weeks at the University of Nevada, Las Vegas Library for their assistance with developing the search strategy and for conducting the PRESS (Peer-Reviewed Electronic Search Strategy) review. The authors did not use AI for any portion of manuscript generation.

Data Availability

The datasets generated during and/or analyzed during this study are available from the corresponding author on reasonable request.

Authors' Contributions

Conceptualization was undertaken by MD, BY, and BD. Methodology and project administration was performed by MD, BY, KB, and BD. Formal analysis was handled by KB. Investigation, resources, and data curation was conducted by MD and BY. Writing-original draft preparation was performed by MD, BY, and KB. Writing-review and editing and visualization was conducted by MD, BY, KB, and BD. Supervision was handled by KB and BD.

Conflicts of Interest

None declared.

Multimedia Appendix 1
The PECOS (P-Population; E/I-Exposure/Intervention; C-Comparator; O-Outcome; S-Study design) framework for the eligibility criteria.
[PNG File , 208 KB - resprot_v14i1e60591_app1.png]

Multimedia Appendix 2
Full search strategy for utilized databases.
[DOCX File , 19 KB - resprot_v14i1e60591_app2.docx]

Multimedia Appendix 3
Elements included in data extraction for meta-analysis purposes.
[DOCX File , 18 KB - resprot_v14i1e60591_app3.docx]

Multimedia Appendix 4
National Heart, Lung, and Blood Institute scoring checklist.
[DOCX File , 16 KB - resprot_v14i1e60591_app4.docx]

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Abbreviations

LV: left ventricle
LVEDV: left ventricular end-diastolic volume
LVEF: left ventricular ejection fraction

LVESV: left ventricular end-systolic volume
MACE: major adverse cardiac events
MeSH: Medical Subject Headings
MI: myocardial infarction
MSC: mesenchymal stem cells
NHLBI: National Heart, Lung, and Blood Institute
PECOS: Population, Exposure, Comparator, Outcome, Study Design
PRISMA-P: Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols
PROSPERO: International Prospective Register of Systematic Reviews
RCT: randomized control trial

Edited by A Schwartz; submitted 15.05.24; peer-reviewed by YY Kristian; comments to author 18.09.24; revised version received 10.10.24; accepted 08.11.24; published 06.02.25.

Please cite as:
DiCaro MV, Yee B, Lei K, Batra K, Dawn B
Mesenchymal Stem Cell Therapy for Acute Myocardial Infarction: Protocol for a Systematic Review and Meta-Analysis
JMIR Res Protoc 2025;14:e60591
URL: https://www.researchprotocols.org/2025/1/e60591
doi:10.2196/60591
PMID:

Protocol

Just-In-Time Adaptive Interventions to Promote Behavioral Health: Protocol for a Systematic Review

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Abstract

Background: The goal of just-in-time adaptive interventions (JITAIs) is to use mobile, digital tools to provide individuals with personalized interventions at the optimal time and in the optimal context. Accordingly, JITAIs are promising for advancing accessible, equitable, and evidence-based treatment for behavioral health. To guide future inquiry in this space, a review of the literature is needed to describe the state of research on JITAIs for behavioral health.

Objective: This study aims to systematically review the literature to describe the landscape of existing JITAIs for behavioral health at any stage of intervention development. In addition, conditional upon a sufficiently homogeneous literature, we will conduct meta-analyses to investigate the effectiveness of JITAIs for promoting distal outcomes (here, aspects of behavioral health) and proximal outcomes (eg, emotion regulation).

Methods: This systematic review is being conducted in accordance with the PRISMA-P (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols). We developed our search strategy and executed the literature search in collaboration with biomedical librarians; 5 databases (PubMed, Embase, Cochrane Library, Web of Science: Core Collection, and APA PsycINFO) were searched, and results were managed using EndNote 20 (Clarivate). We are screening (title, abstract, and full text) all records in duplicate in Covidence according to eligibility criteria. Data items will be extracted, and risk of bias will be assessed in duplicate from the included articles in Covidence. We will summarize JITAI characteristics in tables and text. We will conduct meta-analyses for the distal and proximal outcomes conditional upon sufficient homogeneity in subgroups. Moderation (conditional upon sufficient heterogeneity of outcomes) and mediation (ie, whether changes in proximal outcomes mediate the relation between JITAIs and distal outcomes) will be conducted as appropriate. We will investigate publication bias and use the Grading of Recommendations Assessment, Development and Evaluation to characterize the quality of evidence of our estimates.

Results: The search strategy was developed between July 2023 and November 2023. The literature search was executed between November 2023 and December 2023. Title and abstract screening began in December 2023, and full-text screening began in May 2024. Data extraction and analyses have not begun.

Conclusions: Here, we propose a systematic review to assess the state of the literature on JITAIs for behavioral health. The insights derived from this study will describe the literature on JITAIs in promoting behavioral health, reinforce JITAI definitions, clarify JITAI elements, and inform the next steps in JITAI research.

International Registered Report Identifier (IRRID): PRR1-10.2196/58917

(JMIR Res Protoc 2025;14:e58917) doi:10.2196/58917

KEYWORDS

just-in-time adaptive interventions; JITAI; behavioral health; systematic review; behavior change; health outcomes; accessibility; digital treatment delivery; mobile phone

Introduction

Background

Mental illness has devastating consequences for individuals, their families, and society. Those in need of treatment are woefully underserved, with a dearth of professionals relative to patients [1]. Race and ethnicity, geography, and socioeconomic status influence who can and who cannot access care [2]. For the subset of individuals who receive treatment, lack of evidence-based care [3] and issues with dropout [4] and nonresponse [5,6] limit recovery. New solutions are critical for reaching and equitably and effectively treating people suffering from mental illness. Technological advances may provide a pathway to more equitable evidence-based care at scale. While structural barriers (eg, cost and transportation) impede access to in-person health care, mobile devices are plentiful and may allow for greater population coverage [7,8]. Furthermore, while treatment may be perceived as stigmatizing, further reducing service use [9,10], research provides preliminary support for willingness to initiate and maintain engagement with digital interventions (even in severe mental illness) [11]. Beyond accessibility and acceptability, treatment delivered through technology allows for the provision of therapeutic support when and where it is most needed—outside of the clinic and within patients' daily lives [12,13]. After a prescribed treatment is delivered, technological solutions can be seamlessly integrated and accessed again to boost skills and maintain treatment gains [12,13].

Just-In-Time Adaptive Interventions

Despite the potential benefits of digital treatment delivery, evidence for the effectiveness of intervening using standalone mobile applications is limited [14]. Still, just-in-time adaptive interventions (JITAIs) are promising [15-18]. The goal of JITAIs is to target mechanisms for therapeutic change at the time and in the context that is optimal for the individual [19,20]. JITAIs have the potential to capitalize on states of vulnerability and opportunity [20]. That is, JITAIs can intervene when individuals are susceptible to negative or positive change. For example, capitalizing on a state of opportunity might be prompting an adult with social anxiety disorder to approach others while in a public place. JITAIs may be able to intervene when individuals are maximally receptive or most likely (willing and able) to accept a specific intervention [20]. To do so, JITAIs leverage real-time data collected passively or actively from smartphones, including or excluding paired wearable devices in combination with personalized algorithms [19-21].

JITAIs are defined by six elements: (1) distal outcome (long-term goal of the JITAI), (2) proximal outcome (short-term goal of the JITAI, which may be a mediator of the distal outcome), (3) tailoring variable (baseline or time-varying information on the individual that informs which interventions to deploy at which decision points), (4) decision point (time frame when an intervention option is, or is not, deployed), (5) decision rule (operationalization of which intervention option should be used, when, and for whom), and (6) intervention options (set of potential components that may be deployed toward behavior change at a given decision point). JITAIs are being developed for a variety of problems, including substance use [18,22], affective disorders [23], and stress management [24]. The potential impact of an intervention (here, a JITAI) is dependent on the potency of its mechanistic target. Some, but not all, JITAIs that aim to augment behavioral health outcomes describe doing so through purported proximal outcomes [23]. Importantly, to increase the likelihood that JITAIs will be effective, their development must be informed by well-established findings from psychiatric research. For example, deficits in emotion regulation, or efforts to modify the intensity or duration of an emotion, are a transdiagnostic pathway in the development and maintenance of psychopathology [25,26]. Importantly, emotion regulation is malleable in that it can be augmented with intervention [27]. As such, emotion regulation is a key exemplar candidate transdiagnostic treatment target for behavioral health. Emotion regulation skills are aspects of empirically supported treatments for psychopathology [28,29] and have been shown to mediate and moderate the effects of interventions on outcomes [27]. Increasingly, emotion regulation skills have been incorporated into digital health interventions [30-33].

There are 2 major gaps in understanding the potential use of JITAIs in behavioral health care [34]. Henceforth, we use the term "behavioral health" to refer to psychological disorders and symptoms (including substance use disorders), as well as physical symptoms related to life stressors and crises. First, little research has summarized the effectiveness of JITAIs for behavioral health conditions. Intervention development is a multistage process that involves iteratively tailoring a program through repeated evaluation and from accumulating evidence [35-37]. For example, the National Institutes of Health's Obesity-Related Behavioral Intervention Trials (ORBIT) model provides a framework for intervention development that starts with establishing a significant clinical question and progresses through design (ie, defining, refining), preliminary testing (eg, proof-of-concept, feasibility pilots), efficacy trials, and finally effectiveness research. At any stage, in the case of a suboptimal outcome, the model would dictate that the investigator returns to an earlier phase for intervention refinement. All considered, the development of an intervention can take over 10 years before the program settles into its finalized form. What's more, by design, a finalized form of an intervention may never be achieved. Interventions must be optimized to strike a strategic balance between effectiveness, affordability, scalability, and efficiency. That strategic balance may vary across time and context [36]. Frameworks like multiphase optimization strategy (MOST) can be used to guide these optimization efforts. Experimental designs should be matched to the research question and stage of development (eg, microrandomized trial [38] or sequential multiple assignment randomized trial [SMART] [39]

during optimization, randomized controlled trial during evaluation [35]). JITAIs as intervention frameworks were conceptualized 10 years ago [19]. Considering the intervention development process, the majority of published JITAIs likely either do not exist in their finalized form or are constantly evolving through optimization. Still, systematic reviews and meta-analyses exist that have examined the impact of JITAIs on the promotion of physical health, providing some early support for JITAIs as a digital health tool [15,16]. The extant systematic reviews relevant to behavioral health have evaluated JITAIs either within a larger health promotion framework or for a specific psychiatric disorder. In their meta-analysis of JITAIs for physical and mental health (eg, healthy diet, weight loss, diabetic management, addiction, bipolar disorder, and anxiety), Wang and Miller [17] found a large effect of JITAIs relative to a waitlist control (Hedges' g=1.653). In their systematic review of JITAIs for substance use, Perski et al [18] found mixed results. Second, few systematic reviews [23] have described JITAI proximal outcomes despite the important role that proximal outcomes play in elucidating intervention mechanisms of action [40]. Here, we propose a systematic review (and meta-analysis, as appropriate) of JITAIs targeting proximal outcomes (eg, emotion regulation) to improve behavioral health outcomes.

Objective

The objective of this review is to describe the state of the literature on JITAIs for behavioral health outcomes. Given that JITAIs originated in the past 10 years, our primary methodological approach for addressing our objective will be qualitative. That is, through a systematic review of the literature, we will extract, report, and describe the 6 elements (ie, distal outcome, proximal outcome, tailoring variable, decision point, decision rule, and intervention options) for each JITAI, regardless of the stage of intervention development (eg, preliminary testing, feasibility, clinical trial). In doing so, we will reinforce the existing JITAI framework [19,20] and provide a roadmap for the development of future JITAIs to improve behavioral health. Our secondary methodological approach for addressing our objective will be quantitative. That is, if it is determined that our included studies are sufficiently homogeneous, we will conduct meta-analyses to examine the effectiveness of JITAIs in promoting (1) aspects of behavioral health as distal outcomes and (2) proximal outcomes. We will examine moderators (eg, sociodemographic variables, symptom severity) conditional upon sufficient heterogeneity in outcomes. Given the importance of developing JITAIs incorporating empirically supported intervention targets, we will focus our discussion on emotion regulation as one proximal outcome of interest.

Methods

Overview

We used the PRISMA-P (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols) checklist to write this systematic review protocol [41]. Multimedia Appendix 1 shows the PRISMA-P checklist.

Eligibility Criteria

Textbox 1 shows the inclusion and exclusion criteria. After examining a subset of records, it became clear that we were unable to determine with certainty if interventions were JITAIs (ie, just-in-time and adaptive) and if behavioral health outcomes were reported by examining article titles and abstracts. As such, to prevent excluding relevant articles during title and abstract screening, we retained a subset of our inclusion and exclusion criteria for this stage. That is, we focused on identifying articles using digital methods and proposing specific interventions and articles of the correct format (eg, excluding reviews and case reports). The full eligibility criteria are being used for full-text screening.

Textbox 1. Eligibility criteria for systematic review.

Inclusion criteria:

- Population: All individuals, regardless of age, sex and gender, race and ethnicity, socioeconomic status, geographic location, and other aspects of identity.
- Intervention design: Just-in-time adaptive interventions (JITAIs), that is:
  - Just-in-time: deployed when the individual needs it.
  - Adaptive: incorporates time-varying or contextual or both types of information for individualization, leveraged through passively or actively collected data from smartphones or wearable devices.
  - Intervention: activities intended to modify behavior, thoughts, or emotions.
- Outcome: Behavioral health.
- Article format: All languages; empirical research studies; publication in a peer-reviewed journal.

Exclusion criteria:

- Population: None.
- Intervention design: No JITAI.
- Outcome: Physical health and wellness outcomes that do not directly focus on behavioral health.
- Article format: Reviews, meta-analyses, case reports, dissertations, theses, and conference abstracts.

Information Sources

A total of 5 databases were searched by a biomedical librarian (NT): PubMed/MEDLINE (US National Library of Medicine), Embase (Elsevier), Cochrane Library (John Wiley & Sons), Web of Science: Core Collection (Clarivate), APA PsycINFO (Dialog and Clarivate). To identify relevant articles missed by the search strategy, reviewers (LMH, MB-T, CEH, CNR, ET) will scan the bibliographies of included studies and relevant review articles. Protocols, feasibility studies, and acceptability studies were flagged during screening, and reviewers will revisit these records to determine if clinical outcomes were published. The final list of included studies, and additional, relevant studies, will be evaluated by the entire review team, along with relevant unaffiliated collaborators. Articles identified through these supplemental methods will proceed through the full screening process.

Search Strategy

A biomedical librarian (NT) with expertise in systematic review searches developed the search strategy in collaboration with the other members of the study team. A second librarian (Alicia A. Livinski, MPH, MLS) not otherwise affiliated with the project peer-reviewed the search strategy. The review team provided feedback on the search strategy. The search strategy incorporated keywords and controlled vocabulary terms (ie, EMTREE [Embase], MeSH [PubMed], Thesaurus of Psychological Index Terms [PsycNet]) for each concept of interest. The search strategy syntax was adapted for each database searched. Multimedia Appendix 2 shows the PubMed search strategy.

Study Records

Data Management

We used EndNote 20 (Clarivate) to collect and manage the results of the literature search and identify unique records. We used Covidence (Veritas Health Innovations), an internet-based tool for systematic review data management, for selection and data collection. Before selection and data collection, reviewers (LMH, MB-T, CEH, CNR, and ET) were trained in using Covidence.

Selection Process

Before each stage of screening (title and abstract, full text), a 20-article trial was conducted with all reviewers to pilot and refine the eligibility criteria to increase reliability. All reviewers are conducting screening using the stated eligibility criteria. For title and abstract screening, articles with missing abstracts automatically advanced to full-text screening. Following the title and abstract screening, the PDFs of the articles that were included were obtained and uploaded into Covidence for full-text screening. All articles are being double-coded for each stage of screening; that is, each record is independently screened by 2 reviewers. Screening discrepancies are being resolved during a group consensus meeting. Interrater reliability is being recorded in Covidence and will be documented in the final report.

Data Collection Process

Before data collection, a 15-article trial will be conducted with all reviewers (LMH, MB-T, CEH, CNR, and ET) to increase reliability. All reviewers (LMH, MB-T, CEH, CNR, and ET) will independently extract data items from records included after full-text screening. Each data item from each study record will be extracted in duplicate. Coding discrepancies will be discussed and resolved through dyadic consensus meetings, including the two relevant reviewers for each article. Discrepancies that cannot be resolved during dyadic consensus meetings will be resolved at a group consensus meeting. Data extraction forms will be published.

Data Items

Table 1 shows the data items that will be collected.

Table 1. Data items for systematic review

Category	Criteria
Article	Authors, title, journal, year.
Sample demographics	Where the study took place, sample size, age, gender, sex, race, and ethnicity.
JITAI[a] elements	Tailoring variable, decision points, decision rules (including static or adaptive status), intervention options, proximal outcomes (eg, emotion regulation), distal outcomes (eg, depression).
Study	Intervention development framework (eg, National Institutes of Health's ORBIT[b] model, MOST[c]), experimental design (eg, MRT[d], SMART[e]), where the JITAI was developed (eg, university, industry), was the JITAI delivered alongside other support (eg, in-person intervention), was the JITAI delivered alongside sensors or ambulatory devices, types of sensors used, JITAI delivery service (eg, iPhone, personal device), number of intervention days, payment structure (eg, flat fee), user engagement, user compliance (eg, response to prompts or frequency of JITAI use, or both), usability.

[a]JITAI: just-in-time adaptive intervention.

[b]ORBIT: obesity-related behavioral intervention trials.

[c]MOST: multiphase optimization strategy.

[d]MRT: microrandomized trial.

[e]SMART: sequential multiple assignment randomized trial.

Outcomes and Prioritizations

Our primary outcome of interest is the distal outcome of the JITAI. Here, we focus on JITAIs that target behavioral health outcomes. Examples of potential distal outcomes include affective, substance use, disruptive behavior, eating, trauma-related, personality, psychotic, and neurodevelopmental disorders; psychological symptoms (ie, not meeting criteria for a disorder); pain; and well-being. Multimedia Appendix 2 shows the full list of search terms related to behavioral health. Our secondary outcome of interest is the proximal outcome of the JITAI. All proximal outcomes will be collected. We will calculate effect sizes for both the distal and proximal outcomes.

Risk of Bias in Individual Studies

Tools appropriate to the study design of individual records will be used to determine risk of bias. For example, Version 2 of the Cochrane risk-of-bias (RoB 2) tool for randomized controlled trials will be used for randomized controlled trials, including SMARTs [42]; Risk Of Bias In Non-Randomized Studies - of Interventions (ROBINS-I) will be used for nonrandomized studies comparing the effects of two or more interventions [43]; and Risk Of Bias In Non-randomized Studies - of Exposure (ROBINS-E) will be used for observational studies [44]. Risk of bias will be evaluated by 2 reviewers for each study. Disputes will be resolved during dyadic consensus meetings, and discrepancies that cannot be resolved during dyadic consensus meetings will be resolved during group consensus meetings.

RoB 2 includes 5 domains: bias due to the randomization process, bias due to deviations from intended interventions, bias due to missing outcome data, bias in the measurement of the outcome, and bias in the selection of the reported result [42]. Each domain will be classified as low risk of bias, some concerns, or high risk of bias. ROBINS-I includes 7 domains: bias due to confounding, bias in the selection of participants into the study, bias in classification of interventions, bias due to deviations from intended interventions, bias due to missing data, bias in the measurement of the outcome, and bias in the selection of the reported result [43]. Each domain will be classified as low, moderate, serious, or critical risk of bias or no information. ROBINS-E includes 7 domains: risk of bias due to confounding, risk of bias arising from the measurement of exposure, risk of bias in the selection of participants into the study, risk of bias due to post-exposure interventions, risk of bias due to missing data, risk of bias arising from the measurement of outcome, and risk of bias in the selection of the reported result [44]. Each domain will be classified as low risk of bias, some concerns, high risk of bias, or very high risk of bias.

Data Synthesis

Elements (eg, tailoring variables and decision points) of each JITAI will be presented in tables and summarized in the text. Data synthesis will be explored based on outcomes, and a summary of findings table will be presented, as appropriate.

We will categorize studies by design type (eg, randomized controlled trial, observational). If studies in each subgroup are sufficiently homogeneous, meta-analyses will be conducted for the distal and proximal outcomes. Features of the studies collected will inform the selection of the measure of effect size (eg, Cohen's *d* and Hedges' *g*). Subgroup analyses will be considered based on characteristics, including age, gender, type of psychopathology, and type of JITAI. In addition, sensitivity analysis will be carried out, excluding studies of low methodological quality, if necessary.

I^2 statistic will be used to quantify heterogeneity across effect sizes, and *Q* statistic will be used to test heterogeneity reduction through the inclusion of moderators. To address potential heterogeneity, meta-regression will be used to assess clinical characteristics (eg, the severity of symptoms), individual JITAI features (eg, type of emotional regulation strategies used in the intervention), study quality, and demographic characteristics (eg, age, gender, race, and ethnicity) that might influence the effect sizes.

If appropriate, mediation analyses will be considered to investigate whether changes in proximal outcomes mediate the relation between JITAIs and distal outcomes.

Meta-Biases

Publication bias, resulting from selective publication or reporting, will be investigated through visual inspection of funnel plots. Statistical tests for assessing symmetry (eg, Egger's test) will be explored if 10 or more studies have evaluated the same outcome. Trim and fill analyses will be conducted as necessary.

Confidence in Cumulative Evidence

The quality of evidence of estimates will be rated using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) framework [45]. GRADE characterizes the quality of evidence according to publication bias, study limitations, inconsistency, imprecision, and indirectness [17]. Evidence of effectiveness outcomes will be rated from high to low quality by 2 reviewers. Disputes will be resolved during dyadic consensus meetings, and discrepancies that cannot be resolved during dyadic consensus meetings will be resolved during group consensus meetings. Results from GRADE ratings will be included in the summary of findings table.

Results

The search strategy was developed between July 2023 and November 2023, and the literature search was executed between November 2023 and December 2023. We retrieved 1243 records from our literature search. We excluded 91 duplicate records, leaving 1152 records for the selection process. Of note is that we performed a preliminary literature search for systematic reviews related to this topic and found no review identical to the one proposed. Title and abstract screening began in December 2023, and full-text screening began in May 2024. Data extraction and analyses have not begun.

Discussion

Principal Findings

In our systemic review, our objective is to describe the state of the literature on JITAIs for behavioral health outcomes. We

expect that there will be sufficient data available to take a qualitative approach, including describing the aforementioned 6 elements for each JITAI. Conditional upon sufficient homogeneity of the included studies, we will also take a quantitative approach to examine the effectiveness of JITAIs in promoting (1) aspects of behavioral health as distal outcomes and (2) proximal outcomes.

Strengths and Limitations

Our systematic review has numerous strengths, including a comprehensive search strategy, double coding in each stage of screening and data extraction by trained reviewers, assessment of risk of bias of the included studies by reputed tools, evaluation of publication bias, and ratings of quality of evidence of estimates derived from the review.

There are also potential limitations of our work. Primarily, some ambiguity exists in the use of the term "JITAI;" the definition of JITAI has evolved since it was coined in 2015 [19]; the term has been used inconsistently (eg, an intervention with all the characteristics of a JITAI being characterized as a "momentary intervention" or related term) and imprecisely (eg, an intervention labeled as a JITAI despite the lack of an adaptive element); and there is overlap in the definitions of JITAIs and similar intervention frameworks (eg, ecological momentary interventions). As such, we have developed a robust search strategy, including not only the term JITAI but also related terms (eg, ecological momentary intervention, real-time intervention; more details in Multimedia Appendix 2). Furthermore, we developed and implemented detailed eligibility criteria for screening. We also clearly describe the 6 elements that constitute a JITAI in this protocol and will describe each element for each included JITAI in the final report. Accordingly, this systematic review may provide the field with further clarity on the definition and elements of JITAIs. Another limitation is that due to the iterative design process that characterizes JITAIs (and interventions, in general), JITAIs included in this report may not reflect their finalized form. Future scholarship will be needed to capture further JITAI innovations and evaluations. Finally, although we did not limit our search to English language articles, most of our articles are written in English, so the samples and populations represented may be similarly homogeneous. Additional work may be needed to increase the representation of studies published in languages other than English in JITAI effectiveness research.

Comparison With Previous Work

Previous research has typically evaluated JITAIs as digital health tools for the promotion of physical health [15,16]. While a select few reviews have examined JITAIs for specific psychiatric disorders [13], research has yet to robustly summarize the impact of JITAIs on behavioral health conditions.

Conclusions

This systematic review will summarize the evidence on the effectiveness of JITAIs in improving distal (ie, behavioral health) and proximal (eg, emotion regulation) outcomes. Results will provide clarity on JITAI definitions and elements, describe the effectiveness of JITAIs for behavioral health, elucidate targeted proximal outcomes, and inform the development of future JITAIs.

Acknowledgments

This research is funded by the Intramural Research Program (IRP) of the NIMH (ZIA MH002969; MH002981) and the National Institutes of Health's (NIH) Library's and Office Research Service's support of the NIH IRP.

Data Availability

The datasets generated during or analyzed during this study will be available in the OSF repository [46].

Authors' Contributions

LMH, MB-T, CEH, CNR, ET, NT, MK, OM, MAB, and SLG contributed to conceptualization, methodology, writing–original draft, and writing–review, and editing. LMH, MB-T, CEH, CNR, ET, and NT performed the investigation. LMH and MB-T handled project administration. NT, MAB, and SLG handled resources and funding acquisition. MAB and SLG performed supervision.

Conflicts of Interest

None declared.

Multimedia Appendix 1
PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) 2020 checklist.
[DOCX File , 32 KB - resprot_v14i1e58917_app1.docx]

Multimedia Appendix 2
Search Strategy.
[DOCX File , 79 KB - resprot_v14i1e58917_app2.docx]

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Abbreviations

GRADE: Grading of Recommendations Assessment, Development and Evaluation
JITAI: just-in-time adaptive intervention
MOST: multiphase optimization strategy
ORBIT: Obesity-Related Behavioral Intervention Trials
PRISMA-P: Preferred Reporting Items for Systematic Reviews and Meta Analyses Protocols
RoB 2: Version 2 of the Cochrane risk-of-bias tool for randomized controlled trials
ROBINS-E: Risk Of Bias In Non-Randomized Studies - of Exposure
ROBINS-I: Risk Of Bias In Non-Randomized Studies - of Interventions
SMART: sequential multiple assignment randomized trial

Edited by T Leung; submitted 13.05.24; peer-reviewed by J Yap, J Strayhorn, H Bhurawala; comments to author 13.07.24; revised version received 07.09.24; accepted 31.10.24; published 11.02.25.

Please cite as:
Henry LM, Blay-Tofey M, Haeffner CE, Raymond CN, Tandilashvili E, Terry N, Kiderman M, Metcalf O, Brotman MA, Lopez-Guzman S
Just-In-Time Adaptive Interventions to Promote Behavioral Health: Protocol for a Systematic Review
JMIR Res Protoc 2025;14:e58917
URL: https://www.researchprotocols.org/2025/1/e58917
doi:10.2196/58917
PMID:39932763

Protocol

Posttraumatic Growth Among Suicide-Loss Survivors: Protocol for an Updated Systematic Review and Meta-Analysis

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Abstract

Background: Losing a loved one to suicide is an event that can have strong and potentially traumatic impacts on the lives of the bereaved survivors, especially regarding their grief, which can be complicated. These bereaved individuals are also less likely to receive social support following their bereavement. However, besides these adverse impacts, growing evidence supports the concept of posttraumatic growth following suicide bereavement. Posttraumatic growth is the personal improvement that occurs as a consequence of experiencing a traumatic or extremely challenging event or crisis. Only 1 systematic review and meta-analysis on posttraumatic growth following suicide bereavement has been conducted; this protocol is for the planned systematic review and meta-analysis update of the original systematic review and meta-analysis, as the original review collected its data in 2018.

Objective: This review aims to investigate demographic characteristics, correlational relationships, and facilitative factors of posttraumatic growth in individuals bereaved by suicide. In addition, as this is an update of a previous systematic review and meta-analysis, we aim to compare our findings with the original review and to identify any similarities or differences.

Methods: This protocol outlines the planned procedures of the updated systematic review and meta-analysis. MEDLINE, PsycINFO, Embase, CINAHL, Scopus, and Web of Science (Core Collection) were examined, and the search results were imported to Covidence, where title and abstract screenings and full-text screenings occurred. The inclusion and exclusion criteria for this updated review match those in the original review: (1) the study population must contain participants bereaved by suicide, (2) the study data must be quantitative, and (3) the study must report data on posttraumatic or stress-related growth. The original review conducted its search before 2019; thus, this updated review searched databases for the timeframe of January 2019 to January 2024. The updated meta-analysis will synthesize data from both the original and updated reviews to examine trends over time. The Newcastle-Ottawa Scale (NOS) will be used to assess publication quality. Random-effects meta-analyses will be conducted using RStudio (R Foundation for Statistical Computing).

Results: The review was funded in October 2023 and is currently in progress. Results are expected to be finalized in October 2024. There are 21 articles that have been included in the review and are being analyzed at this time. We aim to submit the full article for publication in December 2024.

Conclusions: The results of this updated systematic review and meta-analysis will be used to examine key relationships and findings regarding posttraumatic growth in individuals bereaved by suicide. The discussion will also investigate the findings of this updated review in comparison to the findings of the original review. Any differences would be highlighted. Limitations of the current review will be discussed, such as the quality of the articles included.

Trial Registration: PROSPERO CRD42024485421; https://tinyurl.com/3hzpnzr3
International Registered Report Identifier (IRRID): DERR1-10.2196/64615

(JMIR Res Protoc 2025;14:e64615) doi:10.2196/64615

KEYWORDS

posttraumatic growth; suicide-loss survivors; trauma; systematic review; meta-analysis; posttraumatic; suicidal; systematic review; meta-analysis protocol; traumatic impacts; bereaved survivor; social support; bereavement; data collection; sociodemographic; psychological; databases

Introduction

When someone dies by suicide, those who lose this individual in their lives often face significant stress. These feelings can be inundating and are often accompanied by a sense of complicated grief and, at times, depression [1]. It is a tragic event that can generate negative emotions as well as many questions that may be left unanswered in the minds of these surviving individuals. In addition, this population of people bereaved by suicide is at an increased risk of suicidal behavior themselves [2]. Based on data that over 700,000 people die by suicide each year globally [3], and that for each suicide, there are from 6 family members to 135 community members considered to be bereaved or exposed, respectively [4,5], up to 94.5 million can be affected by suicide annually. Thus, many people affected by suicide loss each year are subsequently at increased risk of dying by suicide themselves.

There are commonalities between bereavement of suicide and other forms of death; however, some features of suicide bereavement are more pronounced, such as feelings of guilt, blame on self or others, or a longing for answers [6,7]. While all bereaved people may experience feelings of grief, loss, and depression, people bereaved by suicide specifically can begin to develop symptoms of posttraumatic stress disorder (PTSD) [8,9]. However, some individuals show signs of posttraumatic growth (PTG) more so than symptoms of PTSD. PTG is the personal improvement that occurs as a consequence of experiencing a traumatic or extremely challenging event or crisis. Literature has begun to show that, on average, PTG occurs more often than the development of pathological disorders following exposure to a traumatic event [10,11]. This is, of course, not to say that PTG is always the result of trauma, but rather, psychological suffering allows the opportunity for a person to grow and for new meaning to flourish in the face of trauma. An inverted U-shaped curve best describes the relationship between the developments of PTG—both too much and too little suffering are detrimental to the development of PTG [12,13]. This concept of PTG following a traumatic event [14] has since been applied to learning more about the bereavement experiences of individuals bereaved by suicide. Some authors have also used the phrase “personal growth” [15] or “stress-related growth” [16] in place of PTG. This study will use the terminology of PTG rather than personal growth or stress-related growth.

Determining a metric for PTG can be difficult as it is seen as both an ongoing process and a final result. However, the Posttraumatic Growth Inventory (PTGI) has been developed and shown to capture and highlight well many of the defining characteristics of PTG [10]. These characteristics are broken down into 5 domains: “greater appreciation of life and changed sense of priorities; warmer, more intimate relationships with others; a greater sense of personal strength; recognition of new possibilities or paths for one’s life; and spiritual development” [14]. It does not, however, fully account for all idiosyncratic differences that occur over time; in this regard, a more longitudinal approach for the measurement of such a complex construct (ie, PTG) could provide valuable insight [17].

For those who lose someone to suicide, there can be variables that affect their desire or willingness to seek both formal and informal help and work towards the development of PTG. Each of these variables can influence how well someone bereaved by suicide copes with and grows following their loss. For example, some individuals who have experienced suicide bereavement have reported that their primary support came from nonprofessional sources and that they were disappointed by their family and friends’ responses to their bereavement [18]. Suicide and the survivors’ grieving process can also be seen from a variety of perspectives depending on the culture from which someone comes, such as being seen as stigmatized, taboo, and isolating [19,20]. Along with these responses, some individuals have reported generally negative attitudes toward professional support systems, such as tactlessness and being unaligned in the grieving process [21]. Unfortunately, these detrimental experiences can be an additional stressor on top of what can already be a tragic and intense time of grieving. These factors could contribute to why up to 25% of people bereaved by suicide receive neither informal nor formal support [22]. Each of these variables (ie, poor support, stigmatization, tactless professional help, etc) can hinder PTG development.

This systematic review and meta-analysis is an update of a previous systematic review and meta-analysis conducted by Levi-Belz et al [23]. Our searches have found that the latter is the only one to ever be conducted on this topic. As their original review gathered data from literature before 2019, this review will include data found from searches between January 2019 and January 2024. This updated meta-analysis will synthesize data from both the original and updated reviews to search for any new or consistent trends. As some authors and databases call for a systematic review to be updated every 2 years [24], and with the paucity of understanding that exists on this subject, examining new literature, in conjunction with the previous review, could allow for a more in-depth understanding of which factors facilitate PTG in people bereaved by suicide. The aforementioned evidence suggests that PTG can and does occur following suicide bereavement; therefore, investigating further

which factors might facilitate, as well as detract from, PTG development could greatly benefit people bereaved by suicide.

We have three primary aims with this review: (1) to investigate whether PTG can occur in the aftermath of a suicide loss, (2) to examine the sociodemographic and psychological correlates of PTG among people bereaved by suicide, and (3) to observe which factors facilitate PTG in the aftermath of suicide bereavement.

Methods

Overview

This systematic review will locate and summarize applicable data from the peer-reviewed literature [25]. The findings will be reported using PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) [26] formatting and follow the PRISMA-P (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols) checklist [27]. A meta-analysis will be conducted using the data extracted from this update as well as the data from the original review.

Inclusion Criteria

Population

Study populations must include individuals bereaved by suicide. No limitations on age will be implemented.

Study Design

In accordance with the original review, only quantitative studies that report data on PTG will be included. While qualitative studies could offer a more comprehensive perspective on the topic, this update excluded them in order to follow the criteria of the original review. Gray literature and dissertations will be excluded such that peer-reviewed studies will be the only data involved. This was also done to follow the parameters set by the previous review.

Concept

Studies must report data on PTG in individuals bereaved by suicide. Studies that report data on PTG following various forms of bereavement but which do not separate the effects of suicide bereavement from other forms of bereavement will be excluded.

Context and Date of Publication

This systematic review and meta-analysis is an update of a previous systematic review and meta-analysis that gathered data before January 01, 2019. This update reviews literature published on or after January 01, 2019, and uses the same inclusion criteria as the first study. This updated meta-analysis will include the data from the 2019-2024 range as well as the initial study's findings so as to paint a full picture.

Language and Location

There are no restrictions on language or location.

Search Strategy and String

As this review is an update of a previous systematic review, the inclusion criterion for the date range is publication on or after January 01, 2019. The initial systematic review, upon which this update is based, included all dates up to December 31, 2018, in its search. Databases searched include MEDLINE (through Ovid Platform), PsycINFO, Embase, CINAHL, Scopus, and Web of Science (Core Collection). We used the MeSH (Medical Subject Headings) terms "Posttraumatic Growth, Psychological," and "Suicide" in databases that allowed for them (ie, MEDLINE [through Ovid Platform] and [PsycINFO])—the rest of the search string was free text and was used for each of the 6 databases mentioned. Multimedia Appendix 1 shows the search included in each database.

Data Extraction

Using Covidence [28], a title and abstract screening was conducted by 2 reviewers (SW and BM) to exclude studies outside the criteria as well as to remove duplicate search results. A further full-text screening was performed in Covidence by the same 2 reviewers (SW and BM), and studies deemed inapplicable were excluded; reasons for exclusion of these studies were recorded. Any disagreements on the inclusion or exclusion of an article by the 2 reviewers were brought to the review team for further opinion to resolve the dispute. Data extracted included author's name, year, location (country), study design, sample size, participants' age and sex distribution, participants' time since onset of bereavement, participants' relationship to the deceased, outcome measures, names of the instruments used, and primary findings of the study. To allow for the analysis of subgroups, we also extracted information related to demographic factors, loss-related factors, intrapersonal factors, and interpersonal factors (see the *Analysis of Subgroups or Subsets* subsection). The authors of the original review shared their data from the first review; it will be used for the meta-analysis portion of this update.

Risk of Bias (Quality) Assessment

The risk of bias will be assessed using 2 adapted versions of the Newcastle-Ottawa Scale (NOS) [29]. One adapted version will be for cross-sectional studies (7 questions), and the other for longitudinal studies (8 questions). This tool allows for the overall quality of a study to be assessed by the summation of "stars," which each question can provide based on quality. Questions are broken into categories of "selection" (4 questions), "comparability" (1 question), and "outcome" (2 questions for cross-sectional and 3 questions for longitudinal). The highest grade a study can receive is 8 stars for cross-sectional studies and 9 stars for longitudinal studies. The total number of stars is then used to determine a quality ranking for each study, where quality levels range from poor (<5 stars), fair (5-6 stars), and good (6-8 stars) in cross-sectional studies and poor (<5 stars), fair (5-6 stars), and good (7-9 stars) in longitudinal studies. Studies from all quality levels will be included as there is a paucity of literature on this topic; however, the inclusion of any "poor quality" articles will be addressed in the limitations of this updated systematic review and meta-analysis.

Strategy for Data Synthesis

The analysis will be conducted in RStudio (R Foundation for Statistical Computing) [30]. When studies did not report *r* coefficients, raw effects will be converted to *r* coefficients using the R package *effectsize* (version 0.8.3) [31]. Before conducting the analysis, we will apply a Fisher's *r*-to-*z* transformation to

the extracted effect sizes. Sampling variances and standard errors for the effect sizes will be calculated using the R package *esc* (version 0.5.1) [32].

Random-effects meta-analyses will be conducted using the R package *metafor* (version 4.4.0) [33]. This approach posits that individual study effects deviate not solely due to sampling error but also stem from another source of variance [34]. Heterogeneity will be assessed by Cochran Q, I^2 statistics, τ^2, and prediction intervals as recommended by Borenstein [35]. Publication bias will be assessed visually through a contour-enhanced funnel plot [36] and also by Egger regression test. To identify and assess the impact of potential outliers on the pooled effect and heterogeneity, influential analysis will be conducted using the R package *dmetar* (version 0.1.0) [37], using the leave-one-out method and the Baujat plot.

Analysis of Subgroups or Subsets

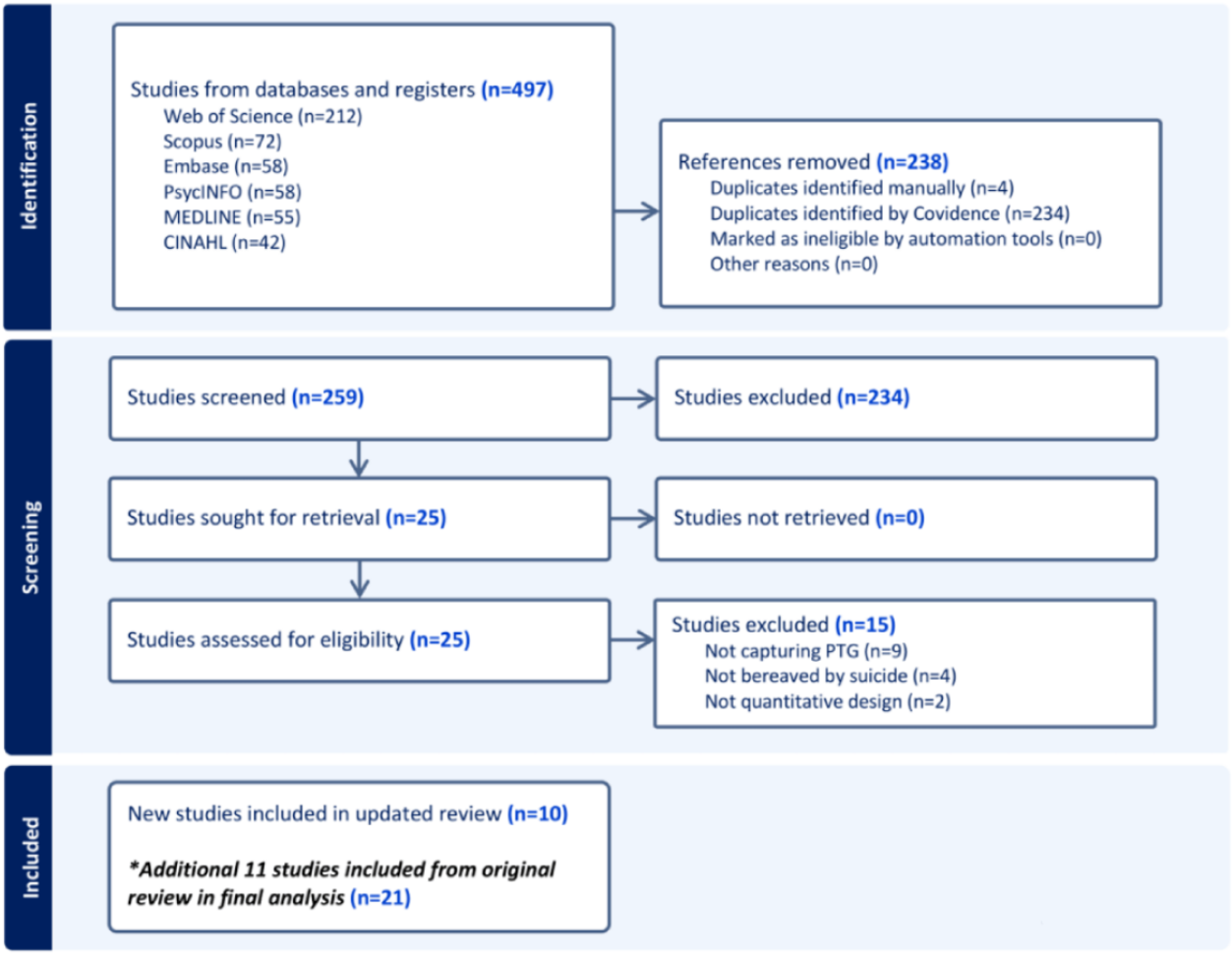
In line with the original review, moderating factors will be categorized into 4 categories, with effect sizes calculated for each subsequent variable. The following examples are from the original review:

1. Demographic factors (eg, age, gender, race, religious affiliation, educational level, marital status, and voting or civil involvement).
2. Loss-related factors (eg, grief experience, time since loss, and closeness to and type of relationship with the deceased).
3. Intrapersonal factors (eg, resilience, coping, rumination, personality, optimism, and emotional experience).
4. Interpersonal factors (eg, self-disclosure, social support, help-seeking, suicide stigma and secrecy, interpersonal burdensomeness, lack of belonging, and attachment style).

Results

This updated systematic review and meta-analysis was funded in October 2023 and is currently underway. It is expected to have results in October 2024. A total of 21 studies are included in this review; this will be reported by a PRISMA flow diagram (Figure 1). These 21 studies are currently being analyzed. All data produced in this review is included in Multimedia Appendix 2. A meta-analysis will be conducted using the data from both the studies of this updated search as well as the studies from the original review's search. Doing so will allow for any varying or static trends to be revealed. Moderating factors will be examined to determine which variables may influence PTG development in people bereaved by suicide. We aim to submit the full paper for publication in December 2024. The PRISMA-P checklist will be abided by to ensure a higher quality of research practices are followed (see Multimedia Appendix 3).

Figure 1. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram. PTG: posttraumatic growth.



Discussion

We hypothesize that interpersonal variables of self-disclosure and social support, as well as the loss-related factor of time since loss and the intrapersonal variable of resilience, will have a positive influence on PTG. A full discussion will further examine these key relationships and general findings identified in the Results section. These findings will then be discussed in relation to 3 research aims identified in this review. The discussion will also investigate the findings of this updated review in comparison with the findings of the original review. Any differences would be highlighted and expounded upon to discover which factors have changed. Overall, we anticipate that the moderating variables will have varying effects on PTG and will deliberate on any potential correlational relationships, as this could emphasize which specific factors are correlated to greater PTG facilitation.

Implications and strengths, future work, and subsequent research, which could build upon the findings of this updated review will be discussed. The limitations of this review will be considered as well, such as the quality of the journal articles included in this review. Similarly, we will discuss how this systematic review has chosen to exclude qualitative articles as well as gray literature and dissertations and the strengths and limitations that follow this decision. We will also examine the impact of using solely the NOS for quality assessment of studies. While the NOS is a widely recognized tool for assessing the risk of bias, it may not fully capture the complexities associated with PTG. PTG involves multidimensional psychological, social, and emotional processes, which may be influenced by a variety of factors not entirely accounted for by the NOS. As such, relying solely on the NOS may limit the ability to assess the nuanced methodological challenges present in studies of PTG. Future research may benefit from supplementing the NOS with other bias assessment tools or qualitative methodologies to provide a more comprehensive assessment of study quality and the contextual factors influencing PTG outcomes. This paper will be submitted for peer-reviewed publication. It will also be part of a thesis submitted to the University of Strathclyde.

Acknowledgments

This PhD studentship is being funded by the University of Strathclyde's Global Research Award.

Data Availability

All data generated or analyzed during this study are included in this published article and Multimedia Appendices 1-3.

Authors' Contributions

This review is being completed as part of a PhD thesis by SW with the University of Strathclyde and is being supervised by SR, NC, and DT. The 3 authors of the original review—YL-B (Ruppin Academic Center), KK (University of Melbourne), and KA (University of Melbourne)—have joined this updated review as coauthors and team members. The meta-analysis is also under specific supervision by VS. BM is assisting in the screening, extraction of data, and writing of this article.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Search strategy.
[PNG File , 119 KB - resprot_v14i1e64615_app1.png]

Multimedia Appendix 2
Systematic review and meta-analysis data extraction form.
[XLSX File (Microsoft Excel File), 77 KB - resprot_v14i1e64615_app2.xlsx]

Multimedia Appendix 3
PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist.
[DOC File , 89 KB - resprot_v14i1e64615_app3.doc]

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Abbreviations

MeSH: Medical Subject Headings
NOS: Newcastle-Ottawa Scale
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRISMA-P: Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols
PTG: posttraumatic growth
PTGI: Posttraumatic Growth Inventory
PTSD: posttraumatic stress disorder

Edited by A Schwartz; submitted 22.07.24; peer-reviewed by H Sami; comments to author 30.09.24; revised version received 08.11.24; accepted 15.01.25; published 14.02.25.

Please cite as:
Whittaker S, Rasmussen S, Cogan N, Tse D, Martin B, Andriessen K, Shiramizu V, Krysinska K, Levi-Belz Y
Posttraumatic Growth Among Suicide-Loss Survivors: Protocol for an Updated Systematic Review and Meta-Analysis
JMIR Res Protoc 2025;14:e64615
URL: https://www.researchprotocols.org/2025/1/e64615
doi:10.2196/64615
PMID:

Protocol

Acceptance Factors and Barriers to the Implementation of a Digital Intervention With Older Adults With Dementia or Caregivers: Protocol for an Umbrella Review

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Abstract

Background: The increase in average life expectancy, aging, and the rise in the number of people living with dementia contribute to growing interest from the scientific community. As the disease progresses, people with dementia may need help with most daily activities and need to be supervised by their carer to ensure their safety. With the help of technology, health care provides new means of self-managing health that support active aging, allowing older people and people with dementia to live independently in their homes for a longer period of time. Although some systematic reviews have revealed some of the impacts of using digital interventions in this area, a broad systematic review that examines the overall results of the effect of this intervention type is mandatory.

Objective: The aim of this review is to further investigate and understand the acceptability and barriers to using technology to monitor and manage health conditions of people living with dementia and their caregivers.

Methods: A review of systematic reviews on acceptability factors and barriers for people with dementia and caregivers was carried out. Interventions that assessed acceptability factors and barriers to the use of technology by people with dementia or their carers were included. Each potentially relevant systematic review was assessed in full text by a member of a team of external experts.

Results: The analysis of the results will be presented in the form of a detailed table of the characteristics of the reviews included. It will also describe the technologies used and factors of acceptability and barriers to their use. The search and preliminary analysis were carried out between May 5, 2023, and August 1, 2024.

Conclusions: This review will play an important role as a comprehensive, evidence-based summary of the barriers and facilitators to the use of digital interventions. This review may help to establish effective policy and clinical guideline recommendations.

(JMIR Res Protoc 2025;14:e56584) doi:10.2196/56584

KEYWORDS

dementia; aging; telemedicine; implementation; digital intervention; older people; elderly; geriatrics; mobile applications; barriers; adherence; caregivers; self-management; acceptability

Introduction

The increase in average life expectancy and aging population give rise to numerous health problems, including a decline in physical performance; changes in sensory, cognitive, and psychological abilities; and changes in social interactions [1]. Decreased physical and cognitive function is associated with a high risk of falls, increased memory loss, and difficulty completing daily tasks such as eating, dressing, medication management, and shopping [1]. Deterioration in cognition may be important, resulting in interference with occupational, domestic, or social functioning [2], making it difficult to communicate and manage activities of daily living [3,4].

The number of people with dementia worldwide is expected to increase from 46.8 million today to approximately 131.5 million by 2050 [5-7]. According to the Global Dementia Observatory and World Health Organization (WHO), dementia is the seventh leading cause of death worldwide [8]. The impact of dementia on society is well known, so early detection, timely intervention, and prevention are extremely important [9]. This issue is attracting increasing interest from the scientific community [10] and WHO, and many policies [11] are being developed worldwide.

With advances in medicine and the aging population, there is a growing number of older adults with cognitive, motor, and sensory limitations who need support to continue to be at home and maintain some degree of autonomy. For these individuals, the alternative is to live in a residential structure for older adults, where (in theory) they will have more specialized support, free from the problem of managing a home or daily activities. However, the type of care provided is usually depersonalized, often not directed toward the disease and the patient, and often too basic and not specific to individual needs. Growing economic difficulties also imply greater difficulties in this solution. Therefore, many people choose to stay at home, being cared for by other people—family members or friends—who become informal caregivers [12].

It is increasingly important to realize how we can promote the independent living and safety of people with dementia. As the disease progresses, people with dementia may need help with most daily activities, and there is a need for caregiver supervision to ensure their safety [13,14]. However, in the face of rising demand and scarce resources, the ability of health care systems and caregivers to provide equitable, responsive, and timely postdiagnostic support on a sustainable basis is a growing concern [15].

The physical, psychological, social, and economic impacts on not only people with dementia but also their caregivers, families, and society in general are another point of alarm [12,16-18]. The characteristics and complexities of dementia give rise to concerns such as frustration, risk of psychological stress, depression, reduced quality of life (QoL), and poor health on the part of the caregiver, leaving them with a great deal of responsibility and less free time to look after themselves [13,16,17,19-21]. Individuals with dementia and their carers have a range of educational and support needs that vary throughout the different stages of dementia. Information resources, caregiver training or skills development, support groups, counseling, respite care, care coordination programs, transportation services, grocery and meal delivery, personal care, and care planning are essential to help and support caregivers and patients [14].

The COVID-19 pandemic highlighted the relevance of innovative technologies in guiding the interventions of professionals and carers and supporting frail older people. It seems essential to use technologies as a means of supporting and analyzing individual behaviors, identifying the need for and barriers to specific interventions by caregivers, and maintaining the QoL of people living with dementia and their caregivers and supporting active aging for people with dementia.

The use of the internet and digital technologies is increasing rapidly around the world, including among older adults [7,22]. Digital technology encompasses a range of interconnected innovations, including the Internet of Things with next-generation telecommunication networks (eg, 5G); big data analytics; artificial intelligence using deep learning; and blockchain technology [23]. These technologies play a crucial role in active aging, as digital interventions [10] and monitoring systems [11] have been reported to be important for enabling older people and individuals with dementia to live autonomously in their own homes for a longer period of time [10]. The complexity of behavior and context in which the most diverse situations occur makes measuring this effect challenging [11]. However, the importance of 24-hour monitoring of older people has been emphasized [11]. Technology is increasingly being used in health care, such as the provision of services, home monitoring, interactive communication (eg, between patient and doctor), the transfer of health information, and peer support [24]. The benefits of telehealth or information and communication technologies to support family carers at home are increasingly being studied [7]. In this way, digital interventions can offer several advantages, including the promotion of autonomy and self-management of health and allowing patients to maintain a certain degree of independence [12-14]. These types of digital tools can provide advantages and disadvantages of residential care by providing quick access to medical information and remote support for health care professionals, as well as reducing the need for in-person visits to doctors' offices and hospitals, resulting in transportation and other associated costs [12-14]. However, these interventions may also present limitations, such as technical barriers due to a lack of technical knowledge among older adults and caregivers, concerns about the privacy and security of personal and medical data, and accessibility and adaptation challenges, as all older adults neither have access to nor are adapted to the use of digital technologies, especially individuals with severe sensory or cognitive disabilities [12-14].

Considering the complexity of this issue, it is extremely important to understand what problems occur at this stage of life and how the use of technology can help people with dementia maintain their independent living and QoL, improve their health, and prevent possible emergencies [11]. However, the use of this type of technology to assist and monitor people with dementia and their carers should not be accepted uncritically. Older people are often referred to as reluctant users

or opponents of technological change [10], and the use of technology by carers reportedly increases their burden [15,16].

This knowledge is crucial for developing more effective and personalized strategies that can improve QoL for patients and their caregivers [13,17,19,25]. In this way, by better understanding the specific challenges faced by this population, both formal and informal caregivers can adapt technological interventions to ensure greater adherence and effectiveness, thereby promoting more integrated and patient-centered care [6,7,9,13,22].

With this umbrella review, we set out to gather the data available in the literature in detail, which will allow research teams and policymakers to identify the technologies that have been successful and the objections to their use in supporting active aging and carers. The main aim of this review is to investigate, understand, and summarize the acceptability and barriers to using technology to monitor and manage health conditions in people with dementia and their carers, using more recent data. Another aim is to contribute to a theoretical debate and offer suggestions for future research in this area of work, as well as categorize the barriers and motivations for using technology. This scientific evidence will help with clinical guideline development and support political orientations.

To the best of our knowledge, this is the first general review that specifically addresses issues related to acceptability factors and barriers to the use of digital technology in people with dementia and their caregivers. We will be able to summarize the effectiveness of digital technology to support people with dementia and their carers, which is a challenge that requires an umbrella review approach.

Several research questions will be addressed: (1) What are the barriers to implementing digital interventions for people with dementia and/or caregivers? (2) What are the facilitators in implementing digital interventions for people with dementia or caregivers? (3) What digital interventions have been proposed for people with dementia or caregivers? (4) How effective were these digital interventions in alleviating the targeted problems?

Methods

Study Design

With the increase in the number of publications and reviews on the use of technology by older people and people with dementia in recent years, we aimed to use an umbrella review to examine whether the evidence for our research question is consistent or contradictory. Umbrella reviews focus on research questions or clinical practice for which there is a rich, high-quality evidence base. By reviewing all the existing literature on our research questions, we will be able to provide an overview of the main research findings.

To implement this umbrella review, we used the Preferred Reporting Items for Overviews of Review (PRIOR) statement protocol [26]. We selected and analyzed the studies according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. We used the Cochrane PICOS framework (population, intervention, comparison, outcomes, and study design; Table 1). The methods used in all stages of screening, selection and extraction, quality assessment, overlap management, analysis, and synthesis were referenced to ensure that our analysis can be replicated.

Table 1. Eligibility criteria for the inclusion of systematic reviews and meta-analyses.

Category	Specific criteria
Inclusion criteria	
Publication type, date, and language	Systematic reviews (or meta-analyses) published in a peer-reviewed journal
Study design	Systematic reviews and meta-analyses
Population	Male or female individuals with dementia (age ≥60 years) or their caregivers
Intervention	Interventions based on the evaluation of the acceptability and barriers to implement digital interventions for people with dementia or their caregivers
Outcomes	Outcomes will be extracted from systematic reviews that include these aspects. Reviews including effectiveness of implementing digital interventions for people with dementia or their caregivers (eg, Results from the Unified Theory of Acceptance and Use of Technology Questionnaire, Telehealth Satisfaction Questionnaire) and among them, if available, strategies impacting the implementation process (eg, results from the Mini-Mental State Examination, Zarit Burden Interview, Impact of Caregiving Scale, Caregiver Strain Instrument)
Exclusion criteria	
Study design	Articles that were not systematic reviews and meta-analyses were not included.
Time period	Reviews that used studies carried out during the COVID-19 pandemic
Intervention	Reviews using articles with robot intervention

Target Population

We included systematic reviews with or without a meta-analysis focusing on acceptability factors and barriers to the use of technology by people with dementia or carers. The inclusion and exclusion criteria for this umbrella review are presented in Table 1.

Our population includes adults aged 60 years and older with dementia who had been included in studies using technologies.

We did not limit the place (eg, home, clinics, academic centers, nursing home, rural populations) of intervention or the type of intervention carried out. We excluded analyses measuring acceptability factors and barriers of studies performed during the COVID-19 pandemic. The reason for this exclusion was to reduce the influence of compulsion or technology being the only way to access the intervention, which could influence the wanted results.

Intervention, Comparators, and Outcomes

We included all systematic literature reviews that present results on the factors that can limit or enhance the use of technology by older people with dementia and carers. Among these, we focused on factors of acceptability and barriers to use and implementation using technologies. This umbrella review focuses on dementia interventions that are delivered using digital technology. For the purpose of this review, digital technology is defined as technology interventions that use smartphone apps, wearable technology, or mobile text messaging to deliver health care. These digital technologies are developed to support the independence of older people living in the community, alleviating or preventing functional or cognitive impairment, thus limiting the impact of dementia on older people and their caregivers.

The following comparisons were analyzed: technology versus control (no technology), intervention environments, type of technology used, and intervention by carers. Where possible, the intervention of caregivers will be divided into formal and informal caregivers, including factors of acceptability and barriers to the use of technology. The outcomes will be divided into outcomes of people with dementia and outcomes of caregivers. Outcomes of people with dementia include the sociodemographic characteristics of the patients, cost efficiency of using the intervention, changes in health outcomes after using the intervention (eg, Mini-Mental State Examination), patients' adherence to and engagement with the intervention, adverse events, and barriers to using the intervention (eg, The Unified Theory of Acceptance and Use of Technology Questionnaire, Telehealth Satisfaction Questionnaire). Outcomes of caregivers include the quality and reliability of the interventions (eg, Zarit Burden Interview, Impact of Caregiving Scale, Caregiver Strain Instrument), patients' follow-up with health care services after using the intervention, caregivers' adherence to and engagement with the intervention, adverse events, and barriers to using the intervention (eg, Telehealth Satisfaction Questionnaire).

Publication Type, Date, and Language

Reviews published in peer-reviewed journals were included, without any date limitations.

Data Sources and Search Strategy

The search for this umbrella review aimed to identify all systematic reviews of the literature on our research question. ISI Web of Science, Scopus, and PubMed databases were used to search for scientific articles for the development of this umbrella review. In this search, articles were identified using keywords and MeSH words (for PubMed search), individually and/or in combination. The research strategy used in PubMed included the following: (((((Elderly) OR ("Older population")) OR ("Older people")) OR ("Geriatrics"[Mesh])) OR ("Aged"[Mesh])) OR ("Aging"[Mesh])(((("Telemedicine"[Mesh]) OR ("Mobile Applications"[Mesh])) OR ("health informatics")) OR ("healthcare technology")((((implementation) OR (Barriers)) OR (Acceptance)) OR (Adherence)) OR (Restriction)((((("Dementia"[Mesh]) OR ("Cognition Disorders"[Mesh])) OR ("mental deterioration*")) OR ("cognitive impairment*")) OR ("mild cognitive impairment*"))(((((((Elderly) OR ("Older population")) OR ("Older people")) OR ("Geriatrics"[Mesh])) OR ("Aged"[Mesh])) OR ("Aging"[Mesh])) AND ((((("Telemedicine"[Mesh]) OR ("Mobile Applications"[Mesh])) OR ("health informatics")) OR ("healthcare technology"))) AND (((((implementation) OR (Barriers)) OR (Acceptance)) OR (Adherence)) OR (Restriction))) AND (((((("Dementia"[Mesh]) OR ("Cognition Disorders"[Mesh])) OR ("mental deterioration*")) OR ("cognitive impairment*")) OR ("mild cognitive impairment*")).

The research strategy used in Web of Science and Scopus included (((((((Elderly) OR ("Older population")) OR ("Older people")) OR ("Geriatrics")) OR ("Aged")) OR ("Aging")) AND ((((("Telemedicine") OR ("Mobile Applications")) OR ("health informatics")) OR ("healthcare technology"))) AND (((((implementation) OR (Barriers)) OR (Acceptance)) OR (Adherence)) OR (Restriction))) AND (((((("Dementia") OR ("Cognition Disorders")) OR ("mental deterioration*")) OR ("cognitive impairment*")) OR ("mild cognitive impairment*")).

Data Exclusion

Data from the included studies were analyzed by 2 independent reviewers (MVP and RM) and extracted into Microsoft Excel according to the acceptability and barriers of new technologies, reported by people with dementia or their caregivers. Discrepancies will be resolved through discussion with a third author (NP).

Data Synthesis

Results analysis will aim to present the technology used and the factors of acceptability and barriers to its use to support people with mild cognitive impairment or dementia and their carers. It will describe in detail each of the studies analyzed, presenting the study population, site of the intervention, time of the intervention, technology used and its category, evaluation instruments, and site. It will also describe the intervention that was carried out, reasons for acceptability and barriers, impact of the intervention, and limitations or future research with people with dementia and their carers. If possible, we will use the Consolidated Framework for Implementation Research (CFIR) to organize and analyze the factors of acceptance, barriers, and impact of support technologies for people with mild cognitive impairment or dementia and their caregivers. The CFIR tool provides a comprehensive theoretical framework that will help categorize and interpret the results, promoting a deeper understanding of the factors that influence the acceptance of and challenges with implementing technologies for people with mild cognitive impairment and dementia as well as their caregivers.

Methodological Quality and Risk of Bias Assessment

The methodological quality of all the included studies was assessed using the AMSTAR-2 (A Measurement Tool to Assess Systematic Reviews) checklist [27]. The tool helps categorize the quality of reviews according to 7 critical areas and 9 noncritical areas. The assessment will be grouped into low, moderate, and high critical quality categories.

Patient and Public Involvement

No patients nor members of the public were involved in the development of this comprehensive review. However, the scope and methods of this review were based on the literature and discussed with experts.

Ethical Considerations and Dissemination

The proposed comprehensive review was based exclusively on published data from secondary sources and therefore did not involve any interactions with human beings.

The results of the umbrella review will be presented at international conferences in the fields of, for example, gerontology and geriatrics, health informatics, primary care, public health, and social sciences and will be published in a journal aimed at a wide audience. When the results are published, we will make the data generated by our research openly and publicly available. The team also intends to use social networks and the institutional websites of its research centers to disseminate its findings through websites, social media, and newsletters.

Results

We expect to find information on the facilitators and barriers to the implementation of digital interventions for people with dementia or their caregivers. We expect to provide information for politics and practice and to extract guidance for future research.

The search and preliminary analysis were carried out between May 5, 2023, and August 1, 2024. A total of 612 studies were identified across 3 databases. After the removal of duplicates, 400 articles remained. Title and abstract screening further reduced this number to 20 articles for full-text analysis. Ultimately, 5 studies met the inclusion criteria, focusing on the acceptability and barriers to technology use among individuals with dementia or their caregivers. Results were analyzed between August 2024 and October 2024, and the results are expected to be published later in 2025.

Discussion

Overview

As far as we know, this will be the first umbrella review addressing acceptance factors and barriers to the implementation of digital interventions in older people with dementia and their caregivers. Providing information on the facilitators and barriers to the implementation of digital interventions in people with dementia and their caregivers is extremely relevant from a clinical perspective [6,7,9,13,17,19,22,25]. This debate, present in the literature, encompasses several key issues: the effectiveness of digital interventions, the acceptability and usability of these technologies by older adults with dementia, and the various barriers to successful implementation, such as technological complexity and lack of digital literacy [12-14]. Additionally, there is concern about the potential for digital technologies to increase the burden on caregivers, who must learn and manage new technologies while providing care [12-14]. Discussions also focus on how digital technologies can improve QoL and health outcomes for people with dementia and their caregivers, including assessing clinical effectiveness and the impact on daily living and well-being [13,25]. Furthermore, the economic feasibility and broader social implications of implementing digital technologies in dementia care have been debated, including considerations of cost-effectiveness and potential health care cost reductions [6,7,25]. By systematically reviewing and synthesizing the available literature, this review seeks to provide a clearer understanding of these issues, thereby contributing to the theoretical debate and offering insights for future research and policy development.

Our umbrella review can significantly contribute in several ways, as noted in the following paragraphs.

It can identify barriers and facilitators. By synthesizing the results of various systematic reviews and meta-analyses, this review identifies common barriers and facilitators for implementing digital technologies in dementia care. This includes technical, financial, social, and psychological aspects that influence the accessibility and effectiveness of these interventions [12-14].

It can provide information for policies and practices. Insights obtained from this review can inform the formulation of policies and clinical practices, helping to shape guidelines that encourage the adoption of effective and sustainable technologies in dementia care [6,7,25].

Guidance for future research will be obtained. By highlighting gaps in the existing literature, this review can point to areas that need further investigation. This includes the need for studies exploring new technologies as well as studies examining diverse populations and different care contexts [12-14].

The review will also highlight research gaps in the field, pointing to associations and issues that have not been adequately explored. For example, there may be a lack of studies evaluating the impact of emerging technologies or considering the cultural and socioeconomic variability among different groups of patients and caregivers. Additionally, there may be a need for investigations into the long-term effects of using digital technologies in dementia care [12-14].

Overall, this umbrella review will contribute to the current debate on the value of a technological approach in dementia care. By providing a holistic view of the facilitators and barriers, this review can promote a more informed discussion on how to better integrate technology into geriatric care, potentially leading to better support for the autonomy and QoL of patients and their caregivers.

In summary, this review offers a unique opportunity to consolidate and critically evaluate the existing evidence on the

acceptance and barriers to digital interventions in dementia care. Its findings can influence both clinical practice and future research, contributing to a better understanding and implementation of these technologies in a context that continues to grow in importance due to the aging global population.

Limitations

To the best of our knowledge, this is the first general review that specifically addresses issues related to acceptability factors and barriers to the use of digital technology in people with dementia and caregivers. However, we expect to find difficulties: We expect to find systematic reviews with different protocols and different populations with different objectives. That will make the possibility of reaching final conclusions more difficult and, in certain cases, unobtainable.

Acknowledgments

This work was developed within the scope of the Centro de Investigação em Ciências da Saúde Universidade Beira Interior and Centro de Investigação em Desporto, Saúde e Desenvolvimento Humano.

This work was supported by the Portuguese Foundation for Science and Technology (PRT/BD/154440/2022).

Data Availability

The data sets generated or analyzed during this study are available from the corresponding author upon reasonable request.

Authors' Contributions

RM, DE, NP, AV, and MVP conceived or designed the review, performed the analysis, interpreted the data, drafted the work or revised it critically for important intellectual content, provided final approval of the version to be published, and agree to be accountable for all aspects of the protocol in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.
All authors read and agreed to the published version of the manuscript.

Conflicts of Interest

None declared.

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Abbreviations

AMSTAR: A Measurement Tool to Assess Systematic Reviews
CFIR: Consolidated Framework for Implementation Research
PICOS: population, intervention, comparison, outcomes, and study design
PRIOR: Preferred Reporting Items for Overviews of Review
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
QoL: quality of life
WHO: World Health Organization

Edited by T Leung; submitted 25.01.24; peer-reviewed by R Huijsman, DKY Leung; comments to author 19.07.24; revised version received 06.08.24; accepted 24.09.24; published 24.02.25.

Please cite as:
Madeira R, Esteves D, Pinto N, Vercelli A, Vaz Patto M
Acceptance Factors and Barriers to the Implementation of a Digital Intervention With Older Adults With Dementia or Caregivers: Protocol for an Umbrella Review
JMIR Res Protoc 2025;14:e56584
URL: https://www.researchprotocols.org/2025/1/e56584
doi:10.2196/56584
PMID:

Protocol

Use of Educational Technology in Inclusive Primary Education: Protocol for a Systematic Review

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Abstract

Background: Educational technology (EdTech) has been instrumental in the last few decades in promoting inclusive education by overcoming various learning barriers and offering tools and opportunities to all students, including those with special educational needs and disabilities (SEND). However, there is limited understanding of current classroom practices and policies and of the effects of the COVID-19 pandemic on EdTech use in the inclusive classroom.

Objective: This systematic review aims to outline the current knowledge on the use of EdTech to support the learning of students with SEND in inclusive primary schools in high-income countries.

Methods: We followed the PRISMA-P (Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols) and the Generalized Systematic Review Registration Form in reporting the details of this protocol. The inclusion criteria for the systematic review require that studies focus on students with SEND who are attending the primary stage of school in high-income countries. The studies can be qualitative or quantitative and should explore the design and use of EdTech with these students. Eligible studies must be published between 2016 and 2024, be peer-reviewed, and be available in English. We systematically searched the ACM, Directory of Open Access Journals, British Educational Index, ERIC, Google Scholar (first 100 records), IEEE, PsycINFO, Scopus, and Web of Science databases. The titles and abstracts of all records will be screened for relevance according to the inclusion criteria. Following this, the full text of the articles will be screened. To ensure the reliability of the screening process, an independent reviewer will screen a percentage of the records for the first screening round. The data extraction process for this systematic review will start with a pilot stage to validate and eventually update the list of entities to be extracted. Following the pilot stage, the final data extraction will be undertaken. An independent reviewer will extract data from a subsample of the records to ensure the reliability of the data extraction process.

Results: The database search was conducted in July 2024. The database search identified a total of 547 records. It is anticipated that the study findings will be submitted for publication in a peer-reviewed journal by the end of January 2025.

Conclusions: This study will provide up-to-date evidence of the use of EdTech in inclusive primary school settings in high-income countries and will describe the impact of the COVID-19 pandemic on the use of EdTech with students with SEND.

International Registered Report Identifier (IRRID): DERR1-10.2196/65045

(JMIR Res Protoc 2025;14:e65045) doi:10.2196/65045

KEYWORDS

special education needs; disabilities; primary education; inclusive education; education technology; assistive technology; high-income countries; systematic review

Introduction

Background

Educational Technology (EdTech) usually includes a number of broad definitions across disciplines. For the purposes of this systematic review, this term includes any use of information and communication technology and assistive technology. Information and communication technology refers to the technologies used for accessing, processing, and communicating information and encompasses a wide range of technologies, including (1) computers and software applications, (2) internet and network systems, (3) mobile phones and other handheld devices, (4) digital broadcasting technologies (radio and TV), and (5) email and other communication tools [1]. Assistive technology includes any item or piece of equipment that helps a person with a disability to increase, maintain, or improve their functional capabilities as a learner and any related assistive technology service [1].

EdTech has transformed education and learning in the last few decades by offering multiple means to represent information, express knowledge, and engage in learning [2]. Moreover, EdTech has played a crucial role in supporting inclusive education by addressing multiple barriers to learning and by providing tools and opportunities to all students, including students with special educational needs and disabilities (SEND). For instance, EdTech has supported fair and optimized access to the curriculum while developing students' independence, agency, and social inclusion [2]. In addition, it has facilitated personalized learning, enhanced communication, and interaction among peers and teachers, and strengthened social skills [2]. However, as noted in the UNESCO (United Nations Educational, Scientific and Cultural Organization) report [2], the overall benefits and drawbacks of the implementation of EdTech are still not fully understood. Several factors contribute to this lack of understanding. First, the effectiveness of EdTech tools varies by the socioeconomic level of the students and by the income level of the country. It also depends on teacher willingness to adopt these tools and their readiness to use them as well as on the education stage. In fact, students at different stages show distinct behavior habits in terms of web-based learning experiences [3]. Third, the costs associated with implementing and maintaining EdTech, both in the short term and in the long term, may be higher than initially anticipated, posing affordability challenges, especially in poorer countries. These costs include the cost of the EdTech tools as well as the cost of training teaching staff members, which is necessary for the effective use and the appropriate selection of technologies for specific students. Finally, not all technologies are suitable for students with different types of SEND. To be effective, these technologies must be tailored to each student's specific learning needs.

With such numerous factors affecting the effectiveness of EdTech and the wide range of software applications, devices, and other technologies available on the market, teachers and policy makers can easily feel overwhelmed. Therefore, systematic reviews are needed to understand the available options and to help them make informed decisions for effective and manageable employment of EdTech in education to facilitate the inclusion of students with SEND. In recent years, a few systematic reviews have examined the use of EdTech for students with SEND [1,4-6]. Despite the importance of these studies, some are limited in their scope and in the variety of EdTech tools examined, while others encompass all educational levels, preventing a focused analysis of EdTech effectiveness for specific educational stages. In addition, only one study included research published after the COVID-19 pandemic.

The systematic review by [4] investigated the technology practices in special education contexts and included 126 studies published between 2014 and 2018. The results revealed that the most examined technology was games, and the most studied outcome was the improvement of learners' cognitive abilities. The majority of the studies included precollege students with learning disabilities and focused on natural sciences. Interventions were primarily conducted in formal educational environments and were mainly implemented over 5-10 weeks. Based on their results, the authors recommended providing a greater level of detail in reporting research findings and placing more emphasis on promoting life, job, and social skills.

The study by [5] investigated the impact of using augmented reality in the education of students with SEND. The review included 18 studies published between 2016 and 2021. The authors noted a decrease in studies from 2020 onwards, which they attributed to the COVID-19 pandemic and to the consequent closure of educational centers. The majority of the included studies used quantitative methodologies. Most of these studies focused on primary and secondary school students, with very few examining early childhood education or higher education. The experiences were primarily conducted with students with intellectual disabilities, followed by students with autism, learning difficulties, and hearing impairments. The use of augmented reality showed positive results in the learning of students with SEND. Improvements were observed in academic performance, motivation, communication, social interaction, and level of autonomy. However, the authors identified several limitations to the use of augmented reality in the education of SEND. These included low levels of teacher training, limited availability of augmented reality technology, lack of support from educational institutions, and technical and accessibility issues.

The study by [6] presented a systematic review investigating technology-enhanced and game-based learning activities used with children with SEND. The authors included 18 studies published between 2009 and 2019. They reported that about one-third of the studies involved participants with intellectual disabilities, another third included autistic participants, and the remaining studies involved participants with Down syndrome, motor impairments, visual impairments, and hearing impairments. The primary goal of the game-based activities was to support students' cognitive skills. These activities covered a wide range of academic areas, including mathematics, functional skills, and communication. The results of the included studies were mixed, with some interventions improving the learning of participants and others promoting their motivation.

Finally, the systematic review by [1] investigated the use of assistive technology among primary school students with disabilities in low- and middle-income countries. The study included 51 studies published between 2007 and 2020. The findings showed little evidence of the efficacy of educational interventions, with learning outcomes often considered secondary to the technological aspects of the studies. The authors reported a considerable variation in the number of studies addressing different types of impairments, with two-thirds of the studies involving students with sensory impairments. In addition, teachers and parents were often excluded from the process of using and evaluating EdTech. A consistent theme reported in the included studies was the reluctance of teachers to adopt EdTech solutions in their everyday teaching practices. Most of the studies were case studies or small-sample multiple baseline studies and rarely included control groups.

The current systematic review aims to summarize the current understanding of how EdTech supports the learning of students with SEND in inclusive primary schools in high-income countries. Moreover, this study will allow the investigation of the effects of the COVID-19 pandemic on the use of EdTech in this specific setting.

Review Questions

This systematic review seeks to answer the following questions:

1. How can EdTech support students with SEND in primary school settings in high-income countries?
2. What EdTech interventions are used to support students with SEND in high-income countries?
3. What are the gaps in the literature, and what is the potential for further development in this field?
4. How has the COVID-19 pandemic impacted the use of EdTech in primary inclusive classrooms?

Methods

Study Registration

The protocol for this systematic review follows the PRISMA-P (Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols) checklist [7,8] and the Generalized Systematic Review Registration Form [9]. The PRISMA-P checklist used for the development of this systematic review protocol is provided in Multimedia Appendix 1. The systematic review protocol was preregistered before the analysis of the data in the Open Science Framework in July 2024 and was last updated in December 2024 [10].

Inclusion Criteria

To be included in the systematic review, studies must meet the following criteria.

Population

- Students with SEND.
- Attending primary school.

Setting

We will include studies conducted in high-income countries, as classified by the World Bank [11] and based on the World Bank's Gross National Income per capita thresholds for the 2024-2025 fiscal year.

Study Design

We will include qualitative and quantitative studies exploring the design and the use of EdTech tools with students with SEND. We will exclude reviews of the literature.

Publication Date

We will include studies published between 2016 and 2024. This timeframe encompasses 4 years before the COVID-19 pandemic, which provides a baseline, and 4 years after, allowing us to assess the immediate and evolving effects of the pandemic. Moreover, focusing on this timeframe complements existing literature, which already covers earlier years, and provides a comprehensive and up-to-date perspective on the subject.

Publication Type

We will include peer-reviewed journal articles and peer-reviewed conference proceedings. While we originally considered including gray literature, such as reports from nongovernmental organizations, we realized that these sources would require a different approach to data extraction and synthesis, demanding additional time and resources that are not available to our research team. Similarly, Master and PhD theses will be excluded. Although these documents can be valuable resources, they may not be subjected to the same level of scrutiny as peer-reviewed articles, depending on the country in which they are conducted. Their length and the challenge of assessing them raise concerns about data extraction and synthesis of the findings for the systematic review. Moreover, their limited accessibility and dissemination could complicate replicability and comprehensive data extraction. Finally, we assumed that high quality studies are typically published in a peer-reviewed journal, supporting our decision to exclude these sources.

Language

We will include only studies available in the English language.

Exclusion Criteria

Studies that do not involve participants with SEND will be excluded.

In addition, studies focusing on individuals outside the primary school age range (5 years to 11 years) will not be considered. This exclusion criterion will be based on the mean age of the sample of students with SEND, which has to fall within this range.

Research conducted in countries other than high-income nations, as classified by the World Bank [11], will also be excluded.

Studies conducted in contexts other than the classroom settings, such as hospitals, clinical settings, or participants' homes will be excluded.

Furthermore, non–peer-reviewed studies and gray literature will be excluded. Previous reviews of literature will also be excluded.

Finally, studies not available in English will be excluded.

Search Strategy

Literature search strategies were developed using keywords from previous relevant systematic reviews, with guidance from a specialist librarian at UCL. The librarian provided recommendations on both the keyword list and database selection. The databases searched include ACM, Directory of Open Access Journals, British Educational Index, ERIC, Google Scholar (first 100 records), IEEE, PsycINFO, Scopus, and Web of Science. To ensure comprehensive coverage, the electronic database search will be supplemented by scanning the reference lists of studies that meet the inclusion criteria.

Starting from the list of keywords used by [1], the list of keywords was optimized by including synonyms and relevant terms derived from the research questions. The search strategy underwent several iterations to refine the terms and optimize the query string. The desirability of reducing the number of keywords or adding new terms to the query was evaluated based on the effect on the number of hits [12]. The terms evaluated were not considered necessary and hence deleted if the number of hits increased greatly and included a high ratio of nonrelevant references. To further validate the search results, we ran the search using alternative search terms to confirm that the search string captured the relevant studies. Search terms were limited to the title, the abstract, and the keywords of the papers, when possible. Alternatively, they were limited to the abstract of the paper only. When possible, the search was restricted to specific subject areas (such as “psychology” or “education”) or educational levels (such as “primary school”). The search strategy was conducted on July 26, 2024, by ER. Table 1 displays the search strategy for each database.

Table 1. Search strategy formulated for each database included in the study.

Database	Search string
PsycINFO[a]	(blind or deaf* or autis* or neurodiver* or “intellectual dis*” or “learning dis*” or “mental* retard*”).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures, mesh word] AND (tech* or assistive or smartphone or tablet or laptop).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures, mesh word] AND (“primary school” or “elementary school” or “junior school” or “middle school”).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures, mesh word] Filters applied: limit to (english language and abstracts and 180 school age <age 6 to 12 yrs> and journal article and yr=“2016 - 2024”)
Web of Science	(((TS=(blind OR deaf* OR autis* OR neurodiver* OR “intellectual dis*” OR “learning dis*” OR “mental* retard*”)) AND TS=(tech* OR assistive OR smartphone OR tablet OR laptop)) AND TS=(“primary school” OR “elementary school” OR ”junior school“ OR ”middle school“)) AND (DT==(”ARTICLE“) AND TASCA==(”EDUCATION SPECIAL“ OR ”PSYCHOLOGY EDUCATIONAL“ OR ”EDUCATION EDUCATIONAL RESEARCH“) AND LA==(”ENGLISH“) AND PY=2016-2024)
Scopus	(TITLE-ABS-KEY (blind OR deaf* OR autis* OR neurodiver* OR ”intellectual dis*“ OR ”learning dis*“ OR ”mental* retard*“) AND PUBYEAR > 2015) AND (TITLE-ABS-KEY (tech* OR assistive OR smartphone OR tablet OR laptop) AND PUBYEAR > 2015) AND (TITLE-ABS-KEY (”primary school“ OR ”elementary school“ OR ”junior school“ OR ”middle school“) AND PUBYEAR > 2015) AND LANGUAGE (english) AND SUBJAREA (psyc OR soci-edu OR comp-csa OR comp-hci) AND (LIMIT-TO (DOCTYPE,”ar“) OR LIMIT-TO (DOCTYPE,”cp“))
ERIC[b]	Noft(blind OR deaf* OR autis* OR neurodiver* OR ”intellectual dis*“ OR ”learning dis*“ OR ”mental* retard*“) AND noft(tech* OR assistive OR smartphone OR tablet OR laptop) AND noft(”primary school“ OR ”elementary school“ OR ”junior school“ OR ”middle school“) AND rtype.Exact(”Article“) AND la.Exact(”English“) AND lv(”primary education“ OR ”elementary education“ OR ”middle schools“) AND PEER(yes) AND PEER(yes) AND pd(20160101-20240630) Filters applied: Document type: Article; Language: English; Education level: Elementary education, Middle schools, Primary education
British Education Index	AB (blind OR deaf* OR autis* OR neurodiver* OR “intellectual dis*” OR “learning dis*” OR “mental* retard*”) AND AB (tech* OR assistive OR smartphone OR tablet OR laptop) AND AB (”primary school“ OR ”elementary school“ OR ”junior school“ OR ”middle school“) Limiters: Peer Reviewed; Publication Date: 20160101-20241231; Publication Type: Academic Journal; Language: English Expanders: Apply equivalent subjects Search modes: Proximity
Directory of Open Access Journals	blind OR deaf* OR autis* OR neurodiver* OR intellectual dis* OR learning dis* OR mental* retard* AND tech* OR assistive OR smartphone OR tablet OR laptop Filters applied: 2016-2024
ACM[c] Digital Library	[[Abstract: blind] OR [Abstract: deaf*] OR [Abstract: autis*] OR [Abstract: neurodiver*] OR [Abstract: ”intellectual dis*“] OR [Abstract: ”learning dis*“] OR [Abstract: ”mental* retard*“]] AND [[Abstract: tech*] OR [Abstract: assistive] OR [Abstract: smartphone] OR [Abstract: tablet] OR [Abstract: laptop]] AND [[Abstract: ”primary school“] OR [Abstract: ”elementary school“] OR [Abstract: ”junior school“] OR [Abstract: ”middle school“]] AND [E Publication Date: (01/01/2016 TO 30/06/2024)]
IEEE[d] Xplore	(“Abstract”: blind OR “Abstract”: deaf* OR “Abstract”: autis* OR “Abstract”: neurodiver* OR “Abstract”: “intellectual dis*” OR “Abstract”: “learning dis*” OR “Abstract”: “mental retard*”) AND (“Abstract”: tech* OR “Abstract”: assistive OR “Abstract”: smartphone OR “Abstract”: tablet OR “Abstract”: laptop) AND (OR “Abstract”: “primary school” OR “Abstract”: “elementary school” OR “Abstract”: “junior school” OR “Abstract”: “middle school”). Filters applied: 2016-2024 & Journals & Conferences
Google Scholar	(blind OR deaf* OR autis* OR neurodiver* OR “intellectual dis*” OR “learning dis*” OR “mental* retard*”) AND (tech* OR assistive OR smartphone OR tablet OR laptop) AND (”primary school“ OR ”elementary school“ OR ”junior school“ OR ”middle school“) Filters applied: 2016-2024

[a]PsycINFO: American Psychological Association.

[b]ERIC: educational resources information center.

[c]ACM: association computing machinery.

[d]IEEE: Institute of Electrical and Electronics Engineers.

Screening

Rayyan [13], a web-based literature review software, will be used to remove the duplicates and to assist with the screening process. The titles and abstracts of all the records will be screened for relevance against the inclusion criteria by ER. Following this, the same reviewer will evaluate the full text of the articles deemed eligible. The reference list of all the studies that ultimately will meet inclusion criteria from the database search will be screened for any additional records that may have been missed.

An independent reviewer will screen a subsample of all records to establish the reliability of the screening process. The percentage of records to be independently screened will be

determined based on the total number of records, according to the following rule: if there are more than 201 records, 5% will be screened; if there are between 100 and 200 records, 10% will be screened; and if there are 100 or fewer records, 20% will be screened. Disagreements will be discussed and resolved during agreement meetings through consensus or by consulting a third reviewer. The rationale for excluding records that do not meet the eligibility criteria will be documented.

Data Extraction

The data extraction process will begin with a pilot stage, during which ER and MB will independently extract data from a randomly selected sample of the included studies. The sample size will be determined based on the total number of studies included at this stage of the review, following the same criteria used for the screening process. The purpose of the pilot phase is to ensure adherence to standardized procedures and to validate and, if necessary, update the data extraction criteria. After the pilot stage, ER will complete the final data extraction for all included studies, using Microsoft Excel to collect and organize the information.

The provisional list provided in Textbox 1 outlines the data to be extracted. Based on the pilot stage, this list and the corresponding coding rules will be finalized. If significant updates are made to the list of entities to be extracted, MB will independently review the data extraction to ensure the reliability of the final data extraction process. The sample size will be determined based on the total number of studies included at this stage of the review, following the same criteria used for the screening process.

The study's characteristics include the authors, publication year, and the country of data collection. It also includes the study design (cross-sectional or longitudinal) and type of study based on the category used in the Mixed Methods Appraisal Tool (MMAT) [14]. For interventions and single-case research, information about the length and framing of the intervention will also be extracted. The intervention's framing will be coded based on the Multi-Tiered System of Support model, which operationalizes how teachers implement the Universal Design for Learning model and includes three categories: (1) core classroom instruction, (2) targeted small group instruction, or (3) intensive individual intervention [15].

The SEND sample characteristics cover sample size, participant age, sex, socioeconomic status, and the diagnosis or disability categorization.

EdTech characteristics include the terminology used to refer to the tool described in the study (eg, "information and communication technology" or "assistive technology"), cost, level of technology (low-tech or high-tech), and the type of EdTech tools used, categorized according to the World Bank [16], as shown in Textbox 2.

Textbox 1. Provisional list of data to be extracted

Characteristics of the study

- Authors
- Year of publication
- Country where the data was collected
- Study design
- Type of study
- Length and framing of the intervention (limited to intervention studies and single-case research)

Characteristics of the sample with SEND

- Sample size
- Chronological age of participants
- Sex of participants
- Socioeconomic status
- Diagnosis or disability categorisation

Characteristics of Educational Technology (EdTech)

- Use of EdTech terminology
- Overall cost of the EdTech tool
- Level of technology of the EdTech tool
- Type of EdTech employed

Textbox 2. Type of education technology (EdTech).

Type of EdTech

- Augmentative and alternative communication
- Accessible textbooks
- Assistive hearing and listening technology
- Braille reading and writing equipment
- Mainstream accessible software and applications
- Mobility technology
- Personal electronic devices
- Platforms and applications for learning support
- Technology for teaching support
- Technology for vision enhancement
- Text-to-speech technology

Outcomes

The primary outcome of this systematic review will be the overall effectiveness of EdTech tools used in the inclusive classroom, defined as their impact on a range of factors including academic achievement, student engagement, social inclusion, accessibility, and other relevant outcomes that contribute to an inclusive learning environment.

Assessment of Risk of Bias in the Included Studies

To assess the risk of bias in the studies included in this systematic review, we will use the MMAT [14]. The MMAT is a generic critical appraisal tool that was developed for the appraisal of multiple types of studies including qualitative studies, quantitative randomized controlled trials, quantitative nonrandomized studies, quantitative descriptive studies, and mixed methods studies. As the present systematic review includes studies using a range of methodologies, the MMAT was deemed the most suitable approach for ensuring quality and consistency in the evaluation of the risk of bias. The assessment consists of 2 screening questions and 5 category-specific items. Each item can be rated as “yes” if the criterion is met, “no” if it is not met, or “can’t tell” if the study provides insufficient information to score the criterion as met or not met. The MMAT has been applied in previous research, such as in systematic reviews to assess the methodological quality of the included studies investigating the use of EdTech for health and social care practitioners and the use of gamification in education [17,18].

All included studies will be evaluated for quality by one reviewer of the research team. In addition, an independent reviewer will reassess 20% of those studies to ensure consistency and reliability in the evaluation process. Disagreements will be resolved through discussion, and if consensus cannot be reached, a third reviewer will be consulted.

Data Synthesis

We will present the collated results in a structured format, aligned with the research questions of the systematic review. This review will use a mixed methods analysis, incorporating both quantitative and qualitative approaches to analyze the results from the included studies.

For the interventions, we will assess the primary outcome by comparing pre- and posttest scores of students with SEND using specific EdTech tools. Tables will be created to describe the characteristics of the studies, populations, and EdTech tools used.

Qualitative data will be analyzed using content analysis to synthesize and interpret key issues and themes related to Review Question 1 across the studies. If a sufficient number of comparable studies are included, a subgroup analysis will be conducted. Potential subgroups may be based on the type of EdTech used, the population involved, or the country where the study was conducted.

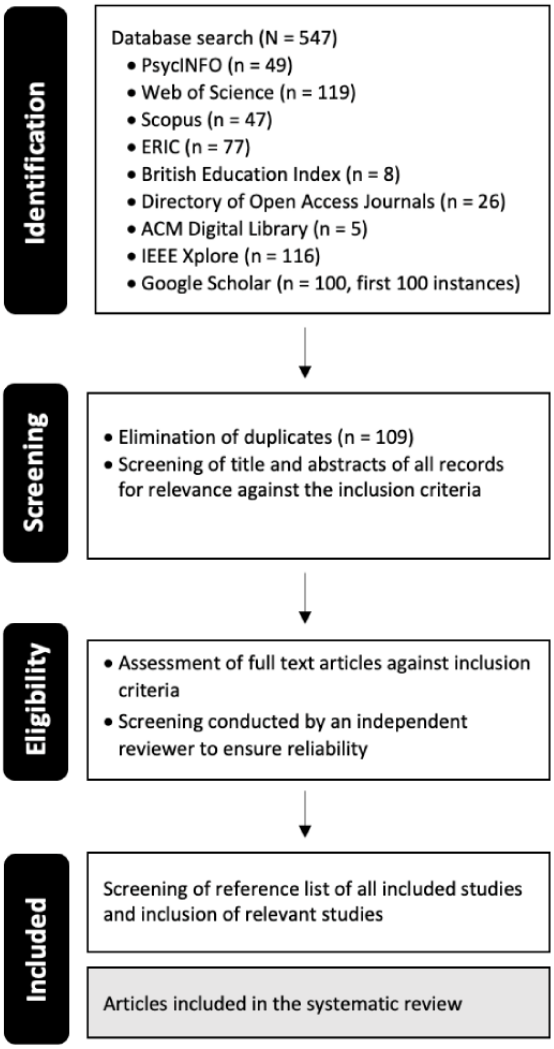
Assessment of Meta-Biases

We anticipate that assessing publication bias may not be feasible due to the heterogeneous nature of the included studies. Similarly, assessing outcome reporting bias may be challenging because of the potential lack of registered protocols for these studies. However, we will provide a narrative discussion on the potential for publication bias, focusing on whether negative results were excluded or difficult to identify, and we will highlight any inconsistencies in outcome reporting where possible.

Results

As shown in Figure 1, a database search was conducted in July 2024, identifying 547 records. We expect to complete the screening process by November 2024 and submit the manuscript for peer review by the end of January 2025. The results of the completed study will be submitted to a journal relevant to the SEND population, and findings will be presented at relevant conferences and shared with stakeholders, such as nongovernmental organizations, education and health care organizations, assistive technology developers, and policy makers.

Figure 1. Flow diagram of the search process PsycINFO: American psychological association; ERIC: educational resources information center; ACM: association computing machinery; IEEE: Institute of Electrical and Electronics Engineers.



Discussion

Principal Findings

Many reviews have already been conducted on the use of EdTech with students with SEND. However, these reviews are limited by their focus on specific tools, such as augmented reality or educational game-based activities. In addition, some reviews encompass all educational levels, which prevents a detailed examination of the effectiveness of these tools for specific educational stages (such as primary, secondary, or higher education). These limitations reduce their usefulness for making targeted decisions about EdTech implementation. Furthermore, some reviews have a narrow scope regarding publication years, covering studies only up to 2021. It is essential to have current insights into classroom practices, as technology and devices used just 5 years ago may now be outdated or unavailable, and new EdTech devices may have been introduced and evaluated. To fill this gap, our systematic review will collect and analyze data on the use of EdTech in inclusive primary school settings in high-income countries and will also discuss findings in comparison with previous reviews of literature in this field. Finally, this study will describe the impact of the COVID-19 pandemic on the use of EdTech in the field of research education. We anticipate that the review will reveal an increase in the use of EdTech in the inclusive classroom following the COVID-19 pandemic. These findings are expected to inform the use and the design of inclusive EdTech and assistive technology tools to support students with SEND in the primary classroom and to establish best practices for the seamless integration of EdTech, ultimately producing positive outcomes for these students.

In addition, one of the outcomes of our systematic review will be the creation of an updated database that catalogs all studies investigating the use of EdTech in inclusive primary schools in high-income countries. This database will offer accessible, current evidence on how EdTech supports students with SEND in this setting. The final database, which will be published in the Open Science Framework platform and as supplementary material following the publication of the systematic review, aims to facilitate evidence-based decision-making, support the development of guidelines, interventions, and policies, and identify gaps in the current research landscape. It is expected to serve as a valuable resource for researchers, educators, assistive technology developers, policy makers, and other stakeholders.

Limitations

While we will use a comprehensive search strategy, it is possible that relevant studies could be overlooked. In addition, our search is restricted to English-language and peer-reviewed publications, potentially excluding studies in other languages and unaudited studies and thereby limiting the comprehensiveness of the evidence available. Finally, a limitation of this systematic review is that it may not be feasible to meta-biases. As a result, the confidence in the conclusions drawn from this review may be somewhat limited, and this limitation should be considered when interpreting the findings.

Conclusions

To our knowledge, this will be the first systematic review to describe the impact of the COVID-19 pandemic on the use of a wide range of EdTech to support the learning and inclusion of primary school students with SEND in high-income countries. This review aims to facilitate evidence-based decision-making and contribute to the future improvement of guidelines for the effective use of EdTech to support inclusion in primary school settings. Such knowledge is crucial for promoting educational equity, enhancing learning outcomes, and supporting the diverse needs of all students.

Acknowledgments

This research was funded by the EPSRC ICT Public Engagement Grant (EP/W033674/1). The funder had no role in the study design, analysis, and interpretation of data, writing of the manuscript, or the decision to submit the manuscript for publication.

Data Availability

The dataset generated during this study is available in the OSF repository [10] and will be published as supplementary material alongside the main systematic review paper.

Authors' Contributions

MB and ER contributed to conceptualization, methodology, and writing–original draft, and editing. ER handled data curation. CH and MB handled funding acquisition. MB performed project administration. CH handled supervision, writing–review, and editing.

Conflicts of Interest

None declared.

Multimedia Appendix 1
PRISMA-P (Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols) checklist.
[DOCX File , 41 KB - resprot_v14i1e65045_app1.docx]

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Abbreviations

EdTech: educational technology
MMAT: Mixed Methods appraisal Tool
PRISMA-P: Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols
SEND: special educational needs and disabilities
UNESCO: United Nations Educational, Scientific and Cultural Organization

Edited by A Schwartz; submitted 02.08.24; peer-reviewed by P Ozmizrak, A Jafarizadeh; comments to author 11.11.24; revised version received 13.12.24; accepted 10.01.25; published 25.02.25.

Please cite as:
Ranzato E, Holloway C, Bandukda M
Use of Educational Technology in Inclusive Primary Education: Protocol for a Systematic Review
JMIR Res Protoc 2025;14:e65045
URL: https://www.researchprotocols.org/2025/1/e65045
doi:10.2196/65045
PMID:

Protocol

Efficacy and Safety of Acupuncture for Post–COVID-19 Insomnia: Protocol for a Systematic Review and Meta-Analysis

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Abstract

Background: The COVID-19 pandemic has had a profound global impact, leading to a range of persistent sequelae referred to as post–COVID-19 condition or "long COVID" that continue to affect patients worldwide. Among these sequelae, post–COVID-19 insomnia (PCI) has emerged as a significant issue. Conventional treatments, including cognitive behavioral therapy and pharmacological interventions, face limitations such as variable efficacy, potential side effects, and substantial costs. Recently, acupuncture has gained traction due to its efficacy, cost-effectiveness, and safety profile.

Objective: This study aims to conduct a meta-analysis and systematic review evaluating the efficacy and safety of acupuncture for the treatment of PCI to delineate the optimal modality, intervention frequency, and duration for achieving the most beneficial outcomes, thereby providing a comprehensive understanding of acupuncture's role in managing PCI, contributing to evidence-based clinical practice, and informing clinical decision-making.

Methods: Electronic searches will be performed in 12 databases from inception to October 2024 without language restrictions. This includes both English databases (PubMed, Cochrane Library, Web of Science, Embase, OVID and Scopus), as well as Chinese databases (China National Knowledge Infrastructure, Wan-Fang Data, Chinese Biomedical Literature Database, Chinese Scientific Journal Database, Duxiu Database and the Chinese Clinical Trial Registry Center). Randomized controlled trials on acupuncture for PCI will be included. Primary outcomes will include the response rate and insomnia severity; secondary outcomes will include the Traditional Chinese Medicine Symptom Scale (TCMSS) and adverse event rates. Data synthesis will use risk ratios for dichotomous data and mean differences for continuous data. Study selection, data extraction, and quality assessment will be conducted independently by 2 reviewers. Methodological quality of eligible studies will be evaluated following the *Cochrane Handbook for Systematic Reviews of Interventions* (version 6.3). Meta-analysis will be performed with RevMan 5.3.

Results: Based on the data on response rate, insomnia severity, TCMSS score, and adverse event rates, this study will provide an evidence-based review of the efficacy and safety of acupuncture for PCI treatment.

Conclusions: This systematic review will present the current evidence for acupuncture for PCI, aiming to inform clinical practices and decision-making and to enhance the understanding of acupuncture's role in managing PCI. Furthermore, it will identify research gaps and suggest potential areas for future investigation.

Trial Registration: PROSPERO CRD42024499284; https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=499284

International Registered Report Identifier (IRRID): DERR1-10.2196/69417

(JMIR Res Protoc 2025;14:e69417) doi:10.2196/69417

KEYWORDS

acupuncture; traditional Chinese medicine; post–COVID-19 condition; long COVID-19; insomnia; sleep disorder; depression; complementary and alternative medicine; treatment; public health; study protocol; systematic review

Introduction

Background

The COVID-19 pandemic caused by the SARS-CoV-2 virus has emerged as one of the most significant public health challenges in recent years [1], with over 770 million cases and approximately 6.9 million deaths worldwide [2,3]. Despite the World Health Organization having declared the end of the global public health emergency in May 2023, evolving virus variants continue to impact the world, exacerbating the global effects of the pandemic [4]. Nearly 90% of hospitalized patients with COVID-19 develop post–COVID-19 condition [5,6], commonly referred to as "long COVID" according to the National Institute for Health and Care Excellence, which includes a range of signs and symptoms that continue or develop after the acute phase of the illness [7]. These symptoms include sleep disturbances, depression, fatigue, tinnitus, and anxiety [8,9].

Studies indicate that insomnia has a high prevalence, impacting roughly 20% to 35% of the general population [10-13], and this rate is even higher among health care workers and patients with COVID-19, reaching up to 75% [8]. Substantial evidence indicates that post–COVID-19 insomnia (PCI) frequently persists over the long term [14-17], leading to serious health issues such as increased depression, prolonged work absences, and a heightened risk of hypertension [15,18,19]. Insomnia poses a significant threat to public health, not only by impairing physical, emotional, and social well-being but also by reducing quality of life [20]. It can degrade psychological functioning and decision-making, compromise the immune system, raise the risk of accidents, and cause mood alterations, all while boosting medical expenditures [21,22]. Moreover, the interaction between sleep deprivation and SARS-CoV-2 infection could potentially raise the risk of developing neurodegenerative diseases like dementia [16]. Consequently, PCI has become widely acknowledged as a critical and pressing issue affecting the entire world. The emergence of SARS-CoV-2 subvariants in the postpandemic COVID-19 era, particularly the highly mutable Omicron lineage and its numerous subvariants, presents new challenges to public health interventions [23].

Current standard treatments for PCI include cognitive behavioral therapy for insomnia (CBT-i) and pharmacotherapy [24,25]. Although these methods have demonstrated efficacy, they are not without limitations. For instance, the 2017 clinical practice guidelines of the American Academy of Sleep Medicine indicate that CBT-i alone may not be beneficial for all people with insomnia due to issues like noncompliance, treatment unresponsiveness, access barriers, and financial constraints [25]. Pharmacological therapies for insomnia comprise benzodiazepines, nonbenzodiazepines, antidepressants, melatonin receptor agonists, and other sedatives [24,26]. While these medications can offer short-term relief, their long-term, routine use is not recommended due to the risks of developing tolerance, dependency, and withdrawal issues [20,26-28]. Moreover, these medications can lead to rebound insomnia, residual daytime sedation, cognitive and memory impairments, and motor incoordination, particularly increasing the risk of falls among older people [20,26-29]. Given these concerns, there is a pressing need to find alternative therapeutic approaches that are both efficacious and safe for treating PCI.

In recent years, complementary and alternative medicine (CAM) has become widely used to address insomnia in various countries, including the United States, Australia, and numerous Asian nations [30-32]. Acupuncture, recognized as one of the most popular and safest CAM therapies [28,33], has a long-standing history of treating sleep disorders dating back to ancient times [26]. Based on traditional Chinese medicine, acupuncture works by inserting fine needles into acupoints throughout the body. It seeks to reestablish the equilibrium between yin and yang, thereby facilitating the body's return to a state of physiological homeostasis [34-36]. A multitude of studies indicate that acupuncture is highly effective in improving both sleep quantity and quality [37-42]. The underlying mechanisms include regulating neurotransmitters such as gamma-aminobutyric acid [43-46] and serotonin [47-50], increasing melatonin levels [51-53], and modulating the hypothalamic-pituitary-adrenal axis and the expression of corticotropin-releasing hormone and adrenocorticotropic hormone [54-57], thereby improving sleep quality. Furthermore, acupuncture can also regulate inflammatory cytokines such as interleukin-1, interleukin-6, and tumor necrosis factor-α [58-62], and it can influence the gut microbiota to regulate sleep-wake behavior [63,64].

Much of the research supporting the use of acupuncture for insomnia is constrained by the limitations of low- or moderate-quality evidence and inconsistent reports regarding its clinical efficacy and safety. Furthermore, the effects of acupuncture on PCI remain largely unknown. Through an extensive literature review, we identified a notable absence of systematic reviews specifically addressing the efficacy of acupuncture for PCI. In light of this gap, we will conduct a meta-analysis and systematic review to assess and synthesize the available evidence on the efficacy and safety of acupuncture for PCI. This review aims to establish a robust theoretical foundation for clinical practice, thereby providing credible evidence on the therapeutic potential of acupuncture for PCI.

Objectives

This review has 3 objectives: (1) to evaluate the efficacy and safety of acupuncture for the treatment of PCI in comparison to comfort therapy (such as placebo, sham acupuncture, or a blank control) or other therapies (such as Western medicine or nondrug therapies); the results will provide a comprehensive understanding of acupuncture's role in managing PCI, thereby contributing to evidence-based clinical practice and informing clinical decision-making in practice; (2) to assess the methodological quality and the strength of the evidence supporting the use of acupuncture for PCI, offering a thorough

appraisal of the existing literature; and (3) to delineate the optimal modality, intervention frequency, and duration to achieve the most beneficial outcomes.

Methods

Overview

This study will be conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA) statement [65]. This protocol has been prepared in accordance with the Cochrane recommendations and registered on PROSPERO (CRD42024499284).

Study Eligibility Criteria

The inclusion and exclusion criteria for this review are detailed in Textbox 1.

Textbox 1. Inclusion and exclusion criteria.

Inclusion criteria

- Types of studies
  - All randomized controlled trials (RCTs) focusing on the treatment of insomnia after COVID-19 using acupuncture therapy
  - Studies involving single acupuncture therapy, as well as those comparing acupuncture with other interventions
  - Studies published in English or Chinese
  - Studies published from the inception of the database up to October 2024
  - No restrictions on publication status or type
- Types of participants
  - Participants who developed insomnia following COVID-19 infection without a prior history of insomnia who were subsequently enrolled in an RCT; this will include patients with confirmed COVID19 or asymptomatic SARSCoV-2 infections based on the results from nucleic acid testing, antigen testing, and clinical criteria
  - Participants meeting the diagnostic criteria for insomnia, including the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* [66], *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* [67], *International Classification of Sleep Disorders, Third Edition)* [68], and *Chinese Classification and Diagnostic Criteria of Mental Disorders, Third Edition* [69] or equivalent standard diagnostic criteria
  - No restrictions on gender, age, race, onset time, or source of cases
- Types of intervention
  - Simple acupuncture therapy
  - Trials where acupuncture is used as an adjunct to other interventions (eg, behavior therapy, psychotherapy, or pharmacotherapy) only included if the control groups receive the same additional interventions
  - No specific restrictions on acupoints or course of treatment; the selection of acupoints and acupuncture methods should be derived from traditional Chinese medicine
  - The specific length, thickness, and model of the acupuncture needle will not be considered in this review
- Types of comparisons
  - Comfort therapy (placebo, sham acupuncture, or blank control)
  - Other therapies (Western medicine or nondrug therapy)
- Types of outcome measures
  - The primary outcomes will include response rate and insomnia severity as measured by validated instruments (eg, the Insomnia Severity Index, Pittsburgh Sleep Quality Index, or Athens Insomnia Scale)
  - The secondary outcomes will include the Traditional Chinese Medicine Syndrome Score Scale score and adverse events

Exclusion criteria

- Non-RCTs, such as reviews, animal experiments, commentary articles, letters, and case reports
- Participants with primary insomnia or a serious underlying disease that makes them unsuitable for acupuncture treatment
- Studies that explored interventions using nontraditional acupoints, such as ear acupuncture, scalp acupuncture, and other methods
- Duplicate publications
- Studies found in gray literature
- Studies with incomplete data

Electronic Searches

A search strategy will be designed and conducted following the guidelines outlined in the *Cochrane Handbook*. The meta-analysis will be reported based on the PRISMA guidelines.

Electronic searches will be carried out by 2 independent researchers (YL and JZ) from initiation until October 2024. English databases (PubMed, Cochrane Library, Web of Science, Embase, OVID, Scopus) and Chinese databases (China National Knowledge Infrastructure, Wan-Fang Data, Chinese Biomedical Literature Database, Chinese Scientific Journal Database, and Duxiu Database) will be included in the search. The Chinese Clinical Trial Registry Center will also be searched for ongoing

trials. There will be no restrictions on countries or publication types.

The search will use keywords such as *COVID-19, 2019-nCoV infection, SARS-CoV-2 infection, acupuncture therapy, acupuncture treatment, pharmacoacupuncture treatment, sleep initiation and maintenance disorders, sleeplessness*, and *insomnia disorder*. To ensure a comprehensive search, a combination of subject headings (Medical Subject Headings) and free words will be used, regardless of the language or type of publication. The search will be conducted across all databases to identify all relevant articles. An example search strategy for the PubMed database is provided in Multimedia Appendix 1.

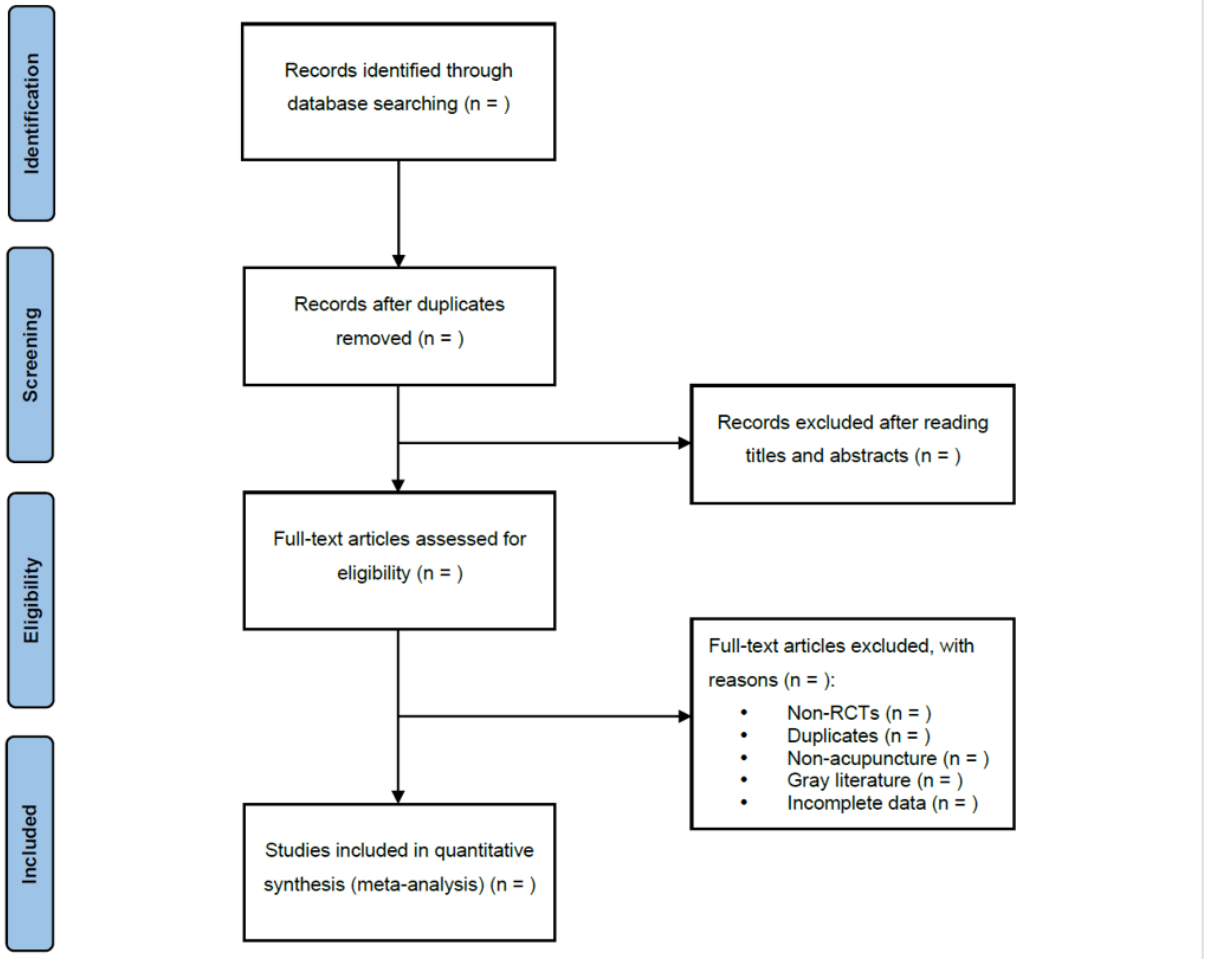
Similar search strategies will be used for the other databases. Additionally, in the case of studies for which the full text is not available, efforts will be made to contact the first author or corresponding author to obtain the necessary full text.

Study Selection and Data Collection

Selection of Studies

All reviewers have undergone training to ensure a fundamental comprehension of the context and purpose of the review. In this step, EndNote X9 (Clarivate) will be used to screen the search results. Two reviewers (YL and JZ) will independently conduct the screening process and cross-check the results. Based on the predefined inclusion and exclusion criteria, relevant studies will be selected after reviewing their titles, abstracts, or full texts. In instances of duplicate publications, the original publication will be selected. Should there be any incomplete data or ambiguous details, efforts will be made to contact the first author or corresponding author for clarification. In cases where disagreements arise, a third reviewer (KS) will be consulted, and a final decision will be reached through discussion. A comprehensive overview of the selection process will be depicted with a PRISMA flow chart (Figure 1).

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow chart. RCT: randomized controlled trial.



Data Extraction and Management

Two reviewers (ZW and LL) will independently perform data extraction using the provided data extraction form (Multimedia Appendix 2). Any disagreements that emerge during the process will be addressed through discussion between the 2 reviewers. If a resolution cannot be achieved, the input of a third reviewer (HX) will be sought. The following information will be recorded using a standardized data extraction form: (1) basic information on the study (first author, year, and country of publication); (2) study characteristics (study inclusion criteria, sample size, and participants' details, including age, gender, complications, severity, and course of insomnia); (3) details of the study intervention and control intervention, including modality, frequency, and treated acupoints; (4) a risk of bias assessment; and (5) outcome data, adverse effects, and drop-out rate.

EndNote will be used by the reviewers to facilitate data management and to identify duplicate publications. In cases where 2 or more reports describe the same trial, only one of these publications will be considered for inclusion in the analysis.

Assessing Risk of Bias in Included Studies

The methodological quality of selected studies will be assessed using the Cochrane Risk of Bias 2.0 tool. Two reviewers (HX and CL) will independently assess the risk of bias for each included randomized controlled trial according to the guidelines provided in the *Cochrane Handbook for Systematic Reviews of Interventions* (version 6.3). The assessment will cover the following domains: (1) bias arising from the randomization process, (2) bias due to deviations from the intended intervention, (3) bias due to missing outcome data, (4) bias in measurement of the outcome, and (5) bias in selection of the reported results.

Each study will be classified as "low risk," "high risk," or "some concerns" based on the evaluation. Should any disagreements arise, a third reviewer (GL) will be engaged to facilitate consensus.

Measures of Treatment Effect

Statistical analysis will be conducted using RevMan (version 5.3; Cochrane Collaboration), with forest plots being used to visually represent the comparative efficacy of the treatments. For continuous variables, the mean difference (MD) will be used to express the treatment effect, whereas for dichotomous data, the risk ratio (RR) will be used. For each treatment effect, the estimated value and 95% CIs will be determined and reported within the analysis.

Dealing With Missing Data

For studies with missing or ambiguous data, efforts will be made to contact the first author or corresponding author for assistance. Should the missing data remain unobtainable despite attempts to contact the authors, the study will be excluded from the analysis.

For studies with missing data, the intention-to-treat analysis will be used to conduct statistical and omission analysis. Intention-to-treat analysis helps maintain the integrity of the original randomized allocation of participants, even in cases where some data may be missing. This approach guarantees that participants are evaluated based on their original randomized groups, irrespective of any missing data.

Assessment of Reporting Biases

Should more than 10 studies report on the same outcome measure, a funnel plot and an Egger regression test will be applied to assess the potential for reporting bias.

Data Analysis

RevMan will be used for the calculation of the RR for dichotomous data and the MD for continuous variables. For each effect, the estimated values and the 95% CIs will be determined.

The RR is calculated as follows:

where a and b are the number of events and nonevents in the intervention group, and c and d are the number of events and nonevents in the control group.

The MD is calculated as follows:

where  and  are the means of the intervention and control groups, respectively.

Heterogeneity will be assessed using the I^2 statistic, calculated as follows:

where Q is the Cochrane Q statistic and k is the number of studies.

If the research results exhibit low heterogeneity (I^2<50%), a fixed-effect model will be applied for the meta-analysis. On the other hand, in case of significant heterogeneity (I^2>50%), a random-effects model will be used for the meta-analysis, after which, further analysis will be conducted to ascertain the sources of heterogeneity.

When the data are not amenable to quantitative synthesis, a narrative summary will be provided to elucidate the findings of the included studies.

For trials that report only pre- and postintervention values, the mean change will be derived by computing the difference between post- and preintervention measurements. Consequently, the SD for these changes will be estimated.

Subgroup Analysis

When significant heterogeneity is observed, a subgroup analysis will be performed to investigate the possible sources of this variability. The following factors will be examined as potential subgroup variables: age, gender, duration of COVID-19 infection, severity of insomnia, the type of acupuncture intervention, treatment frequency and duration, and other relevant parameters.

When sufficient data are available for each subgroup, a quantitative subgroup analysis will be performed to assess the influence of these factors on the treatment effects. Nonetheless, if the data for subgroup analysis are inadequate, a qualitative synthesis will be conducted. In this approach, the results from individual studies will be summarized and compared without a formal quantitative synthesis.

Sensitivity Analysis

If significant heterogeneity persists even after the subgroup analysis, a sensitivity examination will be implemented. This process involves reconducting the meta-analysis after discarding studies of low quality or those with possible biased sources.

The comparison of the meta-analysis results before and after sensitivity analysis allows for a thorough assessment of the

findings' stability and reliability. This approach aids in understanding the impact of individual studies on the total results, offering a more in-depth insight into the meta-analysis outcomes.

Grading the Quality of Evidence

Researchers will assess the quality of evidence using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach. The quality of evidence will be classified into 4 levels: very low, low, moderate, or high.

The GRADE methodology facilitates a systematic and transparent assessment of the certainty and strength of the evidence, thereby enabling researchers to present a comprehensive and reliable summary of the evidence in a distinct and dependable way.

Ethical Considerations

Ethics approval is not required since this protocol is solely for a systematic review and does not involve private data.

Dissemination

The results will be disseminated electronically through publication in a peer-reviewed journal or presented at a relevant conference.

Results

The study will be conducted following the methodology in the *Cochrane Handbook for Systematic Review of Interventions*. Two independent researchers will perform comprehensive searches across 12 databases, encompassing English databases (PubMed, Cochrane Library, Web of Science, Embase, OVID, and Scopus) and Chinese databases (China National Knowledge Infrastructure, Wan-Fang Data, the Chinese Biomedical Literature Database, the Chinese Scientific Journal Database, the Duxiu Database, and the Chinese Clinical Trial Registry Center). Focusing on the outcomes such as response rate, insomnia severity, TCMSS score, and adverse event rates, this study will deliver an evidence-based review of the efficacy and safety of acupuncture for PCI treatment.

Discussion

Overview

The COVID-19 pandemic has become one of the most formidable public health crises in recent years. As the persistence of post–COVID-19 condition continues, a considerable number of individuals have been grappling with PCI. This issue is escalating and poses a critical challenge to public health, placing a substantial economic burden on society. Not only does PCI negatively impact physical and mental well-being, but it also contributes to a decline in social functioning and a lower quality of life [20]. PCI is often accompanied by other symptoms, such as anxiety and depression [70]. Although CBT-i and pharmacological interventions are widely used in clinical settings, they face certain constraints, such as variable efficacy, adverse effects, and high costs. These limitations have sparked a surge of interest in CAM therapies.

As a significant component of CAM therapies, acupuncture has gained increasing recognition for its effectiveness, affordability, and favorable safety profile. It is rooted in the basic theory of traditional Chinese medicine, which emphasizes the interconnectedness of nature and humanity, viewing the body, mind, and spirit as a unified whole [71,72]. Considering that PCI affects both physical and mental health, acupuncture's natural, potent, and low-risk attributes, along with its holistic approach, make it a compelling alternative for individuals with PCI. However, given that PCI is a relatively novel condition, it is imperative to conduct a thorough analysis of acupuncture's therapeutic efficacy and safety as a treatment option.

This paper presents the protocol for a systematic review that constitutes the first quantitative analysis of the efficacy and safety of acupuncture for PCI. Through a meticulous evaluation of evidence gleaned from published randomized controlled trials, we aim to provide a comprehensive appraisal of acupuncture's impact on PCI. Furthermore, the study endeavors to delineate the optimal modality, frequency of intervention, and duration of treatment to achieve the most favorable outcomes. The findings from this meta-analysis and systematic review are expected to offer valuable insights to clinical practitioners, establishing a robust theoretical foundation and essential reference for the application of CAM therapies in PCI treatment. This evidence may significantly enhance the quality of informed clinical decision-making, particularly in the selection of therapeutic strategies for patients with PCI.

All amendments to this protocol will be meticulously recorded, including the amendment date, a description of the changes, and the corresponding rationale.

Limitations

Due to language barriers, some relevant electronic databases might not be included, potentially limiting the comprehensiveness of the findings.

Conclusion

This review will offer a thorough synthesis of the literature on acupuncture as a treatment for PCI, thereby enriching the current scientific discourse on this subject. By examining the evidence base, the review will deliver significant insights aimed at optimizing clinical practices in practical health care environments. It will also present health care professionals with a novel viewpoint on the use of complementary and alternative medicine in addressing PCI, facilitating more informed clinical decision-making.

Acknowledgments

The authors would like to express their gratitude to the anonymous reviewers for their perceptive comments and constructive suggestions.

Authors' Contributions

Conceptualization: YL, JZ, ZW and KS
Data collection, data analysis and interpretation: YL, JZ, ZW, LL, HX, CL, GL, WL, YX and XW
Writing: YL, JZ, ZW, LL, HX, and KS
Critical revision: YL, JZ, ZW, LL and KS

Conflicts of Interest

None declared.

Multimedia Appendix 1
Search strategy in PubMed database.
[DOCX File , 16 KB - resprot_v14i1e69417_app1.docx]

Multimedia Appendix 2
Data extraction tool.
[DOCX File , 16 KB - resprot_v14i1e69417_app2.docx]

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Abbreviations

CAM: complementary and alternative medicine
CBT-i: cognitive-behavioral therapy for insomnia
GRADE: Grading of Recommendations, Assessment, Development, and Evaluation
MD: mean difference
PCI: post–COVID-19 insomnia
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RR: risk ratio
TCMSS: Traditional Chinese Medicine Symptom Scale

Edited by A Mavragani; submitted 29.11.24; peer-reviewed by A Murat Ringot, SH Sung; comments to author 31.01.25; revised version received 03.02.25; accepted 05.02.25; published 03.03.25.

Please cite as:
Li Y, Zhou J, Wei Z, Liang L, Xu H, Lv C, Liu G, Li W, Wu X, Xiao Y, Sunzi K
Efficacy and Safety of Acupuncture for Post–COVID-19 Insomnia: Protocol for a Systematic Review and Meta-Analysis
JMIR Res Protoc 2025;14:e69417
URL: https://www.researchprotocols.org/2025/1/e69417
doi:10.2196/69417
PMID:40053784

Protocol

Epidemiological Characteristics of Intestinal Protozoal Infections and Their Risk Factors in Malaysia: Systematic Review and Meta-Analysis Protocol

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Abstract

Background: Intestinal protozoal infections caused by *Entamoeba histolytica*, *Giardia lamblia*, and *Cryptosporidium parvum* are prevalent in Malaysia. They cause severe diarrheal diseases with symptoms such as bloody stools, abdominal pain, stomach discomfort, and bloating. These infection outbreaks have been reported in diverse socioeconomic backgrounds and geographical regions usually during the rainy season or in areas with poor sanitation. Despite the importance of these infections, data on its overall prevalence, risk factors, and diagnostic methods remain limited.

Objective: The aim of this study is to systematically review and synthesize evidence on the risk factors, prevalence, and detection methods for intestinal protozoal infections in Malaysia, offering insights that are applicable to other tropical and low-income regions.

Methods: Studies on intestinal protozoal infections among Malaysian patients published after January 2010 up to November 2024 will be eligible for inclusion. The eligibility criteria include studies investigating infections caused by *E. histolytica*, *G. lamblia*, and *C. parvum* using validated diagnostic methods such as microscopy, molecular techniques, or immunoassays. Case reports, reviews, and studies without original data will be excluded. Comprehensive database searches will be conducted in PubMed/MEDLINE, Scopus, ProQuest, Web of Science, Google Scholar, and the Cochrane Library. The reference lists of selected papers are also checked. A standardized data extraction form will be used to record study characteristics, outcomes, and associated variables. Risk of bias will be assessed using the Joanna Briggs Institute tools and Newcastle-Ottawa Scale approach. Data synthesis will utilize a random effects model to estimate pooled prevalence and identify risk factors associated with these infections. Subgroup analyses will examine variations by geographic region and diagnostic method. Statistical heterogeneity will be assessed using I^2 statistic and meta-regression. Publication bias will be assessed using Egger and Begg funnel plot test. The results are reported in accordance with PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines.

Results: This systematic review was funded in June 2024. Database searches were started in July 2024, and we identified 1652 papers as of December 2024 for screening. Completion of study screening is anticipated by May 2025, with data extraction and analysis expected to conclude by December 2025.

Conclusions: Our study will address critical knowledge gaps in the epidemiology and risk factors of intestinal protozoal infections in Malaysia. Study limitations include potential bias in study selection, heterogeneity in diagnostic methods, and differences in the reporting quality of the included studies. Our findings will provide valuable insights into the prevalence of these infections,

the associated risk factors, and the diagnostic techniques employed, which should strengthen public health measures, improve diagnostic procedures, and guide future research to reduce the prevalence of intestinal protozoal infections in Malaysia.

Trial Registration: PROSPERO (International Prospective Registry of Systematic Reviews) registration CRD42023456199; https://www.crd.york.ac.uk/PROSPERO/view/CRD42023456199

International Registered Report Identifier (IRRID): DERR1-10.2196/66350

(JMIR Res Protoc 2025;14:e66350) doi:10.2196/66350

KEYWORDS

intestinal protozoa; infection; gastroenteritis; epidemiology; parasite; risk factor; Malaysia; contamination; diarrhea; outbreak; socioeconomic; sanitation; systematic review; meta-analysis; protocol; observational; PRISMA

Introduction

Intestinal protozoal infections are the most common parasitic infections and are a serious global health concern. An estimated 3.5 billion people are affected, with approximately 450 million individuals currently experiencing intestinal protozoal infections [1]. The typical intestinal protozoal infection cases are reported from *Entamoeba histolytica*, *Giardia lamblia*, and *Cryptosporidium parvum*. The transmission of these protozoa occurs via the oral-fecal route, which involves either indirect or direct contact with the infection. This includes various modes of transmission such as human-to-human, zoonotic, waterborne, and foodborne transmission [2,3]. The most common symptoms of an intestinal protozoal infection include nausea and watery diarrhea, which are caused by the release of enterotoxins, and are often accompanied by inflammation in the stomach, small intestine, and large intestine [3]. Individuals infected with *E. histolytica*, the causative agent of amoebiasis, show characteristic symptoms such as abdominal pain, bloody diarrhea, fever, and in severe cases, liver abscesses. *G. lamblia* causes giardiasis, which is characterized by watery diarrhea, abdominal pain, flatulence, and weight loss. Similarly, *C. parvum*, which is responsible for cryptosporidiosis, primarily manifests with watery diarrhea accompanied by stomach cramps, nausea, vomiting, and fever, with an increased risk in immunocompromised individuals. These different clinical signs emphasize the importance of targeted diagnostic approaches and tailored therapeutic interventions, with the severity of the disease depending on the immune status of the affected individuals [4,5]. The causes can be difficult to determine because the majority of enteric pathogens cause similar symptoms. There can be multiple infectious agents that can cause acute gastroenteritis, and contamination may come from food, water, the environment, or animals. Therefore, it is difficult to make accurate and fast reports via epidemiological analysis [6,7].

The primary method for detecting intestinal protozoa is the microscopic analysis of stool samples, which is laborious and requires specialized personnel. Molecular approaches such as real-time polymerase chain reaction offer increased sensitivity and efficiency and require only 1 sample for testing. Immunodiagnostic approaches targeting parasite antigens or host antibodies improve sensitivity and specificity. Despite advances, there is no one-size-fits-all strategy for diagnosis, which requires careful evaluation of aspects such as the suspected parasite, the nature of the sample, and the resources available [8]. A comprehensive approach may involve a combination of microscopic, molecular, and immunodiagnostic approaches to ensure accurate detection and treatment of intestinal protozoal infections.

Currently, intestinal protozoa, including *E. histolytica*, infect nearly 50 million individuals annually, leading to 100,000 deaths. Moreover, *Entamoeba* infection affects 50% of the global population, notably in Central and South America, Africa, and Asia, with rates up to 25% in certain limited-income and heavily indebted poor countries [9]. Giardiasis, caused by *G. lamblia*, is prevalent in the United States, the United Kingdom, Africa, Asia, and Latin America, and affects approximately 200 million people annually. In temperate countries such as Spain, the United Kingdom, and France, the prevalence in children is approximately 1.1%-2.1% [10,11]. *Cryptosporidium spp.* infection is widespread in the United States and tropical countries, with rates as high as 13% in India and 7.3% in Thailand [12,13]. These infections impose a significant burden, especially in heavily indebted poor tropical nations and parts of Central/South America, Africa, and Asia. Addressing sanitation and hygiene is crucial in prevention efforts.

In Malaysia, helminths and protozoa are the most common types of parasites causing diarrheal diseases. Diarrheal diseases are the leading cause of death in children younger than 5 years, with a mortality rate of 0.8% in 2019 [14]. The occurrence and wide distribution of intestinal protozoal infections in Malaysia represent significant events in the epidemiology of infectious diseases. Unfortunately, only limited data are currently available on the epidemiology and the risk factors associated with these diseases. Moreover, overall data on the diagnostic approach used to detect intestinal protozoal infections in Malaysia are lacking [15]. To address this knowledge gap, we will conduct a comprehensive systematic review with meta-analysis, aiming to synthesize the available data and overcome the limitations of individual studies. This study will be conducted to gain a better understanding of the prevalence and distribution of different intestinal protozoal infections, risk factors associated with intestinal protozoal infections among patients, and update on the diagnostic methods primarily used to detect intestinal protozoal infections, with a specific focus on the Malaysian population. Although this study focusses on Malaysia, the outcomes are also relevant for other tropical regions with similar socioeconomic, environmental, and health challenges. These findings can guide strategies to manage intestinal protozoal infections in regions such as Southeast Asia and beyond.

Methods

Patient and Public Involvement Statement

This protocol was not developed with the involvement of patients.

Study Design

The systematic review and meta-analysis will be reported in accordance with PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement, which was considered in the development of this protocol (Multimedia Appendix 1) [16]. This protocol is registered with PROSPERO (International Prospective Registry of Systematic Reviews; registration CRD42023456199). The methodology chosen for this study is designed to be replicable in different settings. Although the focus is on Malaysia, the search strategy and data extraction can also be applied to other regions to gain comparable insights.

Study Area

We will include studies published on intestinal protozoal infections among patients in Malaysia, except for case reports, reviews, and studies without original data, and the studies will be divided according to region. Malaysia is an ideal case study for the study of protozoal infections due to the unique intersection of tropical climate, diverse population, and varied socioeconomic conditions. These factors combined with the limited epidemiological data underscore the urgent need for comprehensive research in this context.

Types of Participants

We will include primary studies that investigate patients without age restrictions that provide estimates of any symptoms of intestinal protozoal infection (eg, amoebiasis, giardiasis, cryptosporidiosis). We will include studies that explicitly describe the detection methods and definitions of intestinal protozoal parasites. Studies on intestinal protozoal infections in which at least one of the 3 protozoa were detected will be included. We will exclude case reports, reviews, and studies without original data. If we find multiple studies with the same data, then we will use the study with the largest sample size. The results will be presented in tables and figures.

Types of Outcome Measures

This meta-analysis will have 2 main outcomes. The primary outcome will be the prevalence of intestinal protozoal parasites in Malaysia. The second aim is to investigate the risk factors associated with the diseases and the update on the primarily used detection methods for intestinal protozoa, that is, *C. parvum*, *E. histolytica*, and *G. lamblia*.

Information Sources

The following electronic databases of scientific literature that have been peer-reviewed, as recommended by Siddaway et al [17], will be carefully searched without language restrictions and limited to human research only: PubMed/MEDLINE, Scopus, ProQuest, Web of Science, Science Direct, Google Scholar, and Cochrane Library databases. A manual search of reference lists of identified papers will be added to the electronic searches. The authors of the research will be contacted for explanation or to provide any additional crucial missing metadata when necessary. Google Scholar will be used meticulously to search for relevant literature, including grey literature and unpublished data, to compile a thorough understanding of the prevalence rates, socioeconomic impact, and various diagnostic techniques employed for these infections within the Malaysian population. Studies completed after January 1, 2010, with no language constraints will be considered.

Search Strategy

The proposed search term for the first theme will be developed in MEDLINE by using medical subject headings (MeSH) combined with free-text terms around the 3 search components for intestinal protozoal infection, that is, giardiasis, cryptosporidiosis, and amoebiasis. The second theme will be prevalence, including epidemiology, incidence, epidemiological studies, and observational studies. The third theme will be risk factors and detection methods of intestinal protozoal infection and other similar names used (see detailed list in Multimedia Appendix 2) and then adapted for use in the other databases. The search, the evaluation of the titles and abstracts, and the review of the complete texts will be performed independently by an author. After removing duplicates and irrelevant entries, the reference lists of the studies received were checked for further studies that were not found in the database search.

Eligibility Criteria

The selection or exclusion of studies is based on the criteria proposed in Table 1. Studies published after January 2010 up to November 2024 will be eligible for inclusion. The literature search is limited to papers published after 2010, highlighting the significant change in the diagnostic process when molecular techniques began to replace traditional microscopic methods for detecting intestinal protozoal infections. This time frame allows for studies that include both the transition period and the continuous use of microscopy, including the more recent implementation of molecular techniques. This methodology allows for a full assessment of the evolution of diagnostic methods across time. We will not apply any language restrictions as part of the eligibility criteria. The PICO (Population, Intervention, Comparison, Outcome) classification technique is a popular method for creating search methods and describing meta-analyses.

The study population includes individuals with intestinal protozoal infections identified through positive laboratory test results, physician diagnoses, self-reported infection status, treatment registries, or other medical records. Both asymptomatic and symptomatic cases will be included, with no restrictions on age, gender, ethnicity, or geographical location within Malaysia. Eligible populations encompass mixed communities, outpatients, inpatients, and residential settings, spanning diverse socioeconomic backgrounds. This inclusion criterion ensures a representative sample of intestinal protozoal infections across Malaysia.

Table 1. Criteria for inclusion and exclusion.

Category	Included	Excluded
Population	Both asymptomatic and symptomatic cases from diverse socioeconomic backgrounds, including all ages, genders, ethnicities, and geographical locations in Malaysia (including non-Malaysians) will be considered, with identification based on laboratory tests, physician diagnoses, or medical records	Both asymptomatic and symptomatic cases conducted outside Malaysia or non-Malaysian settings will be excluded, including cases from mixed communities, outpatient, inpatient, and residential settings, regardless of age, gender, ethnicity, or non-Malaysians
Intervention/exposure	Studies conducted on the 3 common intestinal protozoal parasites (*Entamoeba histolytica*, *Giardia lamblia*, and *Cryptosporidium parvum*) and using any of these methods: microscopic examination, immunoassay technique, and molecular methods	Studies excluding these 3 intestinal protozoa (*E. histolytica*, *G. lamblia*, and *C. parvum*) and other intestinal protozoa parasites unrelated to this study or using other detection methods as mentioned
Study design	Quantitative studies, cross-sectional studies, cohort, and case controls will be included	Case reports, reviews, and studies without original data will be excluded
Outcome	Diarrhea and presence of intestinal protozoa	Nonenteric infection and studies without detection method mentioned

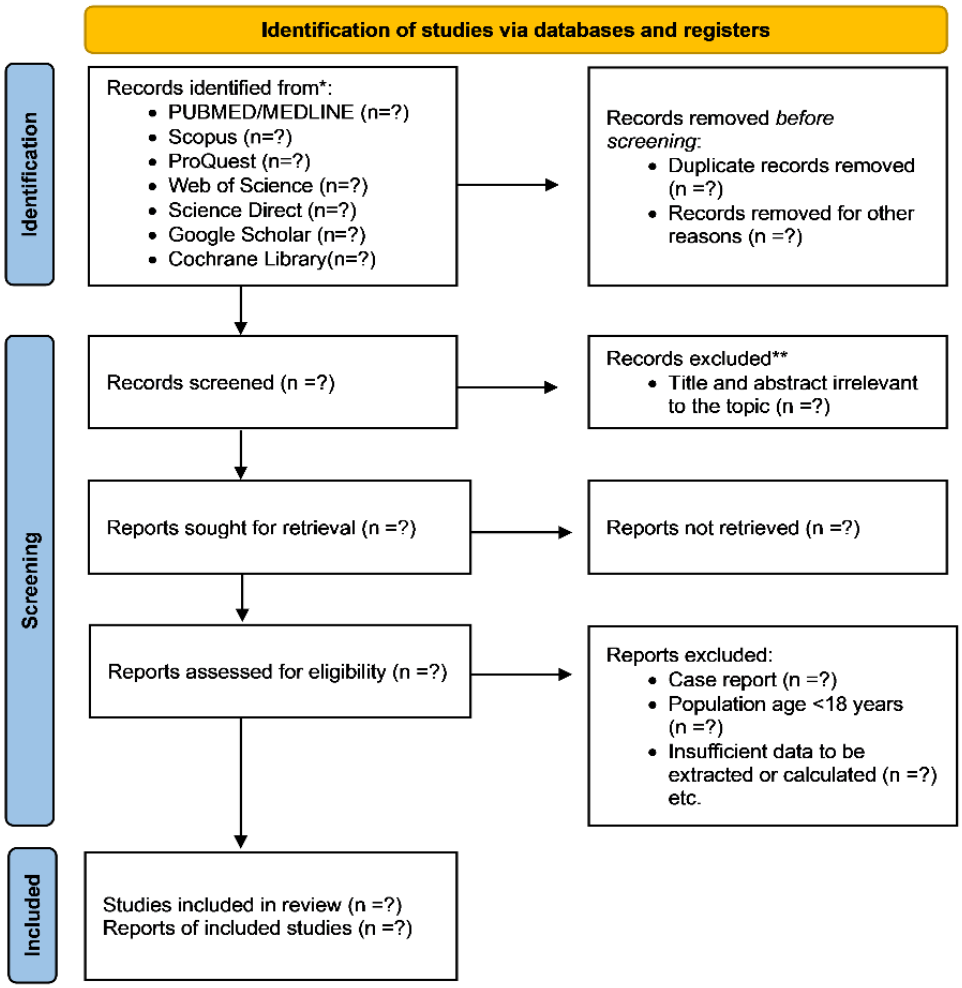
The primary outcome measure is self-reported diarrhea, which is commonly defined as the occurrence of 3 or more watery stools or bloody diarrhea within a 24-hour period. This information is reported by the patient's family or caretaker and covers a 2-week period preceding the assessment. Additionally, laboratory confirmation of diarrheal illness involves the identification of specific pathogens in the patient's stool. This confirmation can be achieved through microscopic examination or culture techniques. Furthermore, the presence of intestinal parasites is confirmed through laboratory procedures, including microscopy, serological tests, or molecular methods.

This study will focus on the prevalence of intestinal protozoal infections in Malaysia, exploring the epidemiology, diagnostic methods, and contributing factors to these infections. This research aims to investigate the extent to which individuals in Malaysia are affected by these parasitic infections and the various factors contributing to their occurrence, shedding light on their epidemiology and diagnostic methods. We will consider both randomized and nonrandomized controlled trials, along with observational studies that have examined the connection between the exposure and outcome of interest. We will collect data on the measures of association. However, we will put a lower priority on unadjusted measures (please refer to the "Risk of bias assessment for eligible studies" section for details).

Screening and Selection Procedure

In the research methodology, citations retrieved from diverse search engines will be imported into EndNote and subjected to a deduplication process to eliminate redundant entries. The exclusion criteria are usually unrelated, duplicate, unavailable full texts, or pure abstracts. These exclusions should be stated in advance to prevent any biases. The inclusion criteria would be studies with the target patients, interventions studied, or the comparison between the 2 interventions studied. These are publications that contain information relevant to our study subject. The most critical aspect is that the information provided is clear and adequate to answer the problem, whether positive or negative. Then, the required data will be meticulously extracted by the primary researcher (NSM). To ensure accuracy and reliability, the extracted information from all papers will undergo a thorough cross-checking process conducted independently by 2 other researchers (HA-T and SMW). The goal of this review is to confirm the consistency of the data, identify and mitigate potential biases, and correct minimal errors. The validated studies will be organized and stored in a structured spreadsheet program specifically designed for systematic data extraction. Following this, the collected data will undergo a series of rigorous assessments to evaluate the adequacy of the studies, ensuring a solid and reliable basis for subsequent analysis and interpretation. We will record the selection process in sufficient detail to complete a PRISMA flow diagram shown in Figure 1 [18,19].

Figure 1. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram for systematic review and meta-analysis. *Reporting the number of records identified from each database or register searched (rather than the total number across all databases/registers). **Indicate how many records were excluded by a human and how many were excluded by automation tools.



Data Extraction

We will use a standardized data extraction created in the online Microsoft Excel spreadsheet for study characteristics and outcome data. The data capture sheet will consist of a screening checklist consisting of study details (author, year of publication, period of study, place the study was performed), study characteristics (sample size, mean age, and age range of participants), risk factor analysis (socioeconomic status, population characteristics, geographical area), and outcome (presence of intestinal protozoa status; odds ratios, prevalence ratios, relative risks or hazard ratios [95% CI] with their related variability [SD or SE]). Please see "Eligibility criteria" section and Table 1 for the list and definitions of the aforementioned exposures and outcomes. Any significant limitations of the study will be identified, and any further relevant information will be requested from the corresponding author if necessary.

Data Synthesis

The data will be analyzed using STATA software (version 17.0; William Gould) and REVMAN software (The Cochrane Collaboration). To accurately report the content of each paper under consideration and to explore the relationships between outcomes and risk factors, the data will be summarized in a tabular form and the main findings of each paper will be presented, including descriptive analysis of gender, age, region, and others. We will also calculate the overall prevalence of intestinal protozoal infections among patients by using a random effects model to allow heterogeneity across the included studies and later divide the studies into regions. This study will include a qualitative or narrative analysis to summarize the key features and overall quality of the publications. In addition, a comprehensive assessment of potential bias will be performed for each paper (see the "Assessment of Risk of Bias for Eligible Studies" section). All meta-analyses will be conducted using the random effects model because of the expected epidemiologic and clinical heterogeneity. Because the underlying effects of the different studies are assumed to be normal, we will use random effects modelling to account for variation within and between studies.

Risk of Bias Assessment for Eligible Studies

Risk of bias (quality assessment) will be performed using the Joanna Briggs Institute critical appraisal tools [20]. The primary author and 2 independent reviewers will evaluate each study individually at both the outcome and study levels to provide an

overall assessment of the risk of bias. Each reviewer will examine each study as yes, no, unclear, or not applicable for bias (Multimedia Appendix 3). The quality of the included studies will be assessed using the Newcastle-Ottawa Scale, which is specifically designed to evaluate observational and cohort studies [21]. This tool will ensure a consistent and balanced evaluation of the methodological quality of all studies included in the review, accommodating the variability between experimental and observational study designs (Multimedia Appendix 4).

Assessment of Heterogeneity

We will visually inspect the forest plots for any evidence of heterogeneity. The pooled estimates will be visually assessed using forest plots to determine the degree of heterogeneity between studies. We will also measure statistical heterogeneity by using the I^2 statistic to estimate the difference between studies [22]. The I^2 statistic quantifies the proportion of variability observed in the prevalence estimates that can be explained as genuine variations in treatment effects rather than random sampling error. The I^2 statistic is bounded in the scientific literature by a range of 0% to 100%. Values between 0% and 25% indicate low heterogeneity, while values between 75% and 100% indicate substantial heterogeneity [23]. We will investigate potential sources of heterogeneity by using subgroup analyses and meta-regression. The possible causes will be explored and evaluated in terms of their methodological characteristics to determine whether the degree of heterogeneity can be explained by differences in these characteristics and whether meta-analysis is appropriate. The overall prevalence and 95% CIs estimate of the outcome (presence of intestinal protozoa status; odds ratios, prevalence ratios, relative risks or hazard ratios), with their related variability (SD or SE) will be presented in forest plots. If the selected studies are acceptable for quantitative synthesis, the data will be pooled in a meta-analysis to combine the primary exposures across studies and to provide a summary of effects according to study design/measurement of effects. Where possible, we will also conduct subgroup analyses by age group, detection methods (microscopy, immunoassays, and molecular techniques), study design (ie, cross-sectional or prevalence studies), and geographical region (Peninsular Malaysia and East Malaysia) to assess differences between the strength of association by geographical location and the potential impact of contextual confounders, which may vary by region.

Meta-Biases

To assess the possibility of publication bias, we plan to use funnel plots [24], a widely used graphical tool in meta-analyses, to visually check the symmetry of the data distribution. In addition, we will apply statistical tests such as Egger and Begg funnel plot test [25], which are specifically designed to detect asymmetries in funnel plots and provide quantitative measures of publication bias. In addition, we intend to perform a comparative analysis between the outcomes derived from the fixed effects model and the random effects model. This comparative evaluation will allow us to assess the possible presence of small sample bias in the published literature. Specifically, we aim to determine whether the effects of the studied exposure appear to be more pronounced in studies with smaller sample sizes, indicating a possible bias in favor of smaller studies in the existing literature. By applying these comprehensive analyses, we aim to ensure the robustness and reliability of our results and to rule out potential biases that could affect the interpretation of the results.

Ethical Considerations

No primary data will be collected; thus, no formal ethical approval is required. The results will be disseminated though a peer-reviewed publication and conference presentation.

Results

This systematic review was funded in June 2024. Database searches were started in July 2024 using specific databases such as PubMed, Scopus, ProQuest, Web of Science, Science Direct, Google Scholar, and Cochrane Library databases. As of December 2024, 1652 studies have been identified for title and abstract screening. The screening phase is expected to be completed by May 2025. Data extraction and synthesis will be performed. Data analysis is expected to be completed by December 2025. The results will be published in peer-reviewed journals and presented at conferences in early 2026.

Discussion

Currently, there are few epidemiological data on the prevalence of intestinal protozoal infections in the Malaysian population. A comprehensive study of the prevalence and distribution of intestinal protozoal infections is critical to understanding their public health impact and implementing effective control measures. Given the lack of available data, it is important that Malaysia conduct detailed epidemiological studies that will allow a more thorough assessment of the prevalence, risk factors, and distribution of these intestinal protozoa. Such studies would not only make an important contribution to the scientific knowledge base but also facilitate the development of targeted interventions and public health strategies to reduce the burden of these infections in the region. The results of this study will show that local data are consistent with global data, indicating that socioeconomic factors and diagnostic limitations are key barriers to the treatment of intestinal protozoal infections. For example, the diagnostic challenges in Malaysia mirror those observed in other tropical regions such as sub-Saharan Africa and South Asia. By addressing these gaps, this study provides a framework that can be transferred to other regions with similar public health problems.

The theory under study is that several factors, particularly in vulnerable populations such as low-income societies with poor sanitation and immunocompromised patients, may increase the risk of infection with intestinal protozoa and that differences in the validity of different diagnostic techniques may lead to different rates of detection of intestinal protozoa, that is, false positive or false negative results. The above hypothesis proposes that the combination of various contextual risk factors may jointly contribute to an increase in the overall prevalence of intestinal protozoal infections in the studied population.

In our study, we will conduct a thorough and systematic review, including a meta-analysis, to integrate the available data and address the limitations of individual studies. Our main objective is to better understand the prevalence and geographic distribution of intestinal protozoal disease. In addition, we will investigate the factor analysis that contributes to this infection and its relationship with its detection method. Our work, by synthesizing this extensive information, will provide a more nuanced and comprehensive view of intestinal protozoal infections and add significantly to the current body of knowledge in the field of infectious diseases and public health. No changes to the current protocol are envisioned. If critical changes prove necessary, they will be documented in the published review. Our findings will be published in a peer-reviewed scientific journal. In addition, they will be disseminated to relevant health care organizations.

A limitation of this study is that data on symptoms of intestinal protozoal infections are currently extracted from medical records, which may lead to underreporting due to gaps in documentation. Although documented medical records are often used as the main source of data, this approach has limitations. This method is consistent with real-life situations where diagnostic assessment often depends on accessible clinical data. Implementing a model that requires additional prospective assessments of patients beyond conventional clinical care procedures may be impractical, particularly in a health care setting where such assessments are often not mandatory. It is crucial to understand that the proposed model is preliminary and should not be used in clinical practice without additional validation. Another striking feature of our research design is the possibility of selection bias due to differences in duration of symptoms or time since exposure to protozoal infections at the time of study entry. By excluding individuals with recent protozoal infections who may have different clinical characteristics or outcomes, we aim to create a model that applies only to those who may have overcome the acute phase of infection.

In addition, future research should investigate the serial examination of clinical symptoms and use dynamic modelling techniques to enable the application of the model across different stages of infection. A comparison of the performance of the model we developed with established diagnostic algorithms or clinical guidelines in similar patient populations would also be crucial for validation. However, it should be noted that certain diagnostic indicators required for established algorithms may not be routinely assessed during standard clinical care, necessitating additional assessments beyond the scope of our study.

Even after further validation, predictive models for intestinal protozoal infections are primarily ambiguous, and the goal is to provide guidance to health care providers regarding potential infection outcomes and not to replace clinical assessment. Once the models are externally validated, a clinical decision aid should be available to better identify individuals at high risk for protozoal infections, thereby improving patient care and regulating appropriate diagnostic techniques. The future development of such a decision aid would require collaboration with health care professionals and researchers to ensure its effectiveness and appropriateness in clinical practice.

Acknowledgments

We thank the Institute of Medical Molecular Biotechnology, Faculty of Medicine and Universiti Teknologi MARA, for their tremendous assistance. This research received funds from Ministry of Higher Education (600-RMC/PRGS 5/3 (004/2024).

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Authors' Contributions

Conceptualization: HA-T (lead), NSM (equal)
Data curation: NSM
Formal analysis: HA-T (lead), SMW (supporting)
Funding acquisition: HA-T
Investigation: NSM
Methodology: NSM and HA-T
Project administration: HA-T (lead), NSM (equal), SMW (supporting)
Resources: NSM
Supervision: HA-T, SMW
Validation: NSM, HA-T, SMW
Visualization: HA-T (lead), NSM (supporting)
Writing the original draft: HA-T (lead), NSM (supporting)
Writing – review and editing: HA-T (lead), NSM (supporting), SMW (supporting)

Conflicts of Interest

None declared.

Multimedia Appendix 1
PRISMA-P (Preferred Reporting Items for Systematic Review Protocols) 2015 checklist.
[DOCX File , 37 KB - resprot_v14i1e66350_app1.docx]

Multimedia Appendix 2
MEDLINE search strategy.
[DOCX File , 17 KB - resprot_v14i1e66350_app2.docx]

Multimedia Appendix 3
Joanna Briggs Institute's critical appraisal checklist.
[DOCX File , 17 KB - resprot_v14i1e66350_app3.docx]

Multimedia Appendix 4
Newcastle-Ottawa quality assessment scale.
[DOCX File , 18 KB - resprot_v14i1e66350_app4.docx]

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Abbreviations

MeSH: medical subject headings
PICO: Population, Intervention, Comparison, Outcome
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PROSPERO: International Prospective Registry of Systematic Reviews

Edited by A Schwartz; submitted 12.09.24; peer-reviewed by T Gan; comments to author 12.12.24; revised version received 13.12.24; accepted 18.02.25; published 04.04.25.

Please cite as:
Mizan NS, Al-Talib H, Wang SM
Epidemiological Characteristics of Intestinal Protozoal Infections and Their Risk Factors in Malaysia: Systematic Review and Meta-Analysis Protocol
JMIR Res Protoc 2025;14:e66350
URL: https://www.researchprotocols.org/2025/1/e66350
doi:10.2196/66350
PMID:40184188

Protocol

Mental Health Apps Available in App Stores for Indian Users: Protocol for a Systematic Review

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Abstract

Background: There has been a surge in mental health apps over the past few years. While these have great potential to address the unmet mental health needs of the population, the recent proliferation of mental health apps in the commercial marketplace has raised several concerns, such as privacy, evidence-based, and quality. Although there is mounting research on the effectiveness of mental health apps, the majority of these are not accessible to the public and most of those available have not been researched. Despite the rapid growth of the digital health market in India, there are no comprehensive reviews of publicly available mental health apps for Indian users. Hence it becomes important to review mental health apps freely available to potential end users in terms of their scope, functions, and quality.

Objective: This study aims to systematically evaluate mental health apps available to Indian users in app stores.

Methods: This systematic review of mental health apps will be performed following the Target user, Evaluation focus, Connectedness and Health domain approach and the PASSR (Protocol for App Store Systematic Reviews) checklist. Fifteen key search terms covering various mental health conditions and therapies will be used on the Android and iOS stores. The identified apps will be further screened and reviewed based on the inclusion and exclusion criteria. The pool of eligible apps will be downloaded for detailed review. The following steps will be adopted to streamline the review process and interrater consistency. Six apps will be randomly selected from the downloaded apps, for joint discussion and review by a team of 4 primary reviewers and 2 mentors. Following this, a new set of 6 randomly selected apps will be rated independently by the primary reviewers and the differences in ratings will be jointly discussed for generating consensus. Subsequently, the primary reviewers will individually review the remaining apps in the list. Data will be extracted based on predecided parameters such as privacy policy, basic purpose, type of developer, nature of intervention strategies, and guided versus unguided nature. Additionally, the apps will be reviewed for quality using the Mobile Application Rating Scale. The data analysis and synthesis strategy will incorporate descriptive statistics based on quality evaluation using the Mobile Application Rating Scale and examining the content of the apps for generating descriptive information.

Results: The initial screening of mental health apps available for Indian users on the Google Play Store and Apple App Store was initiated in October 2024. We expect to complete the detailed systematic review by April 2025.

Conclusions: This study will offer a comprehensive review of mental health apps available in digital marketplaces for Indian users and has implications for end users, policy makers, developers, and mental health professionals.

Trial Registration: International Platform of Registered Systematic Review and Meta-analysis Protocols INPLASY2024100035; https://inplasy.com/inplasy-2024-10-0035/

International Registered Report Identifier (IRRID): DERR1-10.2196/71071

(JMIR Res Protoc 2025;14:e71071) doi:10.2196/71071

KEYWORDS

mental health apps; mHealth; review of apps; smartphone apps; MHApps for Indian users; India; mobile phones

Introduction

Background

According to the National Mental Health Survey (2017-2018), approximately 10% of Indian adults experience a diagnosable mental health condition, and the treatment gap for most such conditions exceeds 60% [1]. For example, the treatment gap for depression in India is 85.2%. Factors contributing to this gap include the stigma surrounding mental health issues and their treatment, the uneven distribution of mental health services, affordability challenges, and the scarcity of trained mental health professionals [2]. Some of these same factors have also become the drivers of the growth of digital mental health solutions in India.

There has been an increasing popularization of telehealth and digital mental health services in India [3,4]. This has been fueled by several factors such as the rapid proliferation of smartphone users, increasing internet penetration, the emergent needs and familiarity with digital services during the COVID pandemic, government initiatives promoting digital literacy, digital health, and specifically telemental health, rising number of startups in the mental health space apart from improved awareness about mental health and felt needs for convenient and accessible solutions [4-8].

India's smartphone penetration rate was 71% in 2023 [9]. Mental health apps have seen a 30% increase in downloads, with over 200,000 new users in the year 2023 alone. India's digital mental health market is projected to grow at a compound annual growth rate of 28.16% and is expected to reach a projected revenue of US $62.86 million by 2032 [10].

The last few years have seen a mushrooming of mental health apps, several of which have been developed with peripheral involvement or lack of involvement of mental health professionals, and this can raise significant concerns about the validity and appropriateness of suggestions, messages, and recommendations contained in the apps [11]. Inadequately customized recommendations can delay seeking professional help and extend the period of reliance on self-help alone even when the nature and severity of the problem warrants professional help.

Globally, the last decade has also seen a plethora of scoping reviews, systematic reviews, and meta-analyses of effectiveness and efficacy studies, including a few from India on mental health apps. 1009 psychosocial wellness and stress management apps with varied content were reviewed by Lau et al [12]. Almost all were designed as purely self-help apps, with less than 2% meant to serve as a supplement to in-person therapy or involving therapy via a web-based platform. It was noted that only 4.66% of apps targeted individuals with psychiatric disorders. This review also highlighted that only 2% of the apps in app stores were supported by original research publications. Another review aimed to document the proportion of mental health apps offering comprehensive therapeutic treatments for anxiety and depression available in the app stores and developed using evidence-based frameworks. The authors found that out of the 293 apps shortlisted as offering a therapeutic treatment for anxiety and/or depression, 55.3% mentioned an evidence-based framework in their app store descriptions. However, only 6.2% had published evidence of their efficacy [13].

Alqahtani and Orji [14] examined more than 13,000 user reviews of 106 publicly available mental health apps in app stores. Their review highlighted the value placed by end users on the user interface, user-friendliness, and adaptive functionalities. Lack of variety of content, low scope for personalization, lack of customer service, trust, and privacy issues were cited as some of the pitfalls [14]. In another review, 104 mental health apps on Google Play and App Store were examined through sentiment analysis of 88,125 user reviews, using machine learning and thematic analysis. The emergent negative themes spanned usability, content, ethics, customer support, and billing issues. The positive themes included appealing interface, app stability, customizability, high-quality and diversity of content, personalization, privacy and security, and low subscription cost [15].

Some of the recent research papers on mental health apps continue to use App Store star ratings as a proxy for quality and satisfaction, although there are growing concerns with this metric. Despite the potential clinical applications and benefits, the app marketplace, with an estimated 3,00,000 health apps and 10,000 focused on mental health, poses enormous challenges to users who wish to explore and find apps that may suit their needs [16]. Insufficient regulation of health apps in the commercial marketplace can result in several apps making unsubstantiated claims, offering inaccurate and potentially dangerous information, or posing threats to user privacy. Recent research has shown that the measures that are currently used in the app marketplace for the purpose of evaluating apps (eg, app downloads or star ratings) do not provide adequate representation of apps in terms of important metrics such as security, engagement, or effectiveness [17,18].

Studies on mental health apps and reviews from India have been scarce. An overview of smartphone apps aimed at suicide prevention available for Indian users on Google Play Store found that only 11.62% of 43 apps reviewed provided information about a formal evaluation process or study [19]. It was also noted that only about 16% of the apps intended for direct use by people at suicidal risk had an initial screening aspect. Only 4 of these 43 apps were developed in India. In a review of free apps for depression available for Android phone users in India, 278 apps were identified in the first step and information on coping with depression and stand-alone screening

tools formed the 2 largest types of free apps. Features of interactive self-care apps (N=33) were reviewed further, and this exercise showed that less than 10% of the apps incorporated explicit delineation of their scope or initial screening for suitability. Slightly more than one-third of these apps included content aimed at encouraging professional help-seeking when needed or an explicit mention of their theoretical or empirical basis. Challenges for potential users were highlighted [20].

A recent survey of smartphone users in India highlighted that most of them (69%) were not aware of any mental health apps [21]. In another study involving persons with severe mental illness seeking treatment in a tertiary care setting in India and their caregivers, it was noted that health app use was low, with costs, lack of familiarity, and language being significant barriers to use [22]. An Indian study examined mental health apps in the Google Play Store between 2016 and 2020 by extracting data using various software programs. The keywords used for the search included: “mental health,” “mental illness,” “mental disorders,” “cure of mental disorder,” and “healing of mental illnesses.” As per the content analysis of the apps, the apps targeted various mental health concerns ranging from depression, anxiety, stress, posttraumatic stress, sleep, obsessive compulsive disorder, substance use, and panic symptoms to schizophrenia. This review examined basic content, number of downloads, mention of interactivity, and pricing and ratings of apps. It was observed that most app users did not leave their opinions or share their experiences, and thus, 70% of app ratings were based on a small number of users (100 or fewer users). The intervention approaches mentioned in this review ranged from relaxation, stress management, symptom tracking, calming audio, keeping a diary, interpersonal support meditation, and mood tracking. Connecting to mental health professionals as a strategy was mentioned in less than 2% of the instances. This study did not focus on examining the quality and appropriateness of content, usability, or empirical evidence-based [23].

The need for mental health app libraries independent of commercial biases has been advocated [24-26]. Lagan et al [17] systematically evaluated 278 mental health apps using the Mhealth Index and Navigation Database framework, which comprises 105 questions across 6 categories, namely, app origin or accessibility, privacy or security, inputs or outputs, clinical foundation or evidence base, features or engagements, and interoperability. The most common features offered by the 278 apps were mood tracking and journaling, with much fewer ones offering comprehensive therapeutic interventions that may be useful for addressing the diversity of user needs. Less than 25% of apps were supported by a feasibility or efficacy study [17].

From end users’ perspectives, when selecting apps, they rely mainly on ratings and reviews in app stores or on advice given through social media or word of mouth [27]. However, the lack of involvement of mental health experts in app development and insufficient attention to evidence-based development are factors that can limit the effectiveness of the apps or even pose a risk for harm due to unscientific suggestions or lack of information on limitations of app-based interventions and need for direct professional consultations.

It has been observed that many apps in commercial app stores, including low-quality ones, make it difficult for users to identify a suitable app for various mental health conditions, and evidence-based is often lacking, even for top-rated apps in app stores [28,29].

Rationale for the Review

Studies have highlighted that most well-researched apps are not easily accessible to the public, while a bulk of apps available in app stores are not backed by research evidence or do not involve qualified mental health professionals in their conceptualization, development, or validation [30]. In contrast to the reviews on research studies on the efficacy or effectiveness of mental health apps, there have been fewer studies that have directly reviewed mental health apps themselves, which are available for end users in app stores.

Apart from the lacuna mentioned earlier, data security and privacy concerns are some of the factors that restrict the potential of this field, as mental health apps use sensitive information pertaining to personal concerns, thoughts and moods, and sleep patterns. High attrition rates and inconsistent or infrequent usage of apps are challenges noted across the globe that reduce the potential effectiveness of the apps for users, and this is particularly true of mental health apps that are completely unguided as these do not involve any human interface or assistance for use. The other challenges surrounding mental health apps in India include the diversity of languages spoken across the country and the sociocultural factors that can make it difficult to develop apps that cater to the population's diverse needs.

There is a dearth of systematic reviews of mental health apps available in app stores for Indian users. Reviews that rely on the number of downloads, user ratings, or merely app store descriptions are unlikely to be helpful in guiding the consumers of mental health apps in making informed decisions. This study is designed to address these gaps by conducting a systematic review of mental health apps accessible to Indian users, using a standardized framework for assessment. This systematic review is expected to help in the creation of a user-friendly platform to guide consumers of mental health apps in India. This is especially important as the commercial marketplace offers a confusing array of options with a plethora of apps, a diverse range of content, a lack of clarity on scope or indications for the use of specific apps, and a lack of noncommercial platforms providing detailed information that can assist users in choosing apps that serve their needs.

Hence, we aim to conduct a comprehensive and systematic review of smartphone-based mental health apps available in app stores that are accessible to Indian end users in order to (1) describe these apps in terms of characteristics such as purpose, nature of the intervention, mental health conditions focused upon, involvement of mental health professionals in development, mention of empirical basis, nudges to seek professional help as well as (2) evaluate and document the quality of these apps.

Methods

Ethical Considerations

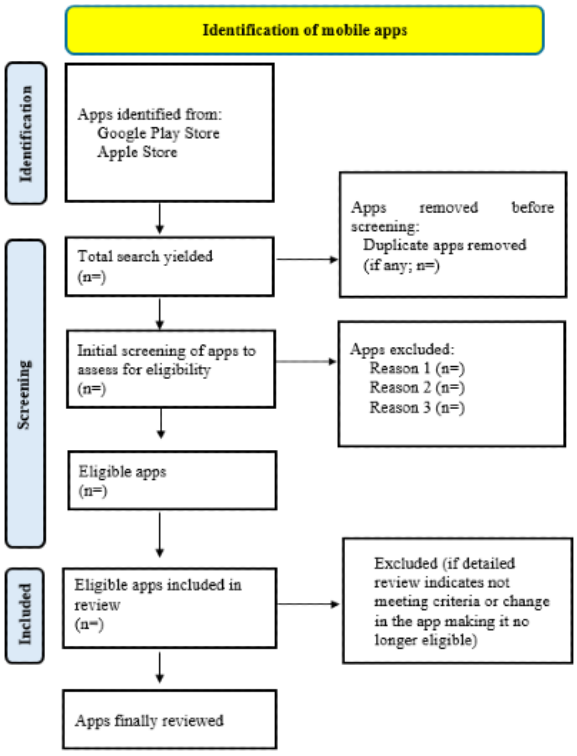
The systematic review has been registered on the International Platform of Registered Systematic Review and Meta-analysis Protocols (INPLASY2024100035). An exemption from the Institute Ethics Committee (Behavioural Science Division), NIMHANS (No. NIMHANS/EC/[BEH.SC.DIV.] MEETING/2024) was sought and obtained for this review.

App Review Approach

An approach called Target user, Evaluation focus, Connectedness and Health domain (TECH) has been developed to formulate research questions and determine eligibility criteria for systematic reviews of commercially available health apps. This is because formats such as Population, Intervention, Comparison, and Outcome (PICO) and Sample, Phenomenon of Interest, Design, Evaluation, Research (SPIDER) are appropriate primarily for a systematic review of studies examining the effectiveness of interventions and for systematic qualitative review, respectively [31]. Here TECH refers to (1) target user (the specific population in question); (2) evaluation focus (eg, app characteristics, quality, usability, techniques, or components); (3) connectedness (whether the app connects with other apps or services); and (4) health domain (eg, specific health condition or concern being focused). This approach is aimed at helping in the development of the research question and for guiding eligibility criteria for the review of apps. Applying the TECH approach in this study context, the target population broadly consists of Indian adults interested in exploring or using apps to understand or manage mental health concerns. The evaluation focus is kept intentionally broad to include descriptive information on app characteristics, content, and quality. The review intends to include stand-alone apps as well as those that may connect to services but apps that connect to wearables or other apps would fall beyond the purview of this review. The health domain focused upon in the review is broad and includes various mental health concerns and conditions, The eligibility criteria mentioned subsequently drew upon these elements of the TECH approach.

Since this is proposed to be a review of mental health apps and not a systematic review of research studies on mental health apps, the Protocol for App Store Systematic Reviews (PASSR) checklist will be used (see flow diagram in Figure 1) [13]. It is a combination and adaptation of the items from A Measurement Tool to Assess systematic Reviews (AMSTAR) and Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklists that can be applied to the systematic search of app stores for any category of apps [32,33].

Figure 1. Flow diagram depicting the exclusion of apps at different stages of the review.



Inclusion and Exclusion Criteria

The inclusion criteria for the review of apps are as follows:

- Apps available in Google Play Store or Apple App Store for Indian adults.
- The store description of the app indicates they are offering guidance on mental health problems or therapy, information, self-help, or support and are thus relevant for the review.
- Apps available in English.
- Free apps and partially free apps (for those involving in-app purchases, what is freely available will be reviewed).

It should be noted that the number of apps that are available in any Indian language that do not have an English version will also be documented but not included in the detailed review.

The exclusion criteria for the review of apps are as follows:

- Mental health apps that are fully paid and do not have a free trial period.
- Apps available solely in a non-English language.
- Apps meant for exclusive use by health professionals (eg, for training or education).
- Apps that require any additional wearable devices or sensors.
- Apps that are solely focused on enhancing wellness without the context of mental health concerns (eg, improving time management, improving productivity, managing relationships).
- Apps available only for research participants of a given study.

The keyword-driven search was carried out during October 2024 and November 2024. Apps that are no longer available to download in January 2025 for a detailed review will be excluded.

The aforementioned search criteria have been set in order to ensure that the research objectives can be adequately addressed while also taking into account feasibility considerations for this comprehensive review. The search will be carried out on Google Play stores and Apple iOS stores as these together comprise about 99% of the Indian market share [34]. Most of the mental health apps for Indian users are in English language. Any app in an Indian language that has an English version will be included for review. India is a multilingual country with 121 languages [35]. Apps available only in a non-English language will be documented but excluded from detailed review as that would require expertise in the given language. There is a very huge and broad range of apps that are on themes related to well-being and these deserve a separate review exercise. The review is restricted to apps that focus on one or more mental health conditions to ensure a focus and enhance the feasibility of the study. Apps that require additional wearable devices are not included in this review as they can have accessibility or affordability issues. These are also likely to be vulnerable to cyberattacks and may require smart intrusion detection systems [36]. Also, apps directed at health professionals would be excluded as the purpose of the review is to evaluate apps for the public.

App Search Strategy

The keywords used in this study are “Mental health,” “Depression,” “OCD,” “Addiction,” “Schizophrenia,” “Anxiety,” “PTSD,” “Bipolar,” “BPAD,” “CBT,” “ACT,” “DBT,” “Cognitive Behaviour Therapy,” “Acceptance and Commitment Therapy, and “Dialectical Behaviour Therapy.”

The selection of these 15 keywords was guided by the purpose of this study which was to cover a broad range of common and prevalent mental health concerns, common psychotherapy interventions as well and their commonly used acronyms. Further, a broad scan of review studies in the last 5 years on mental health apps, as well as an initial scanning of the apps in the app stores helped in finalizing the keywords.

The following search strategy will be adopted:

- Searches will be conducted in each store (marketplace) with each of the aforementioned keywords.
- Will use a clean or reset device to search the data store with a new Gmail or iOS ID.
- Details of the search dates will be recorded.
- The entire search process will be screen-recorded for reference while ensuring slow scrolling from the top to the end of the screen. To avoid missing any apps, scrolling will continue past any advertisements until all content is thoroughly recorded.
- Before the second key term search, the Play Store or Apple App Store history from settings will be cleared and reset.
- All the listed apps in the screen recordings will be carefully entered on a Microsoft Excel sheet.
- If an app is available both on the Google Play Store and Apple Stores Android and iOS phones, the version on the Google Play Store will be reviewed, and the app will be counted only once.
- Four mobile devices (2 Apple and 2 Android devices) will be used for the search.

Initial Screening

After lists of apps on the 2 stores are generated, duplicates will be removed, and the remaining apps will be screened for eligibility using the selection criteria. This screening task will be divided among 4 members of the review team. Any doubts regarding inclusion will be resolved through joint discussions.

The apps meeting the inclusion criteria will be downloaded for detailed review. At this stage too, if any apps are found to be nonrelevant or not meeting any of the inclusion criteria will be excluded from further review.

From the final pool of apps, 6 apps will be randomly selected for joint discussion and review by a team consisting of 4 primary reviewers along with 2 clinical psychology faculty serving as mentors (with more than 10 years of overall experience and familiarity with app review processes). Following this, a new set of 6 randomly selected apps from the remaining ones will be rated independently by the primary review team and the differences in review ratings, if any, will be discussed with all the team members, including the mentors, to arrive at a consensus. This process is adopted to streamline the review process and increase interrater consistency in review and ratings through training and the use of a panel of primary reviewers and mentors. In the last step, the primary reviewers will individually review the remaining apps in the list. In addition, 2% of all the apps, (depending on the number of finally selected eligible apps) will be randomly selected and reviewed collectively by the mentor team in order to note the concordance with the ratings by the primary reviewers.

Data Extraction

The detailed review of downloaded apps will involve documenting the following aspects in Table 1.

Table 1. Information of apps planned to be extracted.

Serial number	Information parameter	Coding format
1	• Privacy-related: • Privacy policy accessible to users • Privacy terms clearly explained • Mention of data-sharing policy with third parties • Mention of data retention duration • Mention of provision for deletion of user account	• Yes or no
2	• Payment requirements	• Completely free to use • Fully paid • Involves in-app purchases
3	• Nature of developer	• Company • Not-for-profit organizations • Academic bodies • Government agency • Insufficient information available
4	• Country of origin	• Mentioned name of the country • Insufficient information available
5	• Release	• Date of first release • Insufficient information available
6	• Update	• Date of last update • Insufficient information available
7	• Downloads	• Number of downloads
8	• Rating	• Number of reviews • Average review rating
9	• Log-in requirements	• Yes or no
10	• Language	• English • Non-English • If in any Indian language
11	• Mental health professionals' involvement in development of the app	• Clearly specified • Generally mentioned • Not mentioned
12	• Empirical research on the app mentioned	• Yes or no
13	• Target users: • Specified minimum age (if any) • Any special group (eg, veterans)	• Yes or no
14	• Basic purpose of the app (as ascertained from the content and features)	• Free text (eg, providing information, psychoeducation, screening, self-help, synchronous or asynchronous chat-based support, therapy or counseling support, artificial intelligence–based counseling, peer-support, symptom monitoring, tracking)
15	• Mental health condition	• Single mental health condition focused • Multiple mental health conditions focused • Not mentioned
16	• Type of intervention: • Type of therapy mentioned • Guided or unguided	• Free text (like CBT[a], DBT[b], and mindfulness) • Yes or no

Serial number	Information parameter	Coding format
17	• Components of the intervention	• Single component or multiple components
18	• Empirical basis of the intervention	• Mentioned or not mentioned
19	• Nature of the intervention • Attempts to dispel common myths related to mental health and illness	• Yes or no
20	• Crisis management • Mentioned helpline, emergency service details, or directories • Basic crisis support strategies	• Yes or no
21	• Sociocultural appropriateness of examples used (case study)	• Yes, no, or could not be ascertained
22	• Inclusion of pointers on when to seek professional help	• Yes or no
23	• Inclusion of nudges to seek professional help when needed	• Yes or no
24	• Any special feature	• Yes (a brief description of the feature) or no

[a]CBT: cognitive behavior therapy.

[b]DBT: dialectical behavior therapy.

Some modifications and refinements in the data extraction parameters and process may be considered if required depending on the review of the initial 15 apps by the primary reviewers.

Evaluation of Quality of Apps Using Ratings From the Mobile Application Rating Scale

In addition to documentation on the earlier aspects, primarily related to the content, the apps will also be evaluated using the Mobile Application Rating Scale (MARS). This scale consists of 19 items across 4 domains, that is, engagement, functionality, aesthetics, and information quality [37]. Each item is rated on a 5-point Likert scale: (1) inadequate, (2) poor, (3) acceptable, (4) good, and (5) excellent. The total score and the 4 objective domains have high internal consistency. An additional 4-item subjective quality scale is also available, though it is not counted toward the total. MARS has been one of the most widely used tools across nations for the evaluation of the quality of mobile health (mHealth) apps, including mental health apps [38-40]. A recent study documented the validity of MARS by using pooled MARS data from 15 international reviews assessing the quality and content of mHealth apps in various health conditions [41].

Strategy for Data Analysis and Synthesis

The analysis will involve the use of descriptive statistics such as frequencies, percentages, mean, and SDs. This would be in addition to the qualitative analysis of the apps as mentioned earlier through the use of MARS ratings. In addition to the overall findings, an attempt will be made to synthesize and present subgroup-wise findings based on apps with a different focus in terms of the nature of mental health conditions (eg, severe vs common mental health conditions) and those with single versus multicomponent interventions, provided there is a sufficient number of apps to form such subgroups. This study is focused on reviewing apps themselves rather than reviewing studies about apps and hence the traditional methods for assessing the risk of bias are not applicable. There is a scarcity of guidelines to assess the risk of bias in studies evaluating apps on app stores. An attempt will be made to describe the potential risk of bias at the stage of inclusion of apps for review, their detailed review by independent reviewers, and the handling of missing data while reporting findings. The risk of bias will also be documented by mentioning whether any apps being reviewed have been examined by any member of the research team for effectiveness or efficacy [13].

Results

The search for mental health apps in virtual stores has been completed. The initial screening has been completed. The initial search yielded 5827 apps, comprising 3708 apps on the Android Play Store and 2119 apps on the Apple App Store. We expect to complete the detailed systematic review by April 2025.

Discussion

Significance of the Systematic Review of Mental Health Apps

In the background of a huge treatment gap, mental health apps can contribute in numerous ways to strengthen mental health care systems, empower communities with low-intensity, affordable, and accessible options for self-care for milder problems as well as enhance mental health literacy and reduce barriers to seeking mainstream mental health services; provided that the challenges related to quality, security, congruency to user needs, and user engagement are appropriately addressed [42-44]. As pointed out earlier, the current regulatory frameworks for mental health apps are still evolving and there is a plethora of apps in the commercial marketplace with little information available on their evidence or use of evidence-based content [18,20]. Hence, a review like the present one can be a stepping stone to exploring the nature of apps and subsequently

coming up with suggestions and recommendations to improve the safety and quality of apps [45]. The review is not focused on outcome research on apps; instead, it delves into examining apps in terms of the nature of content, their scope, and quality. As previous research indicates, the popularity of apps and user experience do not necessarily predict sustained engagement and hence the need for systematic evaluation of apps on a comprehensive set of parameters including sociocultural appropriateness, as planned in this review [29,46,47]. It is important to highlight that the potential impact of the review is not to come up with a list of apps that are "flagged as not useful," instead it attempts to draw the attention of the public, developers, and mental health professionals to make informed decisions for choosing, using, designing, and studying mental health apps judiciously to maximize their potential for serving the mental health needs of the population.

Future Plans

Following the systematic review of the mental health apps in app stores, an attempt will be made to categorize them based on various parameters that may be relevant for potential end users as well as professionals who search for relevant apps on stores for specific purposes (eg, target group, main purposes, level of interactivity, functions, and scope and limits of the app). The outcome of this process will be made available to the public and professionals in a web-based portal in an easy-to-use search or filter format.

Strengths and Limitations

This would be one of the first systematic reviews of mental health apps available in app stores for Indian users, using a comprehensive set of keywords related to mental health conditions and therapies. Also, this review would go beyond app store descriptions and indices such as user reviews and number of downloads and would entail examining the actual content, functionalities, and features of the apps through engaging a panel of raters, including mental health professionals. Unlike literature searches, searching apps in app stores have some limitations. The search can be challenging as the order in which the search results are displayed can be variable and the usual filter functions like those when reviewing research are not available. Moreover, the initial screening would be guided by the app store descriptions that may not always provide clear information being sought by the reviewers and hence may result in the exclusion of some relevant apps, although an attempt will be made to err on the side of overinclusiveness, during the initial round of screening.

Conclusions

The review will provide a comprehensive and critical review of the smartphone apps on mental health that are available for Indian end users. The review findings are likely to have implications for end users, policy makers, developers, and researchers in the field of mental health apps.

Acknowledgments

This study was funded by the Indian Council of Medical Research as part of funding support for the Centre for Advanced Research in Digital Interventions for Mental Healthcare, National Institute of Mental Health and Neuro Sciences.

Authors' Contributions

SM conceptualized and designed the protocol, contributed to the development of selection criteria, supervised the drafting, revising of the manuscript, and finalized the same; RT conceptualized and designed the protocol, contributed to the development of selection criteria, supervised the drafting and helped in the editing of the same; P Sengupta and AK contributed to the drafting of the manuscript and also revised the same along with planning for data analysis. AF and P Sharma reviewed the literature and were also involved in the process of data collection and analysis and contributed to writing up portions of the manuscript; P Sudhir and GNR supervised the analysis plan, writing of the manuscript, and its revision; TKS was involved in the review and write up of technological aspects, contributed to revisions of the manuscript while RS provided supervisory support and helped in finalization of the manuscript. All authors reviewed the final manuscript.

Conflicts of Interest

None declared.

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Abbreviations

AMSTAR: A Measurement Tool to Assess systematic Reviews
MARS: Mobile Application Rating Scale
mHealth: mobile health
PASSR: Protocol for App Store Systematic Reviews
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses

TECH: Target user, Evaluation focus, Connectedness and Health domain

Edited by A Schwartz; submitted 09.01.25; peer-reviewed by S Ashraf; comments to author 10.02.25; revised version received 20.02.25; accepted 17.03.25; published 16.04.25.

Please cite as:
Mehrotra S, Tripathi R, Sengupta P, Karishiddimath A, Francis A, Sharma P, Sudhir P, TK S, Rao GN, Sagar R
Mental Health Apps Available in App Stores for Indian Users: Protocol for a Systematic Review
JMIR Res Protoc 2025;14:e71071
URL: https://www.researchprotocols.org/2025/1/e71071
doi:10.2196/71071
PMID:

Protocol

The Impact of Long-Chain Omega-3 Polyunsaturated Fatty Acid Supplementation in Pregnant Women Toward the Intelligence Status of Early Childhood: Protocol for a Systematic Review and Meta-Analysis

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Abstract

Background: Long-chain omega-3 polyunsaturated fatty acids (LCPUFAs) are essential fatty acids that protect cellular structures and provide energy, particularly for fetal growth and development. The maternal supplementations of omega-3 LCPUFA may affect the rate of intelligence in early childhood development.

Objective: This systematic review aims to synthesize available evidence on the impact of omega-3 LCPUFA supplementation during pregnancy toward intelligence in early childhood development by analyzing the outcomes specifying the aspects of intelligence such as neurodevelopment, social-emotional, language, attention, behavior, cognition, vision, hearing, and motor skills.

Methods: We will only include randomized controlled trials on pregnant women supplemented with omega-3 LCPUFA interventions and the outcome measured is the children's intelligence. Based on the World Health Organization's definition of early childhood, we will include children aged 8 years or younger. Children's intelligence can be indicated using several tools measuring their intelligence index, such as neurodevelopment, social-emotional, language, attention, behavior, cognition, vision, hearing, and motor skills. Irrelevant and unavailable studies will be excluded. A systematic search will be conducted in 3 electronic databases, namely PubMed, Scopus, and Cochrane using relevant and synonymous terms. Study screening and selection will be conducted by the authors based on eligibility criteria. Upon encountering conflicting decisions, a discussion will be held to reach a consensus. The screening and selection process will be recorded using a PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flowchart. The included studies will be subjected to bias and quality assessment in accordance with the Critical Appraisal Skills Programme (CASP) and Grading of Recommendations Assessment, Development, and Evaluation (GRADE) assessment tool for randomized controlled trials.

Results: An initial search was conducted on November 1, 2023, which returned 1998 studies for screening. The extracted data will be classified into groups and subgroups according to the indicator of intelligence measured in the study. Next, the extracted data will be summarized using tables of evidence. Whenever possible, a meta-analysis of homogeneous groups of studies will be conducted using statistical software such as RevMan (version 5.4; Cochrane Collaboration). Studies with significant heterogeneity will be discussed narratively. The systematic review is estimated to be published in November 2025.

Conclusions: This systematic review will systematically pool the evidence on the potential use of omega-3 LCPUFA supplementation to improve children's intelligence status. This review is also important in addressing any existing knowledge gaps on this topic. Finally, a deeper understanding of the association between the consumption of omega-3 LCPUFA

supplementation during pregnancy and children's intelligence will aid policy makers, health care practitioners, and mothers with more informed evidence-based decisions.

Trial Registration: PROSPERO CRD42023463910; https://www.crd.york.ac.uk/PROSPERO/view/CRD42023463910

International Registered Report Identifier (IRRID): DERR1-10.2196/60417

(JMIR Res Protoc 2025;14:e60417) doi:10.2196/60417

KEYWORDS

antenatal; long-chain omega-3 polyunsaturated fatty acids supplementation; pregnant women; systematic reviews; pregnant; pregnancy; maternal; maternity; infant; babies; nutrition; fish oil; docosahexaenoic acid; eicosapentaenoic acid; supplements; cognition; attention; motor skills; languages; behaviors; vision; neurodevelopment

Introduction

Long-chain omega-3 polyunsaturated fatty acids (LCPUFA), also known as omega-3 fatty acids are a part of polyunsaturated fatty acids (PUFA). It is characterized by multiple double bonds (C=C), with the first double bond located on the third carbon chain counting from the terminal methyl group (omega carbon). The 3 forms of this type of PUFA include alpha-linolenic acid (ALA), docosahexaenoic acid (DHA), and eicosapentaenoic acid (EPA). As the body lacks the necessary enzymes to synthesize ALA, it must be acquired through food or supplements, making it an essential fatty acid. Although ALA can be converted to DHA and EPA, the efficiency of its conversion is rather low, hence it is recommended to consume foods that are rich in DHA and EPA [1,2]. The primary source of ALA is plant oils such as canola oils, soybeans, and flaxseed while DHA and EPA are mainly found in fatty oil–enriched fish, which includes sardines, mackerel, and salmon [3,4].

In addition to being essential for the structural integrity of cell membranes, omega-3 LCPUFA also operates as a source of energy and bioactive lipid mediators [5,6]. These functions are critically essential for fetal growth and development, particularly for DHA as DHA plays a key role as part of the cell membrane components in the fetal brain and retina [7]. Placental transfer is the primary source of DHA accumulation in utero, which is involved in neurotransmitter metabolism, neural, and visual functions [8]. Thus, the consumption of omega-3 LCPUFA, in general, is essential to promote optimal fetal growth and maturation for several vital organs, notably the brain and eyes [9]. According to Khalid et al [10], the fetal brain and eyes that were developed in a systematic fashion in response to an adequate intake of omega-3 LCPUFA have some influence on optimal cognitive and visual acuity development in early childhood [10]. DHA prevents cognitive aging by reducing brain apoptosis through upregulating the expression of antiapoptotic proteins or downregulating the apoptotic proteins, thus enhancing early memory and learning ability related to intelligence [11].

According to the World Health Organization, the definition of early childhood corresponds to the period from prenatal development to 8 years of age [12]. While the key factors that determine intelligence in these age groups are hotly debated and vastly described, some genetic and modifiable environmental and nutritional factors contributed to the high intelligence quotient in early childhood [13,14]. Consumption of daily omega-3 LCPUFA during pregnancy as part of maternal nutritional benefits, has been linked to increased early childhood intelligence, according to multiple clinical studies [15-17]. However, as opposed to other clinical studies, randomized controlled trials (RCT) have shown that the most promising outcomes as the confounding factors will be removed in the early phase of the trial to obtain a solid causality that influences the development of early childhood intelligence.

Throughout the years, RCTs related to the consumption of omega-3 LCPUFA have reported varying degrees of results, and several systematic reviews have made an effort to assess the corpus of literature as a whole. The recent Cochrane-based systematic review of omega-3 LCPUFA conducted by Middleton et al [18] has concluded the necessity of conducting a series of follow-ups for completed RCTs for both mothers and children to understand the growth, metabolic, and neurodevelopmental pathways as the RCT outcomes varied by different types of omega-3 LCPUFA, along with the timing, doses, and characteristics of women [18]. This is also supported by a previous systematic review conducted by Gould et al [19]. However, the evidence from these reviews does not conclusively show that the consumption of omega-3 LCPUFA during pregnancy influences the improvement of cognitive and visual development in childhood. This systematic review aims to synthesize available evidence on the impact of omega-3 LCPUFA supplementation during pregnancy toward intelligence in early childhood development as compared to placebo by using a similar approach with added keywords based on the previous systematic review by Gould et al [19] and Middleton et al [18]. The outcome of children's intelligence can be assessed using various tools that measure factors like cognition, attention, motor skills, language, behavior, vision, hearing, social-emotional, and neurodevelopment.

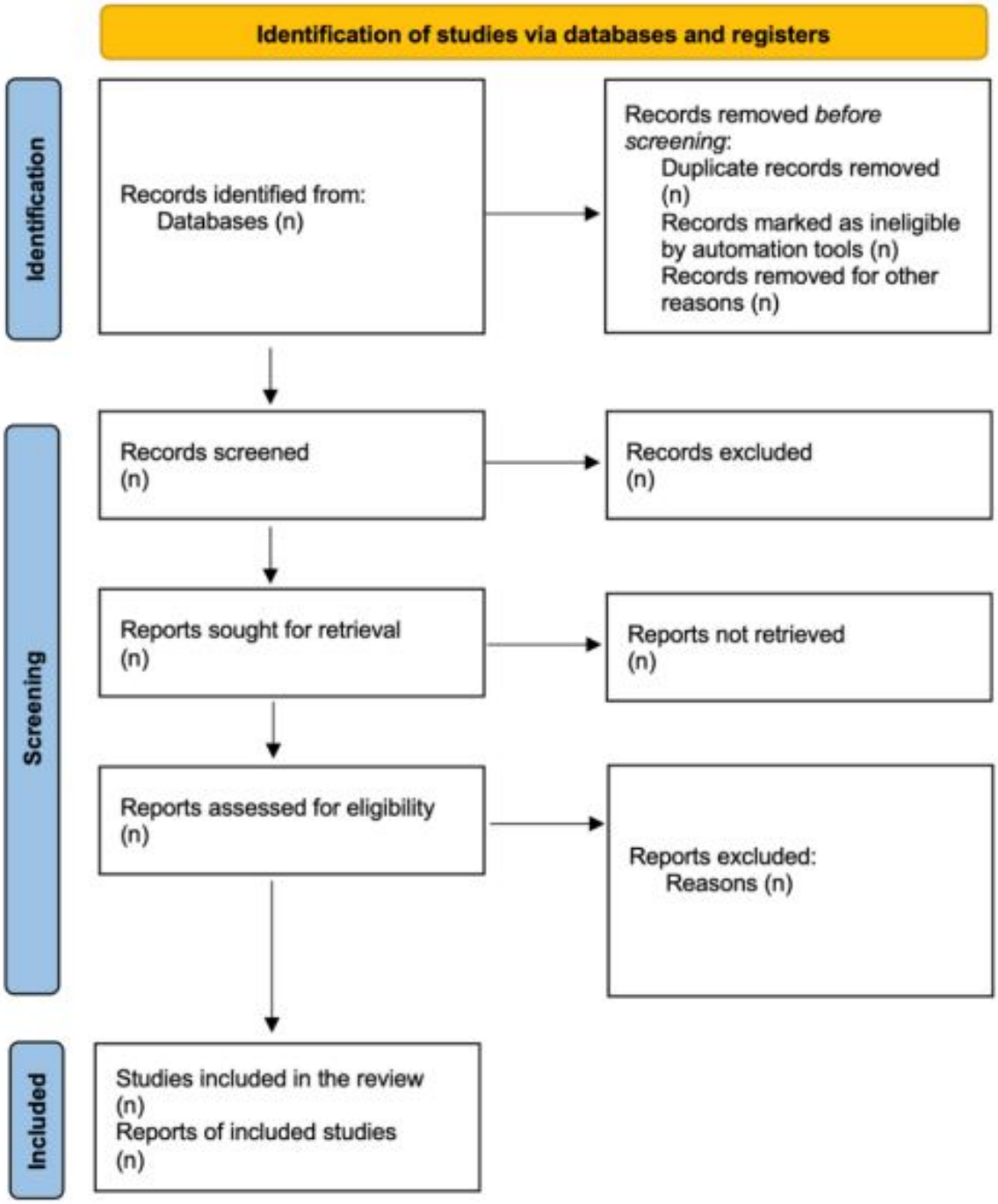
Methods

Overview

We will conduct a systematic review in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) [20]. We will ensure adherence to the PRISMA 2020 guidelines throughout the review process by following their checklist (Multimedia Appendix 1) and flow diagram (Figure 1). All processes will be recorded systematically, precisely, and transparently. The systematic review flow diagram will be divided into three processes: (1) identification, (2) screening, and (3) inclusion. The identification

of studies will be categorized into 2 sections, via databases, registers, and other methods. Records identified from each section will be documented accordingly. The final selection process will display the total number of studies that are eligible to be included in the review. To avoid the potential confounding factors that may affect the relationship between omega-3 LCPUFA supplementation and childhood intelligence, such as socioeconomic status, maternal education, and prenatal care, several review strategies will be used in the methodology phase. First, several effect models, such as fixed effects and random effects models will be reviewed in all studies to account for unmeasured individual-level confounding that might vary over time to help in estimating the causal effects of omega-3 LCPUFA supplementation. Second, during the screening phase, only studies where the participants are randomly assigned to either the treatment group (omega-3 LCPUFA supplementation) or the placebo group will be accepted. This randomization ensures that confounders are evenly distributed between the groups, thereby reducing their potential influence on the study results.

Figure 1. PRISMA flow diagram.



Eligibility Criteria

We will use the Participant, Intervention, Control, Outcomes (PICO) model in constructing eligibility criteria for study inclusion in the review.

Study Selection

We will include individual and clustered RCTs that studied the children's intelligence status between the supplementation of omega-3 LCPUFA during pregnancy compared to placebo or other supplemented intervention or standard perinatal care. Other types of study designs such as unpublished studies, gray literature, reviews, letters, short communications, conference papers, conference abstracts, abstracts, in vitro or in vivo, prospective or retrospective cohort, case-control, quasiexperimental and nonrandomized clinical trials will be excluded. We will include studies published in English. For studies in other languages, we will seek translations, if available.

Population

Our systematic review will focus on studies involving healthy pregnant women who received omega-3 LCPUFA supplementation. These pregnant women must be free from major confounding factors that are not representative of the general population of pregnant women. Additionally, we will consider the outcomes for their children who are aged 8 years or younger, assessing the impact of omega-3 LCPUFA supplementation on the children's intelligence using validated tools. The studies selected will exclusively involve mothers without chronic health conditions as well as children who have not been diagnosed with congenital anomalies, gastrointestinal issues, or metabolic disorders.

Intervention

In the review, we will evaluate the omega-3 LCPUFA supplementation in pregnant women as the intervention. We will not put a restriction on the dose. We will follow the study authors on the dose of omega-3 LCPUFA supplementation. Any RCTs that involve the supplementation before pregnancy or during the postnatal period will be excluded.

Comparison

We will include studies that compare the intervention with pregnant women receiving placebo or other supplement interventions.

Outcomes

We will include studies that measured the intelligence status of children using validated inventory or tools, for example, but not limited to, The Bayley Scales of Infant and Toddler Development, Third Edition, and Kaufman Assessment Battery for Children, Second Edition. The intelligence status may be based on several indicators such as cognition, attention, motor skills, language, behavior, vision, hearing, social-emotional, and neurodevelopment. The children included in the outcome group must be aged 8 years or younger. Studies that did not measure the intelligence status of the children, or studies that used children older than 8 years as an outcome group will also be excluded.

Data Sources, Search Terms, and Search Strategy

The authors have agreed to use 3 prominent journal databases as sources. The selected databases are PubMed, Scopus, and Cochrane Library. These databases were selected since they can fulfill every performance criterion as a search system [21]. All authors participated in a discussion to determine relevant terms and keywords that will be used in database searching. MeSH (Medical Subject Headings) terms will also be used in the search. Advanced search in each database will be performed using Boolean operators such as "AND" and "OR" to build search strings. Databases will be searched from inception to the most recent study publication. Any unpublished studies upon the final search date will not be included. No search filters will be used during the database search. The query search string will be adjusted following the interface provided by the databases (Multimedia Appendix 2).

Data or Reference Management

All studies identified in the final hit will be downloaded using NLM or RIS format. A reference manager software, EndNote (Clarivate) will be used to combine studies identified in the 3 databases. In-apps feature using the reference manager will be used to identify and remove duplicates.

Study Screening

Study screening will commence once database searches have been fully accomplished. A data selection form will be developed using Microsoft Excel and a systematic review tool. We will use Rayyan software (Qatar Computing Research Institute) to streamline the screening process, as it is a widely recognized tool designed for systematic reviews. All identified studies will be uploaded to the Rayyan review panel. Any duplicates identified by Rayyan will be removed. Before the process of selection, at least 5 randomly chosen studies will be pilot-tested to ensure all reviewers are familiar with the software. The references can be filtered by category, which makes the extraction process a lot easier. Collaborators or other reviewers will be invited to join the page and blind will be turned on in collaboration reviews to remove the risk of bias. References can be included by clicking "Include," excluded by clicking "Exclude," or "Maybe," if not sure. The label and reason box can be used to include labels and reasons for exclusion. The probability of the references (included, excluded, or undecisive) will be calculated by Rayyan. Undecided references will have a rating from 1 to 5, where 5 is most likely to be incorporated.

The screening process will be conducted in two phases: (1) title and abstract screening, and (2) full-text screening. Two reviewers (IHAS and MAMF) will be assigned to screen the titles and abstracts based on the eligibility criteria. Following that, the other 2 reviewers (SM and WASM) will conduct the second screening process by evaluating the full-text studies to be included in the review. If both reviewers have different opinions or judgments, a third reviewer (HYL) will be called upon to unravel the disagreements.

Data Extraction

A data extraction form will be constructed in an Excel (Microsoft Corp) sheet and the following information will be gathered from the relevant selected studies such as title, last

name of the first author, year of publication, duration of intervention, study design, single or multicenter, country, source of funding, aims, population (inclusion and exclusion criteria), intervention, indicator, index test, comparison, reference standard, primary and secondary outcomes (including tools and period of measurement), and results. Two reviewers (IHAS and MAMF) will extract the data of eligible studies independently. The other 2 reviewers (SM and WASM) will recheck the data extracted. Any discrepancies will be resolved by discussion to achieve a consensus. Any missing data, incomplete information, or variation in results will be obtained by contacting the corresponding author of the study.

Risk of Bias and Quality Assessment

Assessment of risk of bias will be conducted by 2 independent reviewers (IHAS and MAMF). A third reviewer (HYL) will be the referee for any uncertainties or disagreements in the discussion. All included RCTs will be assessed for study quality and potential biases using the Critical Appraisal Skills Programme (CASP) checklist for RCT. CASP is a checklist widely used for RCT evaluation, chosen for its simplicity, structured approach, and focus on key domains of study quality. This tool considers the following four domains of biases: (1) arising from the validity of the study design for RCT; (2) the soundness of the methodology applied; (3) measurement of the outcome; and (4) whether the results will provide any benefit to the targeted population. Each domain will be judged as "yes," "no," or "can't tell." If necessary, the authors will be contacted to obtain or clarify any information needed. The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) tool will be used to assess the quality and certainty of the evidence for the outcomes analyzed in the meta-analysis. A summary of the risk of bias will be compiled into a table along with the justification for each judgement.

Data Synthesis

Meta-analysis will be performed when there are at least 2 studies reporting on the same outcome of interest between the omega-3 supplementation (intervention) and placebo (control), otherwise, a narrative summary approach will be presented. In the case of RCT with more than 2 arms, each arm will be treated separately. Data extracted from each study will be pooled and analyzed using the RevMan (version 5.4; Cochran Collaboration) software. For outcomes of interest measured in continuous or scale, sample size, means, and corresponding SDs will be used in pooling the effect size of the outcomes across the included studies. The pooled effect estimates for continuous outcomes will be expressed as mean differences with 95% CIs for studies using a similar outcome assessment tool, meanwhile, standardized mean differences with 95% CIs will be expressed for studies using different outcome assessment tools. For outcomes of interest measured in dichotomous or binary, the number of events and total sample size will be used in pooling the effect size of the outcomes across the included studies. The pooled effect estimates for dichotomous outcomes will be expressed in odds ratio with 95% CI. In cases where the data reported in the included studies are not usable (ie, cannot be pooled with other data), the corresponding author of the study will be contacted for access to data or revised statistics. If the corresponding author is uncontactable, or the data are unavailable, we will retain the study as eligible but restricted for meta-analysis. In view of inconsistencies between results in the existing literature highlighted by Gould et al [19] and Middleton et al [18], meta-analysis will later identify patterns of agreement and disagreement, thus offering insights into the reasons behind conflicting results.

The overall effect estimates that have a P value less than .05 will be interpreted as statistically significant. Heterogeneity will be assessed using the I^2 statistic, which represents the percentage of the total variation present between studies included. The I^2 statistic values of over 50% will be considered substantial heterogeneity. To address the variability of dosage, duration, and types of PUFA supplementation, random effects models will be used during analysis to manage heterogeneity. This will ensure a robust analysis of our findings. Sensitivity analysis will be performed when heterogeneity is high to address potential confounding factors and strengthen the study's robustness. We will group the outcomes according to the same assessment tools. Subgroup analyses for outcomes will be conducted when 2 or more studies are available per subgroup of interest. The following prespecified subgroups will be considered: maternal age, duration of intervention, presence of co-interventions (by itself or combined with complementary interventions), baseline nutritional status in mothers, sex of infant, country or geographic region, and risk of bias (low, high, or some concerns). If the dosage of the supplementation varies significantly, we will also do a subgroup analysis based on the dose group if we can pool studies with the same outcome.

Funnel plots will be conducted for the detection of publication bias if there are 10 or more studies available for an outcome. Publication bias is unlikely if data forms a symmetric inverted funnel shape around the mean effect estimate. As the funnel plots will be presented graphically, subjective judgments are required, which might differ from one person to another in interpreting the result. In addition, the Egger test will be conducted to determine funnel plot asymmetry. The presence of publication bias will be considered if the P value of the Egger test is less than .05.

For outcomes with insufficient data or extreme heterogeneity that cannot be analyzed by meta-analysis, a narrative synthesis will be provided.

Registration and Reporting

This systematic review and meta-analysis protocol has been registered on the International Prospective Register of Systematic Reviews (PROSPERO, CRD42023463910) and in the National Medical Research Register Malaysia (03507-WSF). In the event of protocol amendments, the date of each amendment will be accompanied by a description of each change and the rationale on PROSPERO. In preparing this protocol, we followed the PRISMA 2020 checklist (Multimedia Appendix 1). This systematic review will be reported in accordance with the Cochrane Handbook for Systematic Reviews of Interventions [22] as well as the PRISMA-P (Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols) guidelines (Multimedia Appendix 3) [23].

Ethical Considerations

As this systematic review and meta-analysis uses secondary data, ethical approval is not required, and an exemption letter for ethical approval is obtained as per requirement by the Ministry of Health, Malaysia.

Results

After discussing and finalizing the search keywords and search strategy, 1 author conducted the initial search. The first keyword search was run on November 1, 2023. The first database, which is PubMed, yielded 530 hits whereas the second database from Cochrane found 306 hits. The most hits were from Scopus with 1162 hits. In total, our first database search yielded 1998 hits. All references were then imported into a reference manager specified in the search strategy section. All hits will be pooled and screened for duplicates using automation tools. Then, the titles and abstracts will be extracted for the first screening by the authors. We aim to finish extracting and analyzing data from chosen studies and prepare the report by November 2025.

Discussion

Principal Findings

In our planned systematic review, we intend to investigate the existing body of literature concerning the effects of maternal omega-3 LCPUFA supplementation on the cognitive development, specifically the IQ, of children in early childhood. The justification for maternal omega-3 LCPUFA supplementation, often promoted as a means to enhance a child's cognitive development, remains a topic of ongoing debate. Given the extensive systematic review conducted in 2018, this systematic review aims to provide a more rigorous analysis of the available evidence [18]. While previous findings suggest a positive association between omega-3 LCPUFA supplementation during pregnancy and children's IQ, it is important to note that the existing evidence is characterized by relatively low quality due to limitations such as small sample size. Hence, our objective is to enhance the quality of evidence through this review. A consistent body of research indicates a significant link between maternal omega-3 LCPUFA supplementation during pregnancy and a substantial enhancement in the IQ of the children [24,25]. Despite the overall indication of support for the beneficial effects of maternal omega-3 LCPUFA supplementation, it is important to acknowledge the presence of factors that can influence the outcomes [26,27]. Therefore, in our systematic review, we will also look at the variations in indicators of the intelligence status of the children based on several indicators such as cognition, attention, motor, language, behavior, vision, hearing, social-emotional, and neurodevelopment, which may contribute to heterogeneity in the results. The systematic review will adhere strictly to the protocol, and any deviations will be documented and reported in the published manuscript.

The implications of these findings for public health are significant. A more tailored approach to prenatal nutritional guidance, as suggested by Cetin et al [28], may be warranted to ensure optimal cognitive development in early childhood [28]. This, in turn, could have long-term cost-saving benefits for health care systems by potentially reducing the societal burden of cognitive impairments.

Comparison With Prior Work

Previous systematic reviews were published more than 5 years ago and the findings were varied [18,19]. Given the potential impact of maternal omega-3 LCPUFA supplementation on child IQ, there is a strong case for revisiting and possibly refining dietary recommendations for pregnant women. Thus, this review builds on these works by incorporating updated evidence and conducting subgroup analyses to address key factors, such as timing, dosage, and source of supplementation.

Limitations

We will thoroughly examine the limitations and potential sources of bias in the included studies. Despite our review's rigorous evaluation of evidence quality, there may still be sources of bias, such as publication bias or unaccounted confounders, that influence the overall results. To address potential publication bias, we will include a funnel plot analysis to visually assess the presence of asymmetry. Furthermore, the quality and design of the individual studies may vary. It is important for researchers and policymakers to recognize these limitations when interpreting the findings and consider them when making recommendations.

Future Research

This systematic review will address the necessity for further research in this area. It will also help future studies to address the identified limitations and clarify the optimal timing, dosage, and duration of maternal omega-3 LCPUFA supplementation to maximize the potential benefits on child IQ. Additionally, the long-term effects of maternal supplementation in children beyond the age of 8 years warrant exploration. This will not only deepen our understanding of this complex relationship but also help refine practical recommendations for expectant mothers, contributing to the well-being of future generations.

Conclusions

In conclusion, the systematic review will provide valuable insights into the potential impact of maternal omega-3 LCPUFA supplementation on children's IQ. If the evidence suggests a positive association, further research is needed to address limitations, confirm findings, and refine recommendations. The results will be disseminated by publishing the review, presenting at conferences, and sharing with stakeholders such as policy makers, nutritionists, and doctors, following PRISMA guidelines for transparent reporting. The implications for public health are substantial, and addressing these gaps can lead to a more comprehensive exploration of the impact of omega-3 LCPUFA supplementation during pregnancy on children's intelligence. Thus, this systematic review can provide a thorough understanding of the topic and offer valuable insights for future research and practice.

Acknowledgments

The authors would like to thank the Director General of Health Malaysia for his permission to publish this manuscript. The authors also would like to thank Datuk Nor Asiah Muhamad and Izzah Athirah Rosli from the Sector for Evidence-Based Healthcare, National Institutes of Health, Malaysia for reviewing the manuscript. The authors attest that there were no generative artificial intelligence was used in the manuscript generation, figures, or other informational content of this manuscript.

Data Availability

All data generated and analyzed in this systematic review are available upon request from the corresponding author.

Authors' Contributions

HYL, MAMF, SM, IHAS, and WASM designed the systematic review and wrote the original draft; HYL and WASM designed the systematic review and approved the final manuscript. All authors are researchers involved in clinical nutrition research, with several years of experience in nutrient analysis and clinical nutrition at the Institute for Medical Research, Malaysia.

Conflicts of Interest

None declared.

Multimedia Appendix 1
PRISMA 2020 checklist.
[DOCX File , 606 KB - resprot_v14i1e60417_app1.docx]

Multimedia Appendix 2
The protocol search strategy.
[DOCX File , 21 KB - resprot_v14i1e60417_app2.docx]

Multimedia Appendix 3
PRISMA-P 2015 checklist.
[DOCX File , 22 KB - resprot_v14i1e60417_app3.docx]

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Abbreviations

ALA: alpha-linolenic acid
CASP: Critical Appraisal Skills Programme
DHA: docosahexaenoic acid
EPA: eicosapentaenoic acid
GRADE: Grading of Recommendations Assessment, Development, and Evaluation
LCPUFA: long-chain omega-3 polyunsaturated fatty acid
MeSH: Medical Subject Headings
PICO: Participant, Intervention, Control, Outcomes
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analysis

PRISMA-P: Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols
PUFA: polyunsaturated fatty acid
RCT: randomized controlled trial

Edited by T Leung, J Sarvestan; submitted 10.05.24; peer-reviewed by F Shirani, L Aljerf, AM Babker; comments to author 26.10.24; revised version received 16.02.25; accepted 04.03.25; published 17.04.25.

Please cite as:
Lim HY, Mohammad Fadzil MA, Mustar S, Abdul Shukor IH, Mohamed WAS
The Impact of Long-Chain Omega-3 Polyunsaturated Fatty Acid Supplementation in Pregnant Women Toward the Intelligence Status of Early Childhood: Protocol for a Systematic Review and Meta-Analysis
JMIR Res Protoc 2025;14:e60417
URL: https://www.researchprotocols.org/2025/1/e60417
doi:10.2196/60417
PMID:

Protocol

Combining Ecological Momentary Assessment and Social Network Analysis to Study Youth Physical Activity and Environmental Influences: Protocol for a Mixed Methods Feasibility Study

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Abstract

Background: Physical activity (PA) is crucial for youth health, but up to 74% of adolescents fail to meet recommended levels, especially during summer when structured supports associated with school are not available. The social and built environments significantly influence youth PA; yet, their complex interactions remain poorly understood. This study aims to evaluate the feasibility of combining ecological momentary assessment (EMA) and social network analysis to examine bidirectional influences among youth PA, built environments, and social networks during summer.

Objective: The objectives are to (1) evaluate the feasibility and acceptability of the combined EMA and Social Network Analysis protocol, and (2) identify phenotypes using person-level, microtemporal, and dynamic overlap between social and built environments.

Methods: This mixed methods feasibility study with an exploratory observational component will recruit 120 youth aged 12 years to 15 years from an urban school district in Central Texas, US. Participants will first complete a baseline survey to report their general social network patterns and environmental perceptions. Then participants will wear an ActiGraph LEAP accelerometer and respond to EMA prompts via smartphone for 7 days. EMA will assess real-time perceptions of social networks and surrounding built environments, which will be time-matched with accelerometer-assessed PA data. GPS coordinates will be collected with each EMA prompt to assess features of the built environment. Follow-up semistructured interviews will assess protocol acceptability.

Results: This study has been funded by the National Heart, Lung, and Blood Institute. Data collection is expected in the summers of 2025, 2026, and 2027.

Conclusions: This innovative approach combines EMA, SNA, accelerometry, and GPS data to provide unprecedented insights into the dynamic interplay between social networks, built environments, and youth PA during summer. Findings will inform the development of more targeted, effective interventions to promote PA among youth. While limitations include potential participant burden and generalizability, the study's strengths in capturing real-time, contextualized data make it a valuable contribution to understanding youth PA determinants.

International Registered Report Identifier (IRRID): PRR1-10.2196/68667

(JMIR Res Protoc 2025;14:e68667) doi:10.2196/68667

KEYWORDS

physical activity; youth; social environment; built environment; ecological momentary assessment; social network analysis; phenotypes; accelerometry; GPS

Introduction

Background

Physical activity (PA) is crucial for youth health and development, offering a wide range of physical, psychological, and social benefits [1]. However, roughly 74% of young people fail to meet recommended PA levels [2], putting them at risk for various health issues both in the short and long term [1]. Summer presents a unique challenge for youth PA, as it represents a significant departure from the social and built environment supports typically offered by schools [3,4]. During the academic year, schools provide structured physical education classes, organized sports, and supervised recess periods, all of which contribute to youth PA levels [3,4]. The absence of these supports during summer leads to substantial changes and variability in how youth experience and are influenced by their social and built environments [5,6].

The social and built environments have been identified as key modifiable factors influencing youth PA, with research suggesting complex and nuanced relationships between these environmental factors and PA behaviors [7]. The social environment encompasses interpersonal relationships, social networks, and community norms, while the built environment includes physical structures, facilities, and design elements that can either facilitate or hinder PA. Despite growing research in this area, our understanding of how different layers of the social ecological model impact youth PA remains unclear, particularly during the summer months when the structured supports provided by schools are absent [8,9]. This knowledge gap hinders the development of effective interventions to promote PA among youth, especially during critical periods like summer. Moreover, there is considerable variability between youth in terms of the social and built environment factors they are exposed to during the summer months, as well as the impact these factors have on their PA levels [3,4,8]. For instance, some youth may be more affected by built environment barriers (eg, lack of safe parks or playgrounds) despite having a supportive social environment (eg, friends who enjoy physical activities), while others may face disparities in both domains [1,10,11]. This heterogeneity in experiences and influences underscores the need for more sophisticated research approaches that can capture and analyze these complex relationships.

Recent reviews of existing evidence highlight a significant need for more nuanced measurement approaches, including the use of intensive longitudinal data (ILD) to understand the complex variability (both within and between-subject) as well as the independent and mutual effects of social and built environments on youth PA [7,12,13]. Traditional cross-sectional or even longitudinal studies with infrequent measurement points may fail to capture the dynamic nature of these relationships and the day-to-day variations in youth PA behaviors [12,13]. ILD, on the other hand, allows for the collection of frequent, real-time data that can reveal patterns and associations that might otherwise be missed [12,13]. One promising approach to capturing this variability is through the identification of "phenotypes," individual-specific webs of links between social and built environmental determinants [14,15]. These phenotypes have the potential to identify overlaps in ILD and salient intervention targets for health behavior [14-16]. By understanding these phenotypes, researchers and practitioners may be able to develop more personalized and effective interventions to promote PA among youth, considering the unique combination of social and built environment factors that influence an individual's behavior.

Ecological momentary assessment (EMA) has emerged as a valuable method for collecting ILD by gathering real-time self-reports of behaviors, contexts, and perceptions in naturalistic settings [12,13]. EMA typically involves prompting participants multiple times throughout the day to report on their current activities, feelings, and surroundings, providing a rich, contextual dataset that captures the ebb and flow of daily life. This approach offers several advantages over traditional retrospective self-report measures, including reduced recall bias and the ability to capture within-person variability over time [12,13]. However, previous EMA measures of the social environment have been limited to the presence of others or coparticipation in PA, which may not fully capture the complexity of social influences on youth PA [7,13,17]. Social network analysis (SNA) offers the potential to provide more nuanced information, such as dyadic and personal network measures of social bridging, bonding, norms, and influence [17,18]. SNA allows researchers to map and analyze the structure and composition of an individual's social network, providing insights into how social connections and interactions may influence PA behaviors. By combining EMA and SNA approaches, researchers may be able to gain a more comprehensive understanding of the dynamic interplay between social factors and PA in youth's daily lives.

To examine these influences on a more granular level, this project aims to evaluate the feasibility of combining EMA and SNA techniques to collect ILD describing social and built environment associations with youth PA during the summer. This innovative combination of EMA and SNA techniques represents a data-intensive approach, necessitating an evaluation of its feasibility and acceptability in terms of validity, reliability, and respondent burden. The integration of these methods has the potential to provide unprecedented insights into the complex relationships between social networks, built environments, and PA behaviors among youth. For example, EMA data may show a youth's PA spikes when they are with a specific friend, but only if they are within a half-mile radius of a park, as indicated by GPS data. SNA reveals this friend is not particularly active themselves, but rather may be influential in triggering PA in groups, potentially exposing the youth to varied activity opportunities. This complex interplay suggests that interventions targeting both social network dynamics and built environment access could be more effective than addressing either in

isolation, highlighting the value of integrating EMA and SNA approaches to understand youth PA patterns.

This complex framework also presents challenges in terms of data collection, participant compliance, and analytical complexity. The intensive nature of the EMA protocol, combined with the detailed social network data collection, may lead to significant participant burden, potentially resulting in missing data, reduced compliance over time, or even selective attrition of certain participant subgroups. Moreover, the frequent prompts and awareness of being monitored could introduce reactivity, where participants alter their behavior or reporting patterns, while the complexity of the data collected across multiple platforms (EMA, GPS, and accelerometry) presents substantial challenges in data integration, cleaning, and analysis, requiring sophisticated statistical approaches to handle the multilevel, time-varying nature of the data. By conducting a feasibility study, researchers can identify potential barriers and refine the methodology before implementing it on a larger scale. This study seeks to address the critical need for more comprehensive and nuanced understanding of the complex interplay between social and built environments and their impact on youth PA during the summer months. The findings from this research could inform the development of more effective, targeted just in time adaptive interventions to promote PA among youth, ultimately contributing to improved health outcomes and reduced health disparities in this population.

Study Aims

The study has 2 primary aims. Aim 1 is to evaluate the feasibility and acceptability of an EMA protocol that combines the collection of social network characteristics using SNA and built environment characteristics corresponding to PA among youth during the summer. This aim will assess metrics such as EMA response rates, accelerometer wear time, and qualitative feedback from participants to determine the viability of the combined EMA-SNA approach. Aim 2, which is exploratory, seeks to identify and classify phenotypes by using microtemporal dynamic overlaps between social and built environments. Aim 2 will examine these phenotypes and their association with PA among youth in summer. These aims will use cluster analysis to identify subgroups of social and built environment patterns within the sample followed by dynamic structural equation modeling (DSEM) to analyze the bidirectional dynamics of social and built environment factors and PA [19,20]. These aims will provide a comprehensive assessment of the proposed methodology's feasibility and potential for uncovering nuanced relationships between environmental factors and youth PA during summer.

Methods

Study Design

This study will use a mixed methods approach to evaluate the feasibility and acceptability of combining EMA and SNA techniques for assessing social and built environment influences on youth PA during summer. The research design involves recruiting 120 youth aged 12 years to 15 years (entering the seventh to the ninth grades) from a local school district. An initial cohort of 20 youths will be recruited in year 1 of the project to assess initial feasibility and pilot the measures. Participants will be divided into 2 cohorts (n=50 each) across years 2 and 3, with each cohort further split into 5 groups (n=10) to facilitate data collection throughout the summer.

Conceptual Framework

The conceptual model guiding this study is grounded in a social ecological model, recognizing that youth PA is influenced by multiple, interacting layers of environmental factors [21,22]. At its core, the model posits that youth PA is shaped by a dynamic interplay between social and built environment elements, with each exerting both independent and synergistic effects on PA behaviors [7,23]. The social environment component encompasses the structure and quality of social networks, including aspects such as social bridging, bonding, norms, and influence [17,18,24]. These social factors are theorized to provide support, motivation, and opportunities for PA, but may also act as barriers in some contexts [25,26]. The built environment element includes physical structures, facilities, and urban design features that can either facilitate or hinder PA [27,28]. This includes factors such as neighborhood walkability, access to recreational spaces, and perceived safety [29-31].

Critically, the model emphasizes the reciprocal nature of these relationships, acknowledging that youth's PA behaviors can, in turn, influence their perceptions and interactions with both social and built environments [32,33]. This bidirectional conceptualization allows for a more nuanced understanding of how environmental factors and PA behaviors coevolve [7]. The model also incorporates the concept of phenotypes, representing individual-specific patterns of associations between social and built environment factors and PA [14,34]. These phenotypes are theorized to capture the heterogeneity in how youth respond to and interact with their environments, reflecting the complex, person-specific nature of PA determinants [35,36]. By integrating these various components, the conceptual model provides a comprehensive framework for understanding the multifaceted influences on youth PA, particularly during the unique context of summer months when typical school-based structures are absent [8,9].

Participants and Procedures

The study will recruit 120 youth participants aged 12 years to 15 years (entering the seventh to ninth grades) from a local school district. This age range was selected based on previous research indicating significant declines in PA and increases in peer influences during this developmental period [37,38]. Recruitment will be stratified to ensure equal numbers across sex and grade levels. Participant recruitment will occur through a partnership with a school district in central Texas, United States, which serves a diverse student population. The district-wide demographics include 72% of students classified as being at risk of dropping out of school and 77% eligible for free or reduced-price lunch. The student population is approximately 60% Hispanic or Latinx, 18% Black or African American, and 19% White. Recruitment will occur in 2 phases. First, a feasibility and pilot cohort (n=20) will be recruited in year 1. Next, 2 additional cohorts (n=50 each) will be recruited over years 2 and 3 to manage researcher burden and resource allocation. Each cohort will be further divided into 5 groups

(n=10) to facilitate data collection throughout the summer with 1 group participating in data collection each week. Participants will be asked to provide a list of weeks that they would be able to participate in the program to avoid scheduled family vacations and other activities that would alter their normal activity level. Participants will then be assigned a week at random from their available weeks. An informational sheet will be sent to eligible youth and their guardians in cooperation with the school district.

The study protocol consists of three main components: (1) an initial survey, (2) a 7-day EMA period, and (3) a follow-up interview. During the initial study visit, participants will complete researcher-administered surveys assessing their personal social networks and perceptions of the built environment around their home. They will also receive training on the use of the EMA application and the ActiGraph LEAP accelerometer. For the 7-day EMA period, participants will wear the ActiGraph LEAP accelerometer on their nondominant wrist 24 hours per day. They will respond to EMA prompts via a smartphone application 6 times daily over 12 hours [39]. The application (LifeData) will be downloaded onto their personal phones (Android or Apple). If the adolescent does not have a phone, a research device will be provided with all other functionality disabled. Prompts will be delivered at random during six 2-hour windows across the day with no prompt being sent within 30 minutes of the previous prompt. The prompting schedule will be adjusted to accommodate each participant's sleep and wake schedule, with 3 options available (8 AM to 8 PM; 9 AM to 9 PM; and 10 AM to 10 PM). Each prompt will include short questionnaires (2-3 mins) assessing momentary perceptions of social and built environments. Following the 7-day EMA period, participants will return for a follow-up visit to return the equipment and participate in a qualitative interview. This interview will assess the acceptability of the EMA and accelerometry protocols and gather additional contextual information about their experiences during the study period.

Survey Variables

The survey component of this study will assess various aspects of the social and built environments and demographic information. These measures are collected during the initial study visit and provide baseline data for each participant.

Demographic Information

Participants will provide demographic information, including age, sex, race, ethnicity, household income (reported by parents or guardians), parental education level, and home address (for Geographic Information System analysis). These data will be used to characterize the study sample and explore potential moderating effects on the relationships between social networks, built environments, and PA.

Social Network Characteristics

To assess social network characteristics, participants will be asked to list up to 10 people (also termed alter) they interacted with most in person over the last 7 days, a method previously used in personal network research [17,18,24]. For each person listed, participants will provide information on relationship type, frequency of contact, perceived frequency of the alter's PA, frequency of coparticipation in PA, perceived closeness, and likelihood of joining the alter in new activities or PA. Participants will also report if each pair of alters knows each other, allowing for the analysis of network structure [17,18]. These data will be used to calculate various social network measures, including social bridging (network size, effective size, and diversity), social bonding (density, proportion of frequent contact, and mean closeness of connection), social norms (frequency of coparticipation in PA and mean perception of alter PA), and social influence (proportion of likely influencers and mean suggestibility) [17,18,40]. In addition, individuals listed in this survey will also be included in EMA prompts as potential responses to items regarding the social environment. In this manner, SNA alters perceptions can be combined with EMA prompt answers to offer opportunities to connect the data set and better explain the social environment as collected by the EMA prompts.

Built Environment Perceptions

To assess built environment perceptions, the Neighborhood Environment Walkability Scale–Youth (NEWS-Y) will be used [31]. This scale, adapted from the adult version and validated for use with youth aged 12 years to 18 years, assesses several domains of neighborhood walkability including PA resource access, land-use mix, walkability, neighborhood aesthetics, safety (crime and traffic), walking and bicycling facilities, street connectivity, and residential density [29]. These measures provide a comprehensive assessment of youth perceptions of their neighborhood-built environment.

EMA Items

The EMA protocol is designed to capture real-time data on participants' social context, built environment perceptions, and PA. EMA prompts will be delivered 6 times per day over a 12-hour period for 7 consecutive days, using a smartphone application [41,42]. Prompts will be delivered at random during six 2-hour windows across the day with no prompt being sent within 30 minutes of the previous prompt. Each EMA prompt is designed to be completed in 2-3 minutes to minimize participant burden while still capturing key variables of interest. The combination of these EMA items with the continuous accelerometer data and GPS coordinates will provide a rich, contextualized dataset for examining the dynamic relationships between social and built environments and youth PA during summer [36,42]. The specific items included in the EMA prompts are in Table 1.

Table 1. Domains, ecological momentary assessment prompts, and response options.

Domain	Ecological momentary assessment prompt	Response option
Current activity	• "What were you doing right before the beep went off [Choose your main activity]?"	Reading/computer/phone, watching TV/movies, eating/drinking, physical activity/exercising, socializing/hanging out, and others.
Social context	• "WHO were you with just before the beep went off?"	Free response for person(s) listed in the network, other friends, siblings, parents, other family members, others, or people they did not know. (Select all that apply)
Social bridging	• N/A[a]	Measured by the diversity of social context and frequency of persons not known.
Social bonding	• "How close (emotionally) do you feel to those around you at this moment?"	Visual analog scale anchored from "not at all" to "extremely close"
Social norms	• "How physically active do you think the people around you are normally?"	Visual analog scale anchored from "not at all" to "extremely active"
Social influence	• "If someone you are with suggested doing something physically active, how likely would you be to join?"	Visual analog scale anchored from "not at all" to "extremely likely"
Built context	• "Where were you just before the beep went off?"	Home (indoors), home (outdoors), care program (indoors), outdoors (not at home), car/van/truck, and other
Safety	• "How safe do you feel in the current setting?"	Visual analog scale anchored from "not at all" to "extremely"
Pleasantness	• "How pleasant is the physical setting?"	Visual analog scale anchored from "not at all" to "extremely"
Space to be active	• "How much space is there to be physically active where you are right now?"	Visual analog scale anchored from "none" to "a lot"
Affective and feeling states	• "Right now, how SAD do you feel?" • "Right now, how HAPPY do you feel?" • "Right now, how FATIGUED do you feel?" • "Right now, how ENERGETIC do you feel?" • "Right now, how RELAXED do you feel?" • "Right now, how TENSE do you feel?" • "Right now, how STRESSED do you feel?" • "Right now, how FRUSTRATED do you feel?" • "Right now, how NERVOUS do you feel?"	Visual analog scale anchored from "not at all" to "extremely"
Interesting or engaging	• "What is the most interesting/engaging part of the surrounding environment to you right now?"	Free response

[a]N/A: Not available.

Activity Level

Participants will report their current activity at the time of each prompt. Options will include sedentary activities (eg, sitting and lying down), light activities (eg, standing and walking slowly), moderate activities (eg, brisk walking), and vigorous activities (eg, running and sports). This item has been validated against accelerometer measures in previous youth studies [43].

Social Context

To assess momentary social context, participants will respond to questions about who they are with now, the number of people present, how close (emotionally) they feel, their perception of how active those around them are being, and their perception of susceptibility to PA suggestions. Previously mentioned individuals from the initial SNA survey will be provided as response options in these prompts to further understand social influence and norms. These items are designed to capture both the presence of others, social norms related to PA, and susceptibility to influence in the immediate environment.

Built Environment Perceptions

Participants will be asked about their current physical location and their perceptions of the immediate built environment. Questions will address the type of location, perceived safety of the current environment, pleasantness of the surroundings, and availability of space to be physically active. These items are adapted from previous EMA studies on built environment perceptions and PA [36,41].

Mood and Motivation

To capture psychological factors that may influence PA, participants will be asked about their current mood (using a brief affect scale). These items allow for the examination of how momentary psychological states may interact with social and built environment factors to influence PA [41].

Qualitative Inquiry

To complement the quantitative data collected through surveys, EMA, and accelerometry, this study incorporates a qualitative component to gain deeper insights into participants' experiences and perceptions. Following the 7-day EMA period, semistructured interviews (Multimedia Appendix 1) will be conducted with all feasibility participants (n=20). These interviews will serve multiple purposes: (1) to assess the feasibility and acceptability of the EMA and accelerometry protocols; (2) to gather contextual information about participants' experiences during the study period, such as whether they encountered difficulties answering prompts while engaged in physical activities, if the device interfered with their sleep, or if they felt compelled to alter their behavior due to being monitored; and (3) to explore any anomalies or patterns observed in the quantitative data. The interviews will probe participants' thoughts on answering EMA questions in real time, any privacy concerns they may have had, and their overall experience with the study protocol. In addition, an adapted version of the System Usability Scale will be integrated into the interview to further assess the acceptability and usability of the protocol [44]. These interviews will be audio-recorded, transcribed verbatim, and analyzed using thematic analysis to identify key themes related to the study's feasibility.

Analysis Plan for Feasibility Assessment (Aim 1)

The feasibility assessment will examine multiple quantitative metrics including EMA response rates, with a target of at least 70% completion, accelerometer wear time aiming for 5 or more valid days with more than 10 hours per day, and participant retention rates targeting 80% or higher. We will calculate descriptive statistics including means, SD, and 95% CIs for these metrics. In addition, we will assess patterns of missing data and examine whether compliance varies systematically by participant characteristics using logistic regression models.

Qualitative Analysis Approach

The qualitative analysis will follow the Braun and Clarke [45,46] reflexive thematic analysis framework, which emphasizes the active role of researchers in identifying patterns of meaning across the dataset. The analysis process will begin with data familiarization, during which 2 trained researchers will independently immerse themselves in the data through repeated reading of interview transcripts. This will be followed by systematic initial coding using NVivo (Lumivero) software, with researchers generating codes across the entire dataset and paying particular attention to data related to protocol feasibility and acceptability. The researchers will then develop themes by sorting codes into meaningful patterns and creating a preliminary thematic framework that captures key aspects of participants' experiences. These themes will undergo refinement through review in relation to both coded extracts and the full dataset to ensure they form coherent patterns and accurately represent the data. Clear definitions will be developed for each theme to identify the essence of what each captures about participants' experiences with the protocol. The final analysis will be synthesized into a coherent narrative, supported by illustrative quotes.

Ensuring Qualitative Rigor

To enhance the trustworthiness of our findings, we will implement several complementary strategies [45,47]. For credibility, we will use of investigator triangulation, with multiple researchers independently coding data and comparing interpretations, along with member checking conducted with a subset of participants to verify our interpretations reflect their experiences. To establish dependability, we will maintain a detailed audit trail documenting analytical decisions and theoretical development throughout the analysis process. Confirmability will be addressed through researchers' engagement in reflexive journaling to document their positionality and potential biases, with regular team meetings including discussions of how researchers' backgrounds and perspectives might influence interpretation. For transferability, we will provide rich, detailed descriptions of the study context and participant characteristics to allow readers to assess the applicability of findings to other settings.

Integration of Quantitative and Qualitative Findings

The mixed methods analysis will use a convergent parallel design where quantitative and qualitative data are analyzed separately and then merged to provide a comprehensive understanding of protocol feasibility [48]. Areas of convergence and divergence between quantitative metrics and qualitative experiences will be explicitly examined and discussed. This integrated analysis will inform decisions about protocol modifications and provide crucial insights for implementing these methods in larger-scale studies. The combination of rigorous quantitative metrics with rich qualitative insights will allow us to not only assess the technical feasibility of our protocol but also understand the lived experiences of participants engaging with these novel data collection methods [48].

Analysis Plan (Aim 2)

To address the challenge of integrating data collected at different frequencies and levels of analysis, a multistep data processing approach will be used. Initially, accelerometer and GPS data will be aligned using timestamp information, creating a continuous stream of location-tagged PA data. For each EMA prompt, a time window of more than 30 minutes will be established, extracting the corresponding accelerometer and GPS data. This window allows for the capture of PA and location information immediately before and after each self-report, providing context for the EMA responses. Social network data from the initial survey will be treated as a stable characteristic for each participant throughout the study period, with key network metrics (eg, network size and density) linked to each EMA prompt. To account for potential temporal dynamics in social networks, EMA items assessing momentary social context will be used to create time-varying indicators of social influence. The resulting dataset will be structured hierarchically, with EMA prompts nested within days, and nested within participants. This approach allows for the examination of associations between social network characteristics, built environment features, and PA at various temporal scales, from momentary fluctuations to day-level patterns, while accounting for the different data collection frequencies and levels of analysis.

The analysis plan for this study incorporates a range of statistical techniques to address the research aims and account for the complex, multilevel nature of the data. For aim 2, which seeks to identify within-day phenotypes, a multistep analytical approach will be used. Associations will be explored at the hour, day, and person levels to determine which temporal associations are strongest. First, intraclass correlation coefficients (ICCs) will be calculated to estimate the impact of clustering (occasions within days, days within individuals) [49]. DSEM will then be used to analyze the within-person time-series data, accounting for the intensive longitudinal nature of the data and examining the bi-directional effects of social and built environments and PA [19]. DSEM allows for the decomposition of variance in PA into within-person and between-person components, estimating autoregressive parameters and cross-lagged parameters. To identify phenotypes, within-person standardized model estimates from the DSEM model will be used in an individual-level cluster analysis, using Ward's Method with Euclidean distance for hierarchical agglomerative clustering [20]. Validity of the clusters will be assessed using ANOVAs and chi-squared tests to examine univariate differences between clusters in terms of PA. Sensitivity analyses will be conducted with varying clustering methods, item rescaling, and time points included to assess the robustness of the cluster profiling [50]. Throughout the analysis, considerations will be made for potential sex and age differences, with exploratory moderation tests conducted. Missing data will be handled using maximum likelihood estimation in the multilevel models. All analyses will be conducted using appropriate statistical software packages, with a significance level set at $P<.05$, adjusted for multiple comparisons where necessary using the Bonferroni correction.

Sample Size Justification and Power Analysis

Our sample size determination was guided by multiple considerations. For aim 1 (feasibility and acceptability), the planned sample size of 20 participants aligns with recommendations for feasibility studies [51]. We will recruit 20 participants in year 1 for initial protocol testing, followed by 2 cohorts of 50 participants each in years 2 and 3. This sample size will allow us to estimate compliance rates with a margin of error of ±9% (assuming 95% CIs), which is adequate for assessing protocol feasibility. For aim 2 (identifying phenotypes), we conducted power analyses using Monte Carlo simulations for DSEM. Based on these simulations, assuming moderate effect sizes ($\beta=0.3$) and ICCs of 0.2, a sample of 100 participants providing 42 observations each (6 prompts per day for 7 days) will provide 80% power to detect significant cross-lagged effects at $\alpha=.05$.

While the study is primarily powered for overall effects, we acknowledge limitations in detecting sex differences. Given our balanced recruitment by sex (50 participants per group), post-hoc power analyses indicate we would only be able to detect large effect size differences ($d>0.7$) between males and females with 80% power. However, previous research in youth PA suggests that while absolute activity levels may differ by sex, the underlying mechanisms of social and built environment influences are generally consistent across sexes [52]. Therefore, while we will explore potential sex differences as secondary analyses, our primary focus is on identifying overall patterns and phenotypes that can inform future intervention development.

Ethical Considerations

This study was approved by the institutional review board at Texas A&M University (STUDY2024-0473). The study will be performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments. All participants will be asked to provide assent to participate. In addition, guardian permission will also be required for all participants. Data will be deidentified using unique study IDs to protect participants privacy. Participants will receive compensation for their involvement, with a tiered incentive structure to encourage compliance. They will receive US $25 gift cards for the initial survey, return devices after the EMA protocol, and participate in qualitative interviews. An additional US $25 will be provided for meeting compliance benchmarks of at least 5 days of valid accelerometer data (more than 10 hours/day) and at least a 70% response rate for EMA prompts, for a potential total of US $100 throughout the study.

Results

The study received funding from the National Heart Lung and Blood Institute in May 2024. Data collection is expected to occur during the summers of 2025, 2026, and 2027. Findings are expected to be published in the fall of 2027.

Discussion

Principal Findings

This study will yield several important findings. First, regarding aim 1, we expect to demonstrate the feasibility and acceptability of combining EMA and SNA techniques to assess social and built environment influences on youth PA during summer. We also expect to identify potential challenges and areas for improvement in the protocol, which will be valuable for future studies using these methods. For aim 2, we anticipate identifying distinct phenotypes that represent different patterns of associations between social and built environment factors and PA. These phenotypes may reveal subgroups of youth who are more or less influenced by specific social or built environment characteristics. For example, we may find a subgroup for whom social network factors are particularly influential on PA, and another for whom built environment features play a more prominent role [7]. We expect these phenotypes to provide insights into the heterogeneity of environmental influences on youth PA, potentially informing more targeted and personalized intervention strategies.

Strengths

This study has several notable strengths. The combination of EMA and SNA techniques represents an innovative approach to capturing the dynamic interplay between social and built environments and youth PA. This method allows for the collection of rich, contextual data in real-time, reducing recall bias and capturing within-person variability [12]. The use of objective PA measures through accelerometry, coupled with GPS data, provides a comprehensive picture of youth PA

patterns and their environmental contexts [53]. In addition, the mixed-methods approach, incorporating both quantitative and qualitative data, allows for a more nuanced understanding of youth experiences and perceptions. The focus on the summer period addresses an important gap in the literature, as this is a time when youth PA patterns may differ significantly from the school year [8]. Finally, the application of advanced analytical techniques such as DSEM and phenotyping represents a cutting-edge approach to understanding the complex, individual-specific nature of environmental influences on PA [14,19].

Limitations

Despite its strengths, this study has limitations that should be acknowledged. The sample size, while appropriate for a feasibility study, may limit the generalizability of findings, particularly in the identification of phenotypes. The focus on a single geographic area may also limit generalizability to youth in other regions with different social and built environment characteristics. While our sample size is appropriate for our primary aims, we acknowledge limited power to detect sex differences in environmental influence patterns. However, existing literature suggests that fundamental mechanisms of social and built environment influences on physical activity are largely consistent across sexes during early adolescence, even though absolute activity levels may differ. Future larger-scale studies may be needed to fully explore potential sex-specific patterns in these relationships. The intensive nature of the EMA protocol, while providing rich data, may introduce participant burden and potentially affect compliance rates or typical behavior patterns. There is also a possibility of reactivity, where participants may alter their behavior due to awareness of being monitored. In addition, while the study captures a week of data for each participant, this may not represent typical summer PA patterns, which could vary over the course of the entire summer. Finally, while the combination of EMA and SNA provides detailed information on social networks and momentary social contexts, it may not capture all relevant aspects of social influence on PA. Similarly, the built environment measures, while comprehensive, may not account for all relevant features that influence youth PA.

Conclusions

This study represents an important step forward in understanding the complex interplay between social and built environments and youth PA during summer. By employing innovative methodologies and advanced analytical techniques, we expect to gain unprecedented insights into the dynamic, individual-specific nature of these relationships. The findings from this study have the potential to inform more targeted and effective interventions to promote PA among youth, particularly during the critical summer months. While limitations exist, they are outweighed by the strengths of this study's design and its focus on an understudied time period makes it a valuable contribution to the field. Future research can build upon these methods and findings to further elucidate the multifaceted influences on youth PA and develop strategies to promote active, healthy lifestyles among diverse youth populations.

Acknowledgments

The present study was supported by the National Heart, Lung, and Blood Institute under a K01 grant (K01HL169818).

Authors' Contributions

TP conceptualized the study, developed the methodology, and wrote the original draft of the manuscript. GD provided technical expertise on Ecological Momentary Assessment (EMA) methods and contributed to the study design and EMA protocol development. KdH offered expert guidance on Social Network Analysis (SNA) techniques, assisting with the social network measures and analysis plan. CL contributed expertise on spatial analysis, advising on the integration of GPS data and geospatial analysis of the built environment. KPP assisted with the overall study design and methodology. All authors reviewed and edited the manuscript, providing critical feedback and approving the final version for submission**.**

Conflicts of Interest

None declared.

Multimedia Appendix 1
Qualitative questions.
[PDF File (Adobe PDF File), 120 KB - resprot_v14i1e68667_app1.pdf]

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Abbreviations

DSEM: dynamic structural equation modeling
EMA: ecological momentary assessment
ICC: intraclass correlation coefficient
ILD: intensive longitudinal data
NEWS-Y: Neighborhood Environment Walkability Scale–Youth
PA: physical activity
SNA: social network analysis

Edited by A Schwartz; submitted 11.11.24; this is a non–peer-reviewed article;accepted 22.01.25; published 21.02.25.

Please cite as:
Prochnow T, Dunton GF, de la Haye K, Pollack Porter KM, Lee C
Combining Ecological Momentary Assessment and Social Network Analysis to Study Youth Physical Activity and Environmental Influences: Protocol for a Mixed Methods Feasibility Study
JMIR Res Protoc 2025;14:e68667
URL: https://www.researchprotocols.org/2025/1/e68667
doi:10.2196/68667
PMID:

Protocol

Contactless Breathing Monitoring at Home and in the Hospital: Protocol for a Low-Cost Frequency-Modulated Continuous-Wave Radar-Based Device

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Abstract

Background: Contactless monitoring of vital signs, especially the breathing of children, in the hospital is performed on a priority basis because their organs and immune system are immature. Therefore, continuous monitoring of their vital signs with a sensor that is directly attached to their body is not possible, as it irritates the sensitive newborn skin and causes discomfort. A contactless frequency-modulated continuous-wave (FMCW) radar-based device can wirelessly monitor the breathing rate and pattern of a child in the hospital or at home. Signal-processing capability can be added to this device to process breathing data and analyze the apnea condition arising due to irregular breathing patterns.

Objective: This study will develop a contactless FMCW radar-based system to accurately monitor the breathing rate and pattern of neonates and infants in hospitals and at home in order to provide a noninvasive, nonintrusive and contactless alternative to conventional sensor-based methods and address a critical need in neonatal care, potentially improving health outcomes for vulnerable infants.

Methods: The radar transmits a signal toward the body, and the time taken by the signal received to travel from the body to the receiving antenna is analyzed. This time is proportional to the distance between the radar and the body, and the breathing pattern is recognized as a slight, periodic variation in this distance. We will use this concept with multiple antenna systems to monitor the breathing of neonates with improved sensitivity. The radar-based device will be installed, in addition to conventional breathing monitors, in the neonatal intensive care unit. The signals received at the radar and the respiration signals from conventional monitors will be recorded in a database. Signal-processing techniques will be applied to extract breathing signals from the signals received at the radar.

Results: This study was funded in January 2023 by the Science and Engineering Research Board (SERB) of India. The device was designed by May 2024, and a working proof-of concept was verified in the Indian Institute of Technology (IIT) Ropar laboratory. Implementation of the proposed method for initial study began in December 2024. Results are expected to be published in the first quarter of 2025.

Conclusions: The contactless FMCW radar-based system will provide reliable estimation of the breathing rate and pattern, which is close to the conventional reference device values most of the time. Our device will also provide a seamless breathing-monitoring system to be used both in hospitals and at home for newborns and premature babies until they are fully healthy and fit.

International Registered Report Identifier (IRRID): PRR1-10.2196/59532

(JMIR Res Protoc 2025;14:e59532) doi:10.2196/59532

KEYWORDS

radar; contactless vital monitoring; breathing rate monitoring; vital signs; health monitoring

Introduction

In recent times, we have seen advancements in the medical sector, especially in health monitoring, by replacing conventional medical equipment with wireless equipment, which is convenient and accurate for usage. Such advancements have made some vital sign monitoring possible at the home of the patient/subject. As an advanced health-monitoring system, smart homes monitor not only temperature and the environment but also some critical vital signs [1]. Continuously monitoring the breathing rate benefits patient management by early detection of health deterioration and breathing irregularities, if any. For monitoring children and newborns, it is convenient if performed at home. Nearly 15 million infants born prematurely in the world every year need to be monitored until they are healthy and fit [2]. In these children, basic vital parameters, such as breathing, the heart rate, and oxygen saturation, are especially monitored. Initially, these parameters are monitored by a sensor that is directly attached to their body [3], which, however, causes skin irritation and may also lead to pressure necrosis. Regularly observing a patient's vital signs aids medical professionals in identifying early abnormalities and assessing the progression of an illness, as well as evaluating the effectiveness of a treatment method. Contactless monitoring of a patient's vital signs, minimizes inhibition, reduces the risk of infection, and eliminates any discomfort to their skin [4]. Radar is already a promising technology for wireless health parameter monitoring due to its low power, low cost, and security purposes. In this paper, an FMCW radar-based device [5] is proposed to investigate breathing patterns in infants in different scenarios. The device is intended to be used in the hospital or at home for monitoring purposes. Using the proposed design, we will eliminate the requirement of a cannula, which is usually attached to the patient's nose for flow-based breathing-monitoring purposes. Another method that is used as an alternative to interpolate normal breathing is a pulse oximeter, which is attached to the patient's finger for oxygen saturation measurement that correlates with normal/abnormal breathing. Such methods come with the requirement of one or the other kind of attachment to the patient's body, which might create irritation or discomfort for the patient. Thus, we will use a contactless monitoring device for breathing pattern/rate measurement. In this paper, the feasibility of radar technology as a possible means of continuously monitoring vital signs without physical contact will be studied. Radar means detecting an object and estimating its parameters based on its distance from the radar. Continuous-wave radar is used in the microwave range of the spectrum, which means transmit frequencies are within tens of gigahertz [6]. The contactless FMCW radar-based model is based on wireless technology, which includes radio frequency for the transmission of signals and reception after reflection so that direct contact with the patient is not needed, providing an advantage over conventional methods by monitoring health parameters remotely, which is suitable in emergencies and allows health care providers to assess the patient's condition without being physically present at that place.

In this study, we propose a device for contactless breathing rate monitoring. In particular, this device is targeted to be used for the contactless breathing monitoring of newborns to reduce discomfort and potential infection risks due to wired sensor devices by implementing a radar system that will be kept at some distance from the babies so that they do not face any problem during the monitoring of vital signs, especially the respiration rate. For this purpose, we will use the radar for measuring inhalation and exhalation through the outward or inward movement of the abdominal area. This will be monitored in the form of changes in the distance from the radar and the patient being monitored.

Methods

Study Setting

The proposed study will be jointly performed at the Indian Institute of Technology (IIT) Ropar and Government Medical College and Hospital (GMCH) Chandigarh. IIT Ropar is a technology education institute having ~2500 students [7]. The campus also accommodates the staff and faculty members in the on-campus residential facility. The device will be developed at IIT Ropar. The initial study will be conducted on healthy students of the institute who volunteer to be part of the study. The accuracy of the breathing pattern of a healthy human being will be verified. Next, healthy children of the staff and faculty members residing on campus will be enrolled after obtaining informed consent from their parents. Furthermore, a study will be conducted at GMCH Hospital's pediatrics department, which has an inpatient facility for all age groups, including newborn and premature neonates.

Study Design

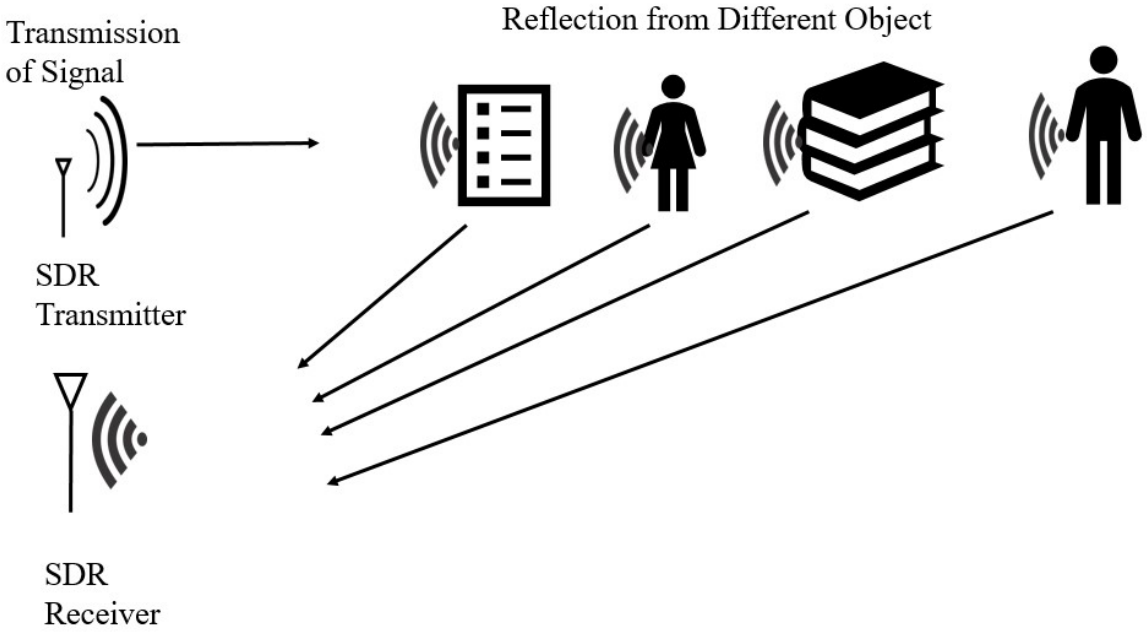
The proposed study is intended to prove the applicability of contactless methods for breathing rate monitoring in neonates. Further, this study will be useful in the detection and management of apnea conditions due to irregularity in breathing patterns. The primary objectives of the study are as follows:

- Designing a device for noncontact breathing rate monitoring using the FMCW radar principle, which transmits a signal with the frequency varying linearly with time. When this signal reflects off an infant's chest, the received signal has a frequency difference (beat frequency) from the transmitted signal. This frequency difference is proportional to the minute movements caused by breathing. Thus, the beat frequency carries information of the breathing pattern. In addition to the breathing pattern, some unwanted reflected components from multiple objects around the patient being monitored are contained in the radar signal, as illustrated in Figure 1. The primary objective is to design algorithms to suppress the effect of reflections from stationary objects.
- Identifying specific signal fluctuations related to the breathing of the patient being monitored and distinguishing these variations from other persons in the room or other body movements, such as those of limbs. Breathing is

periodic, so the beat frequency variation is also periodic. Variation due to limb movements and other people is large and aperiodic. Therefore, signal processing techniques, including filtering, can be used to minimize the effects of unwanted reflections and movements.

- Further extending this setup to analyze breathing signals of multiple persons and separating them.

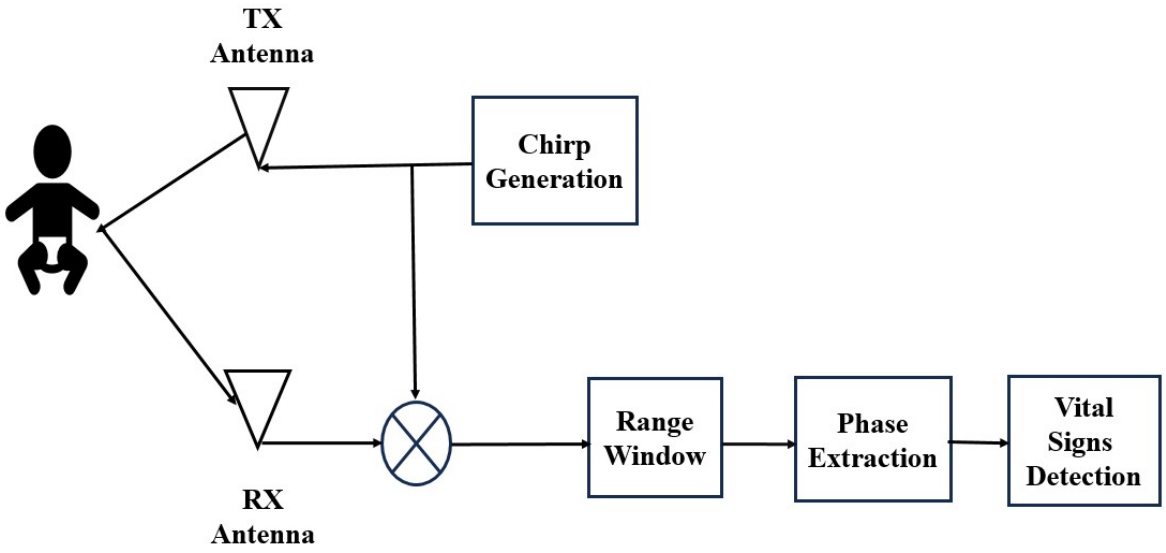
Figure 1. Separating different objects based on reflection. SDR: software-defined radio.



Prototype and Implementation

The main objective of the model is to monitor the breathing of premature and newborn babies without any contact with their bodies. The proposed monitoring device is contactless. Therefore, it will not cause skin injury, irritation, allergy, or infection. Device accuracy is targeted to be more than 90% in all scenarios and more than 98% in a controlled setup [1]. The controlled setup is defined as a laboratory environment or the target patient being instructed to restrict any movement of body parts. This model combines the development of hardware and software, in addition to the testing protocol for the breathing rate. The software contains signal-processing algorithms to clean the received signal after reflection from the target and the other objects or persons in the vicinity, as shown in Figure 2. The waveform is designed and generated to be sent toward the patient being monitored using a software-defined radio (SDR) transmitter [8,9]. The same SDR is used to receive the reflected signal. The broadcast signal is reflected and received with a time delay due to the distance propagated between the device and the target patient. The difference in frequency between the transmitted and received signals, which determines the beat frequency, provides distance information. The distance varies with the state of breathing, such as inhalation results in reduced distance and exhalation results in increased distance due to expansion and contraction of the chest and abdominal region of the patient. The reflected signal's components are reflected from the patient and nearby objects. The reflected signal received at the SDR receiver is converted back to the baseband after dechirping. The dechirped signal is processed further in a general-purpose computer to extract the required breathing signal by mitigating the effects of the reflections from objects other than the patient being monitored. This requires passing the signal through a low-pass filter to obtain the frequency of interest (ie, to retain frequency components that are within the range of the breathing rate). We will also implement the algorithms to separate the reflection from different objects based on their reflection time so that the objects at different distances are separated. Wireless signals travel at the speed of light. Separating these reflections eliminates them from static objects, as their reflections do not change over time [8].

Figure 2. System model design. RX: receiving; TX: transmission.



FMCW Radar and Study Measurement

Effective contactless monitoring of each baby in the hospital was initiated after stability criteria were met, such as respiratory status without serious illness. FMCW radar monitoring is performed continuously during the monitoring period [10]. The benefit of this device is that it can be used in hospitals and homes both. Many times, it is only necessary to monitor the breathing, which can be performed at home with the proposed device without admitting the child to the hospital. For the proposed study and initial trial, the infants will be observed with their chest facing the radar at a distance of roughly 1-1.5 m from the low-vibration tripod to which the radar is attached. A research assistant will track each infant's vital signs for 10 minutes, 3 times a day. The effectiveness of the radar-based breathing rate–monitoring device will be evaluated by comparing the device's measurements with clinical recordings.

Sample Size and Data Analysis

A sample of 20-30 premature newborn babies will be included in the study. Data collection will be performed with the help of the neonatology department at GMCH Chandigarh. The radar-based device will be installed, in addition to conventional breathing monitors, in the neonatal intensive care unit. The signals received at the radar and the respiration signals from the conventional monitors will be recorded in a database. An in-depth analysis of radar signals received from each infant will be carried out. All the factors critical for understanding the complexities of the premature newborn condition and care will be observed, providing the diversity and depth of experience necessary for such research [11]. The main idea is to investigate different effects of collecting radar data from the chest and abdominal region, removing the effect of any interference or movements and reflections from the surroundings. Further analysis and algorithm development will be carried out to extract breathing signals when each infant is with the mother. If monitoring of twins is possible, a minimum safe distance will be required to mitigate the radar interface between them. The basic principle that will guide the data collection protocol will ensure seamless operation at GMCH Chandigarh.

Ethical Considerations

The study was approved by GMCH Chandigarh and the Government of India. Informed consent will be obtained from parents. They will be informed about the purpose of the experiment, the procedure, and benefits. We will ensure that they do not face any type of harm and that they voluntarily agree to participate. Data confidentiality will be ensured, and participants' identities will be protected. Ethical approval (approval number GMCH/IEC/2022/730) was obtained from the GMCH Chandigarh Institutional Review Board (IRB) or Ethics Committee to ensure that the study meets ethical standards and that participants are protected from potential harm.

Results

Data collection and implementation of the proposed device was performed with the help of IIT Ropar and GMCH Chandigarh. The study was funded in January 2023 by the Science and Engineering Research Board (SERB) of India. The device was designed by May 2024, and a working proof-of concept was verified in the IIT Ropar laboratory. Implementation started in December 2024. Initially, we will apply this method to monitor a single child, and then, this study will be extended to monitor multiple infants by modifying the device design and signal-processing algorithms. The main outcome of the proposed method is to obtain breathing patterns of infants at home and in hospitals to predict their health condition based on the breathing patterns. We expect to obtain the results of monitoring a single child by the end of the first quarter of 2025.

Discussion

Summary

The proposed study will develop a device for accurate noncontact monitoring of the breathing rate and patterns of neonates and infants in the hospital and at home using an FMCW radar-based system. The working principle of the device is based on capturing, using radar, the pattern of movements in the chest and abdominal region due to inhalation and exhalation. This

will address the critical need for noninvasive and noncontact continuous respiration monitoring in clinical settings. With the system being noncontact and portable, it can also be used at home to monitor the patient's condition. Unlike wearable devices that may be affected by environmental factors and require direct contact, the proposed system offers a significant advantage over conventional chest-mounted devices that may cause discomfort and privacy concerns. The typical range for an infant's respiratory rate is between 40 and 60 breaths per minute [12]. A breathing rate outside this range indicates that the patient is not healthy. Through the usage of the proposed technology, we plan to demonstrate high accuracy in identifying respiratory irregularities, such as apnea, aligning with the study's objective to enhance neonatal care. Contactless radar systems [13-17] have been proven to be a more convenient option for users compared to wearable devices due to immunity to environmental constraints, wider coverage, the absence of privacy concerns, and importance for heavy-burned and newborn babies, enhancing usability. The ability to detect vital signs, particularly the breathing rate, is typically required to identify human presence in short-range environments. However, the system's accuracy may be affected by movement artifacts, physical abstraction, clothing, cobedding, and positioning. Other constraints related to the proposed method are a trade-off between range and resolution due to bandwidth constraints, and further validation in diverse clinical settings is required. Despite these limitations, the signal-processing techniques will be used to improve the performance and bring about significant advancements in neonatal respiratory care, with broader implications for improving patient care and monitoring in various clinical and home settings. Once the designed device is developed, it will be tested in the neonatology department of GMCH Chandigarh, where breathing rate monitoring will be compared with conventional methods. We will have a database of signals received at the proposed device and those from conventional devices. This database can be used to test various algorithms. Future research will focus on refining the device's accuracy and expanding its applicability to a wider range of patients and conditions. The device design can be modulated to monitor multiple individuals through use of multiple antennas and advanced signal-processing techniques.

Conclusion

An FMCW device can measure submillimeter-range shifts because of its improved precision in measuring displacements. Breathing using an FMCW radar-based device [18-20] is useful for pathologies that are difficult to detect solely with the use of an electrocardiogram (ECG). FMCW devices are cheap and easy to operate. Our model will also have the advantage of better resolution compared to other radar-based model designs and will be based on radio frequency signals from a radar to detect the patient's position and extract respiration data [21-23]. With the help of this system, we can detect the breathing of patients within the range of up to 45 cm and possibly improve spatial resolution and range with additional radar and antenna units.

Acknowledgments

We thank the Indian Institute of Technology Ropar (IIT Ropar) and Government Medical College and Hospital (GMCH) Chandigarh for their help and assistance with data collection. The study was funded by the Science and Engineering Research Board (SERB; grant number SCP/2022/000464).

Data Availability

The data from this trial will be accessible to the public and research community. The research team will decide on the dissemination method once the trial ends and our results are published. Although the data will not be made immediately public, they can be requested from the corresponding author.

Authors' Contributions

All authors have read and approved the final version of the manuscript.

Conflicts of Interest

None declared.

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Abbreviations

FMCW: frequency-modulated continuous-wave
GMCH: Government Medical College and Hospital.

IIT: Indian Institute of Technology
SDR: software-defined radio.

Edited by T Leung; submitted 15.04.24; this is a non–peer-reviewed article;accepted 18.07.24; published 25.02.25.

Please cite as:
Hari A, Kumar R, Kumbhani B, Darshi S, Agarwal S, Sahambi JS, Jain S, Chawla D
Contactless Breathing Monitoring at Home and in the Hospital: Protocol for a Low-Cost Frequency-Modulated Continuous-Wave Radar-Based Device
JMIR Res Protoc 2025;14:e59532
URL: https://www.researchprotocols.org/2025/1/e59532
doi:10.2196/59532
PMID:

Protocol

Codevelopment of an mHealth App With Health Care Providers, Digital Health Experts, Community Partners, and Families for Childhood Obesity Management: Protocol for a Co-Design Process

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Abstract

Background: Childhood obesity is increasing in Singapore, with most cases persisting into adulthood and leading to poor health outcomes. The current evidence for childhood obesity interventions shows a clear dose-response effect, where effectiveness improves with an increasing number of treatment hours. A minimum threshold of ≥26 hours over a 2- to 12-month period is required to achieve significant outcomes. The Kick Start Move Smart program is the first online community-based multidisciplinary program to treat pediatric obesity in Singapore. It has demonstrated feasibility and acceptability, with 70% of participants completing the recommended ≥26 hours of intervention. Preliminary data show significantly lower BMI and improved quality of life in participants compared to controls. Successful families are positive outliers who developed strategies for health in the context of an obesogenic environment. This positive outlier approach indicates that solutions to challenges that a community faces exist within certain individual members, and these strategies can be generalized and promoted to improve the health of others in the same community. A mobile health (mHealth) app targeting parents is a critical missing link in the currently available interventions to support parental self-management of childhood obesity. Using a combination of behavioral theory and user-centered design approaches is important for designing mHealth apps. One recommended framework is Integrate, Design, Assess, and Share (IDEAS), which aims to facilitate the development of more effective interventions by engaging perspectives from different stakeholders.

Objective: This study aims to (1) describe the co-design protocol of an mHealth app using the IDEAS framework as a low-intensity intervention or as an adjunct to more intensive existing pediatric obesity interventions and (2) assess the usability, acceptability, and engagement of the app by parents.

Methods: A clinician-led co-design approach will be undertaken with a multidisciplinary team using the IDEAS framework. Phase 1 involves stakeholder engagement and the formation of a core committee and a parent advisory board. Phase 2 involves developing the app content through focus group and expert panel discussions. Phase 3 involves developing a prototype app and gathering feedback. Phase 4 involves piloting the minimum viable product by parent users and evaluating its effectiveness through interviews and questionnaires.

Results: In April 2023, a parent advisory board was formed, and stakeholders were engaged as part of phase 1. Phases 2 and 3 were completed in June 2024. Focus group discussions were held with the parent advisory board and stakeholders to identify family strategies and patient-centric outcomes and provide feedback on the app. As of January 2025, the app is complete, and

we are now in the middle of data collection from participants. Participants will provide feedback to the research team, and the app will be updated accordingly.

Conclusions: An evidence-based, theory-driven mHealth app developed using a structured design framework can bridge the gap in delivering multidisciplinary care in community settings for families with overweight children.

International Registered Report Identifier (IRRID): DERR1-10.2196/59238

(JMIR Res Protoc 2025;14:e59238) doi:10.2196/59238

KEYWORDS

childhood obesity; mHealth; mobile health; co-design; IDEAS framework

Introduction

Childhood obesity rates are rising in Singapore, with most cases persisting into adulthood and leading to adverse long-term psychosocial and health effects. A recent systematic review and meta-analysis highlighted the importance of access to multidisciplinary interventions for children with obesity. The current evidence for childhood obesity interventions shows a clear dose-response relationship, where effectiveness improves with an increasing number of treatment hours. A minimum threshold of ≥26 hours over a 2- to 12-month period is required to achieve significant outcomes [1]. The Kick Start Move Smart (KSMS) program is the first online community-based program to treat pediatric obesity in Singapore. The pilot evaluation has demonstrated feasibility and acceptability, with 70% of the participants completing the recommended ≥26 hours of intervention. Preliminary data on the effectiveness of the program show significantly lower BMI scores and improved quality of life in program participants compared to the control group. Families who achieved the recommended treatment hours in the program also demonstrated improvements in their child's quality of life, health behaviors (such as increased intake of fruits and vegetables), and BMI. Successful families are positive outliers who developed strategies for health in the context of an obesogenic environment. The theoretical underpinning of the positive outlier approach is that solutions to problems a community faces often exist among certain individuals and that these successful strategies can be generalized and promoted to improve the outcomes of others in the same community [2]. Typically, there is a high degree of heterogeneity in response to lifestyle interventions in pediatric obesity treatment; thus, adopting the positive outlier approach can facilitate the best solutions to support families.

An evidence-based, theory-driven mobile health (mHealth) app that targets parents is a critical missing link in currently available interventions to support parental self-management of childhood obesity [3]. While there has been a rapid growth of mHealth apps to support chronic disease management, achieving meaningful health improvements through the use of mHealth apps remains elusive. Combining approaches from behavioral theory and user-centered design to guide intervention development, coupled with rigorous approaches for evaluation and dissemination, is important to achieve the full potential of mHealth apps. Integrate, Design, Assess, and Share (IDEAS) is one recommended framework, which aims to facilitate the development and dissemination of more effective interventions by engaging the perspectives of different stakeholders [4]. This framework builds on design thinking and integrates user insights throughout the stages of development and the inclusion of theory-driven behavioral strategies.

We hypothesize that codevelopment with health care providers, digital health experts, and successful families to create a high-quality mHealth app for childhood obesity can increase its acceptability and engagement from families. First, we aim to co-design an mHealth app with health care providers, digital health experts, community partners, and successful families using the IDEAS framework. The app will be evidence-based and theory-driven and consist of three core components: (1) consolidation of positive outlier strategies and development of patient-centric outcomes for self-monitoring, (2) synthesis of evidence-based guidelines and integration of theory for behavioral strategies, and (3) incorporation of community resources and integration with community programs. The mobile app is designed to be used independently as a low-intensity intervention or as an adjunct to more intensive existing pediatric obesity interventions to increase overall engagement and effectiveness. Second, we aim to assess the usability, acceptability, and engagement of the mHealth app by parents in the pilot testing phase. Specifically, the usability and acceptability of the mHealth app will be assessed using the validated Mobile App Rating Scale (uMARS) [5] and by self-monitoring of patient-centric outcome measures as determined in the primary aim.

Methods

Overview

A clinician-led co-design approach will be undertaken with a multidisciplinary team of researchers, parents of children with obesity, community stakeholders, and digital health experts using the IDEAS framework [4]. The experience-based co-design principle will be followed to design the mHealth app, including gathering stakeholders to participate in the design process and developing a set of feasible care paths by sharing their experiences [6]. Based on the IDEAS framework and co-design principles, 4 iterative phases for the prototype mHealth app have been developed, which are summarized in Table 1.

Table 1. Phases of the project and their estimated timelines.

Phase	Activities	Duration	Stakeholders (n=21)
1	• Stakeholder engagement • Forming the parent advisory board	• 4 months	• Multidisciplinary health care providers (10/21, 48%) • Parent advisory board (5/21, 24%) • Community stakeholders from Sport Singapore and Health Promotion Board (4/21, 19%) • Digital health experts and app developers (2/21, 10%)

2	• Developing content
	  • Patient-centric outcomes that are clinically relevant
	  • Successful positive outlier strategies
	  • Integration with community resources
	  • Implementation of the app in daily lives
		• 6 months	• Multidiscpilinary health care providers
			• Parent advisory board
			• Community stakeholders

3	• Sharing proposed contents and features based on results from phase 2 and revisions • Sharing prototype app	• 6 months	• Multidiscpilinary health care providers • Parent advisory board • Community stakeholders • Digital health experts and app developers
4	• Evaluating and refining the MVP[a] to assess usability and acceptability and improvement of the app functions	• 9 months	• Parents of children with obesity • Digital health experts and app developers

[a]MVP: minimum viable product.

Ethical Considerations

Ethical approval has been sought from the SingHealth Centralized Institutional Review Board (2022/2035).

Phase 1: Stakeholder Engagement and Formation of the Core Committee and Parent Advisory Board

Stakeholder Engagement

The multidisciplinary team of health care providers will consist of pediatricians, dietitians, nurses, physiotherapists, exercise physiologists, psychologists, and social and medical workers with expertise in childhood obesity, who provide their clinical input in the co-design process. Digital health experts and app developers will also advise on the feasibility of the mHealth app's requirements and involve the vendor at appropriate time points to effectively transform the information into system requirements and design considerations to achieve an optimal design solution. The app's privacy and security features and compliance with the Personal Data Protection Act will also be considered. These features have emerged as fundamental from both clinical and patient perspectives in an evaluation of an mHealth app [7].

Parent Advisory Board to Learn From Positive Outliers

Patient advisory committees have been used in numerous co-design approaches to obtain patient input on a variety of health care processes. This ensures that the posed research questions and selected outcome measures are relevant and important to patients [8]. In this project, we will convene a parent advisory board to inform the mHealth app development. The parent board will consist of at least 5 parents who previously participated in the KSMS pilot study and successfully attended at least 26 hours of the program. The parent advisory board will be part of 2 focus group discussions in phase 2 and 1 focus group discussion in phase 3 of this project.

Formation of the Core Committee

Given the networked nature of the project, which includes the multidisciplinary team, community stakeholders, digital health experts, app developers, and a university partner, the core committee is critical for the project's success. It builds off our 2 years of experience working with multiple stakeholders across institutions for the KSMS program. The core committee will be chaired by the principal investigator with 2 members from the multidisciplinary team, 2 members from community stakeholders, 1 member from the digital health expert team, 1 member from the parent advisory board, 1 member from the partner university, and 1 clinical research coordinator. At defined intervals (intended to be one per quarter and as required), the core committee will meet by teleconference to review the strategic course and resource allocations. The clinical research coordinator, who is also the project coordinator for KSMS, serves as the lead administrator. The core committee is responsible for initiating and reviewing overall project progress and undertaking operational decisions to ensure that the project goals are aligned. This committee plays a vital role in the mHealth app's successful implementation into clinical practice and in ensuring the project's sustainability.

Phase 2: Development of the mHealth App's Contents

Overview

In phase 2, we plan to conduct 2 focus groups with the parent advisory board (5/21, 24%), 1 focus group discussion with community stakeholders (4/21, 19%), and 2 expert panel discussions with the multidisciplinary health care team (10/21,

48%) to develop the 3 main components of the mHealth app, as detailed in the subsequent sections.

Consolidating Contextually Tailored Positive Outlier Strategies and Developing Patient-Centric Outcomes for Self-Monitoring

The 2 focus group discussions with the parent advisory board will identify practices that facilitated their engagement in the intervention and change in health behaviors as well as highlight outcomes that matter most to their families in relation to weight management. These successful positive outlier strategies will be generalized and incorporated into the app with the aim of improving other families' outcomes. Patient-centric outcomes will be incorporated as part of the self-monitored outcome measures for parents. Parents will also provide input on integrating the app into their daily lives. Parents' detailed input on activity and nutrition suggestions will be used to make these recommendations actionable and tailored contextually (eg, based on time and day of the week), increasing the effectiveness of "push" notifications and suggestions.

Synthesizing Evidence-Based Guidelines and Integrating Theory for Behavioral Strategies

The multidisciplinary team of health care providers will consist of pediatricians, dietitians, nurses, physiotherapists, exercise physiologists, psychologists, and social workers trained in pediatric obesity management. Focus groups with the multidisciplinary team will consolidate practices and incorporate evidence-based strategies, guided by expert committee recommendations for pediatric obesity prevention and Singapore's Integrated 24-Hour Activity Guidelines for Early Childhood (0-6 years) [9]. The multidisciplinary team will also review strategies from parent advisory board focus groups and evidence-based guidelines to select optimal theory-driven behavioral strategies for guiding the mHealth app design [10]. Incorporating motivational interviewing (MI) in health care settings has been shown to improve intervention engagement and commitment to the behavioral change process [11]. MI is a person-centered counseling method that supports individual autonomy and uses collaborative and nonauthoritarian interaction to work toward an individual's goal.

Incorporation of Community Resources and Integration With Community Programs

The focus group with community stakeholders aims to integrate currently available community resources (web-based and physical) that are relevant to the target population, such as community-based sports programs designed for families.

Phase 3: Development of the Prototype App

The results of phase 2 will be shared with digital health experts and app developers to outline the required app features and guide the development of multiple prototypes. Studies have shown that developing multiple prototypes in parallel (versus sequentially) leads to a superior final prototype [12]. The prototype will be developed in regulated phases before being shared with the parent advisory board, multidisciplinary team, and community stakeholders to gather their feedback through 3 separate focus groups (one for each stakeholder). The feedback obtained will include user experience, visual design, content, and logic (such as a graphical representation of families' data). Feedback will be gathered from the clinical team on the integration of the app into clinical workflows, its prescription to families, and the visualization of intervention-related data. The digital health experts and app developers will then review the feedback for integration into the prototype app before a final minimum viable product (MVP) is published.

Phase 4: Piloting the MVP and Evaluation

A fully functional MVP will be developed to focus on details beyond the prototype phase. The MVP will be pilot-tested by 10 parents for 4 weeks to detect usability issues before the final prototype is developed. Parents of children aged 4 to 7 years old with obesity will be recruited from outpatient clinics. A sample size of 10 participants in think-aloud studies has been shown to detect 80% of usability issues [13]. At the start of the pilot testing, think-aloud walkthrough interviews will be conducted. Participants will be instructed to use the app as they would any newly downloaded app, verbalizing their thoughts throughout the process. They will be encouraged to freely explore the app and ask questions to provide insights into their user experiences. Following the walkthrough interviews, participants will be asked to use the app for 4 weeks.

At the end of the 4-week period, semistructured interviews and the uMARS questionnaire will be administered. The interviews will consist of open-ended questions on participants' previous experience with mobile apps, general perceptions of the app, its most/least useful features, suggestions for improvement and usage, possible features that could exclude potential users, and factors related to engagement. Inputs on the push notifications will be obtained from parents to optimize their timing and delivery to target behavior change.

Analytics will be integrated into the app to collect a rich dataset, capturing patterns of use, particularly in relation to accessing information and completing patient-centric outcomes as defined in our secondary aims. The usability and acceptability of the mHealth app's "pull" features (educational materials and graphical representations of monitored outcomes) will be evaluated using uMARS, a 20-item measure that includes 4 objective quality subscales (engagement, functionality, aesthetics, and information quality), 1 subjective quality subscale, and 1 perceived impact scale, all measured on a 5-point Likert scale. A score of 4 and above indicates good quality [5].

High usability and acceptability will be defined as a median score of 4 out of 5 in all domains (information, engagement, functionality, aesthetics, impact, and acceptability) for parents. The user engagement aims will be defined as (1) recruited parents accessing ≥70% of the information and (2) completing patient-reported outcome measures over the 4-week period.

Results

This study received funding in February 2023. As part of phase 1, a parent advisory board was formed in March 2023 with parents who had previously participated in the KSMS pilot study and completed at least 26 hours of the program. Stakeholders were engaged in April 2023 to co-develop the mHealth app.

Stakeholders included the multidisciplinary health care team from KK Women's and Children's Hospital, the Health Promotion Board (HPB), and Sport Singapore. Digital health experts and app developers from the National University of Singapore School of Computing were also involved in developing the mHealth app.

Phase 2 was completed between April 2023 and December 2023. The first focus group discussion with the parent advisory board was held in April 2023 to identify positive outlier strategies. A preliminary mock-up app was developed and shared in focus group discussions for feedback with community stakeholders (HPB and Sport Singapore) in May 2023, followed by the multidisciplinary team in July 2023. Discussions were held with community stakeholders between June 2023 and December 2023 to integrate existing community resources and programs into the mHealth app. A second round of individual interviews with the parent advisory board was conducted in October 2023 to identify patient-centric outcomes and review the mock-up app.

Revisions were made to the mHealth app following feedback from the stakeholders and parent advisory board. Focus group discussions and individual interviews were conducted in phase 3 to obtain feedback on the revised mock-up app with stakeholders and the parent advisory board, completed between April and June 2024.

The final stage of the mHealth app development was completed in December 2024 with an MVP app. Participants were recruited to pilot-test the mHealth app and provide feedback from January 2025. Recruitment will resume in April 2025, and feedback will be collected from the participants to enhance the mHealth app.

Discussion

Expected Findings

This study outlines the co-design process of an mHealth app with health care providers, digital health experts, community partners, and families, using the IDEAS framework. We hypothesize that the app, developed through the IDEAS framework, will be usable, acceptable, and engaging for parents in managing childhood obesity.

Patient advisory committees have become increasingly important in health care, offering valuable insights into various health conditions [14]. Engaging parents as active participants in the design of this app is important to ensure that the strategies recommended for other parents will be relevant and meaningful. For patient-centric outcomes, we anticipate focusing on themes related to psychosocial wellness, as seen in other studies [15], especially considering the lower quality of life among Singaporean children with obesity [16].

Some successful positive outlier strategies identified in a United States–based study [15] include (1) making family-centric changes in health behaviors rather than child-centric changes, (2) establishing rules around health behaviors, (3) shared decision-making with health care providers on child weight management, and (4) using community resources for behavioral change. We anticipate some common themes among our local population, especially around family-centric changes, rule implementation on behavior change, and the use of immediate outcomes, which align with findings from our previous study [17]. However, strategies like shared decision-making with health care providers and the use of community resources are less likely to emerge as important themes. This is because obesity is commonly perceived as a lifestyle factor, rather than a chronic disease, with treatment not claimable under private or public health care insurance [18]. These factors may hinder help-seeking for obesity treatment and pose challenges in developing community programs for childhood obesity management. Thus, the development of this mHealth app aims to bridge the gap in available resources for managing childhood obesity.

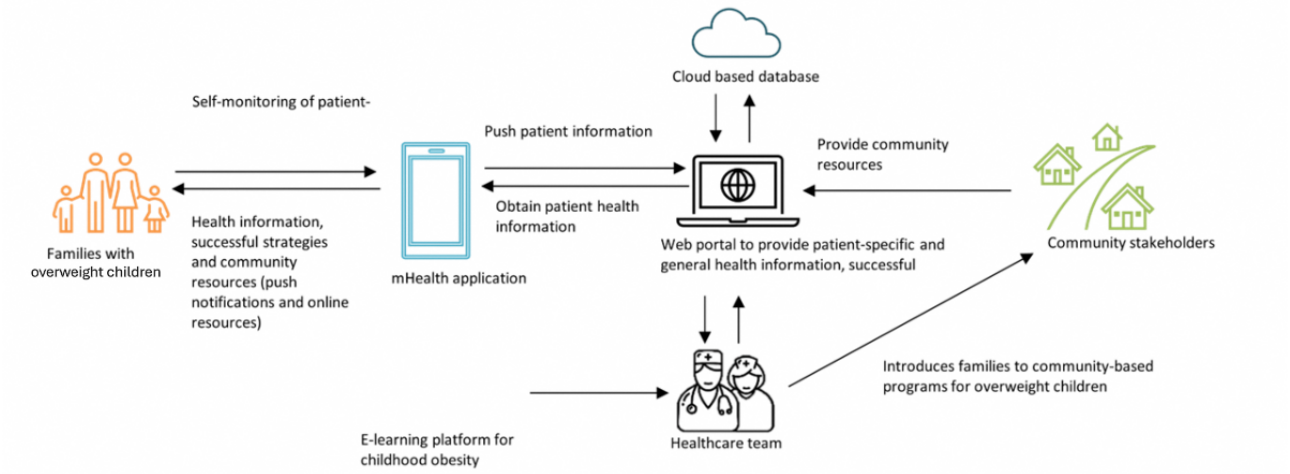
Despite research showing that parents are an integral part of pediatric obesity prevention and treatment, the currently available apps do not target parents or families but focus solely on the child. A review of mHealth apps for pediatric obesity prevention and treatment also found that most apps lacked any expert recommendations. mHealth apps have also been found to lack a theoretical basis for their development, thereby limiting their efficacy [19]. There is currently no mHealth app that integrates the strategies learned from positive outlier families with locally available community resources. Thus, this project will be the first theory- and evidence-informed mHealth app for pediatric obesity management targeted toward parents. The successful development of this mHealth app, through the use of the IDEAS framework, will also provide important information for the future development of mHealth apps for other chronic diseases, such as diabetes mellitus, to facilitate behavioral change and improve patient outcomes.

Currently, primary care providers and patients can only access pediatricians, dietitians, physiotherapists, and exercise physiologists trained in pediatric obesity management when they are referred to tertiary pediatric centers. This reliance on specialized centers can result in these services becoming overwhelmed. An mHealth app that is evidence-based, theory-driven, and developed within a design framework, can bridge this gap in providing multidisciplinary care in the community setting. Health care providers in both tertiary and primary care often face significant time constraints during consultations. Engaging these health care providers in the app's development and evaluation process can enhance its usability and acceptability, enabling its incorporation into clinical care processes.

The proposed mHealth app will thus provide the foundation for accessible multidisciplinary care in the community, scaling up the KSMS program to provide evidence-based treatment to every family with overweight children. This approach aims to help reduce complications associated with obesity.

By evaluating the potential effectiveness of these multimodal complex interventions (Figure 1) in reducing childhood obesity, improving quality of life, and reducing health care visits, this study could provide cost-effectiveness data to support informed decisions for nationwide implementation.

Figure 1. Proposed mechanism of the mobile health (mHealth) app and its future integration into health care settings, health care provider training, and community programs.



Strengths and Limitations

The key strengths of this study include the co-design approach with a multidisciplinary team and parents, as well as the development of an evidence-based, theory-driven mHealth app. These elements are critical for ensuring effective digital interventions that promote behavior change in childhood obesity management.

However, this study has limitations. Nonresponder bias may arise, as responses from participants not identified as positive outliers are not captured. Additionally, the effectiveness of the mHealth app compared to standard care is being assessed in this study.

Conclusions

An evidence-based, theory-driven mHealth app developed within a structured design framework can bridge the gap in providing multidisciplinary care for families with overweight children in the community setting. This app will also empower families to improve self-management of childhood obesity. Future studies are required to examine the effectiveness of this mHealth app in managing childhood obesity and promoting better self-management compared to standard care.

Acknowledgments

This study received funding from the Agency for Science, Technology, and Research in Singapore through the FY 21 Prenatal/Early Childhood Grant Call (H22P0M0010). We thank Prof Hock Hai Teo for his role in critically reviewing and revising the manuscript.

Data Availability

Data sharing is not applicable to this article as no datasets have been generated or analyzed during this study.

Authors' Contributions

SHT drafted, critically reviewed, and revised the manuscript. KBK, CD, ZQO, and EJKL critically reviewed and revised the manuscript. CSEC conceptualized and designed the study and critically reviewed and revised the manuscript. All authors have approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer-review report by the Human Potential Prenatal / Early Childhood Grant Office Agency for Science, Technology, and Research (Singapore).
[PDF File (Adobe PDF File), 179 KB - resprot_v14i1e59238_app1.pdf]

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Abbreviations

HPB: Health Promotion Board
IDEAS: Integrate, Design, Assess, and Share
KSMS: Kick Start Move Smart
mHealth: mobile health
MI: motivational interviewing
MVP: minimum viable product
uMARS: Mobile App Rating Scale

Edited by T Leung; submitted 28.06.24; this is a non–peer-reviewed article;accepted 11.08.24; published 05.03.25.

Please cite as:
Toh SH, Davis C, Bte Khaider K, Ong ZQ, Lim EJK, Chew CSE
Codevelopment of an mHealth App With Health Care Providers, Digital Health Experts, Community Partners, and Families for Childhood Obesity Management: Protocol for a Co-Design Process
JMIR Res Protoc 2025;14:e59238
URL: https://www.researchprotocols.org/2025/1/e59238
doi:10.2196/59238
PMID:40053786

Protocol

Community-Based 4-Level Intervention Targeting Depression and Suicidal Behavior in Europe: Protocol for an Implementation Project

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Abstract

Background: The community-based, 4-level intervention of the European Alliance Against Depression (EAAD) is simultaneously addressing depression and suicidal behavior. Intervention activities target primary care health professionals (level 1), the general public (level 2), community facilitators (level 3), and patients and their relatives (level 4). Activities comprise the digital iFightDepression tool, a guided self-management tool based on cognitive behavioral therapy.

Objective: This study aimed to present the European Union–cofunded EAAD-Best study protocol, aiming at the implementation, dissemination, and evaluation of the 4-level intervention and the iFightDepression tool in several countries across Europe.

Methods: The 4-level intervention has been implemented for the first time in Bulgaria, Estonia, Greece, and Poland. In 3 countries that have already implemented the 4-level intervention (Hungary, Ireland, and Spain), activities have been extended to new regions. In addition, the nationwide uptake of the iFightDepression tool by patients with depression has been promoted in all mentioned countries and Italy.

Results: To evaluate the implementation of the 4-level intervention and the iFightDepression tool, data related to the process, output, and outcome were collected between 2022 and 2024. Data processing and analyses started in 2023. Analyses are expected to be completed in 2024. Results are expected to be published in 2025.

Conclusions: This paper informs researchers, practitioners, and stakeholders on how to implement best practices in mental health promotion and evaluate their effectiveness.

International Registered Report Identifier (IRRID): DERR1-10.2196/64218

(JMIR Res Protoc 2025;14:e64218) doi:10.2196/64218

KEYWORDS

depression; suicide; mental health; European Alliance Against Depression; EAAD; 4-level community-based intervention; iFightDepression; cognitive behavioral therapy; mHealth

Introduction

Depression is one of the most prevalent, severe, and undertreated mental disorders [1]. Having a diagnosis of depression is associated with a reduction in life expectancy of around 10 years or more [2]. Contributing to this is the fact that depression increases the risk of another important mental health issue—suicidal behavior [3]. Approximately 703,000 people die by suicide every year [4] and the number of attempted suicides is considerably higher and rising [5]. The vast majority of completed suicides occur in the context of depressive disorders and other mental illnesses [2].

Due to the numerous factors contributing to suicidal acts, the best approach to address suicidal behavior is multifaceted interventions [6] that have been shown to be most effective [7]. Such multilevel intervention programs have been developed in different countries and either focus exclusively on suicidal behavior or simultaneously aim to improve care for people with depression [6]. A recent systematic review concluded that the most promising multifaceted intervention to prevent suicide is the 4-level intervention approach by the European Alliance Against Depression (EAAD) [8]. The authors reviewed 56 publications (describing 47 unique studies) in Linskens et al [8] on community-based or population-level suicide prevention strategies. EAAD's 4-level intervention offered the most evidence for its effectiveness, while evidence for other single- or multistrategy interventions was either unclear, inconsistent, or lacking. The authors, therefore, suggest that further randomized or observational studies are needed. The EAAD-Best project introduced in this paper will contribute to this identified research need.

The 4-level intervention has been implemented in local communities and simultaneously runs activities at 4 intervention levels (Figure 1).

- Level 1: Interventions aim to improve the capacity of general practitioners (GPs) and mental health care professionals (MHCPs) regarding the management of depression and suicidality. This is achieved by training sessions focusing on early detection, diagnosis, and treatment.
- Level 2: Interventions target the broader public and aim to raise awareness, increase knowledge on depression and suicide, reduce stigma, and improve help-seeking behavior. This is achieved through a public awareness campaign. It emphasizes the need for treatment, the availability of effective treatment options, and support services. Key messages are (1) depression is a real disease; (2) depression can affect anyone; (3) depression has many faces; and (4) depression can be treated.
- Level 3: Interventions aim to improve the capacity of community facilitators and gatekeepers concerning the recognition and handling of depression and suicide risk. Community facilitators and gatekeepers are nonmedical professionals who have a public and social function in society (geriatric caregivers, priests, pharmacists, police, journalists, counselors, midwives, teachers, social workers, managers, and company physicians). They frequently interact with people who are experiencing depression or suicidal ideation and are therefore well positioned to provide general preventive and supportive services. Journalists are informed about the risk of triggering the so-called Werther effect (copycat suicides) and are offered a media guide with recommendations on how to report and not to report about suicidal acts in order to reduce the risk of unwanted effects of media coverage. Capacity building is achieved through train-the-trainer sessions adapted to the specific needs of (subgroups of) community facilitators.
- Level 4: Interventions aim to support patients who are depressed and/or suicidal and their relatives by supporting self-help (eg, implementation of self-help groups and promoting the iFightDepression tool) and providing information about depression, suicidal behavior, and treatments. Identifying locations where people frequently take or attempt to take their lives in a certain region and starting activities to secure these places is also an element within the 4-level intervention.

Implementation of the 4-level intervention is supported by the EAAD coordination center that developed an implementation guide, a catalog of step-by-step recommendations (eg, how to organize a press conference and how to recruit GPs), and has accumulated a broad range of intervention and evaluation materials over the last years. Many materials have already been translated into various languages including the iFightDepression awareness website [9]. This website provides information about depression, its causes, symptoms, and treatments and is publicly accessible. The effectiveness of the 4-level intervention to reduce suicidal behavior was demonstrated by several studies in different countries, although not all evaluated community-based interventions showed the expected positive effects [10-13].

Within the 4-level intervention, the web-based iFightDepression tool is an important intervention component that can help reduce the treatment gap concerning psychotherapeutic interventions [14]. It is based on the principles of cognitive behavioral therapy and supports the self-management of people with mild-to-moderate forms of depression. Access and guidance to the tool are provided by health care professionals. The safety [15] of the tool and its efficacy [14,16] have been assessed for mild-to-moderate symptoms of depression in a randomized controlled trial with an active control group [14] and a study with a treatment-as-usual control group [16]. It is possible that patients with severe depression can benefit from digital interventions [17], but the risk of failing to use the intervention due to motivational problems that are often part of major depression also seems more likely and could cause further frustration and self-criticism. The recommended use of the iFightDepression tool is therefore currently limited to the patient

groups for which solid evidence is available, but as research progresses, this might be extended.

Figure 1. European Alliance Against Depression's community-based, 4-level intervention.

The 4-level intervention has been successfully adapted to different cultures and health care systems in more than 120 regions within and outside of Europe [18]. Important lessons that have been learned with growing experience are summarized as follows:

1. Targeting optimized care of depression and suicide prevention simultaneously is highly cost-effective and sensible for several reasons. Both are highly important mental health issues and depression is one of the key causal factors of suicidal behavior. Suicide-preventive measures unrelated to depression, such as access to lethal means, can easily be integrated in the 4-level intervention program. Given the high prevalence of depression, a public campaign on depression is likely to have a greater resonance than an exclusive suicide prevention campaign. The latter may further bear the risk of reducing the threshold for suicide due to the normalization of suicidal behavior or unfavorable secondary reporting, for example, in social media.
2. Being simultaneously active at all 4 intervention levels creates synergistic and catalytic effects [19]. An example of a synergistic effect is that the public health campaigns (level 2) not only increase awareness and knowledge in the general population but also increase the motivation of GPs and gatekeepers to participate in the training offered (levels 1 and 3). An example of a catalytic effect is the observed improvement of intersectoral cooperation between health professionals in communities participating in the 4-level intervention, an effect that has not directly been targeted by the activities [19].
3. Depending on the culture and health care system, intervention activities must find the right balance between bottom-up and top-down approaches. A bottom-up approach creates an ownership feeling in the community and is helpful to achieve sustainability. However, in countries with a less developed civil society and a more hierarchical political culture, more top-down support is required.
4. The pharmaceutical industry should not be involved in funding and implementation activities as this may reduce credibility and create conflicts of interest.
5. The implementation of the 4-level intervention in an initial model region raises interest in other regions, causing them to follow suit. The creation of a learning network of all implementing regions, which meet 2 or 3 times per year to exchange experiences and support each other, has proven useful.

Taking these and other lessons learned into account, the EAAD-Best project (full title: "Adapting and implementing EAAD's best practice model to improve depression care and prevent suicidal behavior in Europe") was set up and received funding from the Third Health Program (HP-PJ-2020) of the European Union (EU). As the title describes, the overall objective was the improvement of depression care and suicide

prevention in Europe given the strongly identified need for correct diagnoses of depression and suicidality as well as effective, evidence-based interventions. The project ran from April 2021 to March 2024 and allowed us to further adapt the 4-level intervention to new contexts and evaluate its effectiveness to add to the sparse database available for multifaceted suicide prevention interventions [8]. This paper aims to introduce the EAAD-Best project as a best practice model for the implementation of mental health interventions and their evaluation.

Methods

Goals of EAAD-Best

The central goals of EAAD-Best were the dissemination of the 4-level intervention to further regions in Europe and the nationwide uptake of the digital iFightDepression-guided self-management tool. These goals were achieved by:

1. The implementation of the 4-level intervention in model regions of EU countries in which the intervention had not yet been established (ie, implementation countries).
2. The dissemination of the 4-level intervention to new regions in EU countries in which this approach had already been implemented in a model region (ie, transfer countries).
3. The nationwide promotion the iFightDepression tool in participating countries and recruiting health professionals as guides who offer the tool to their patients.

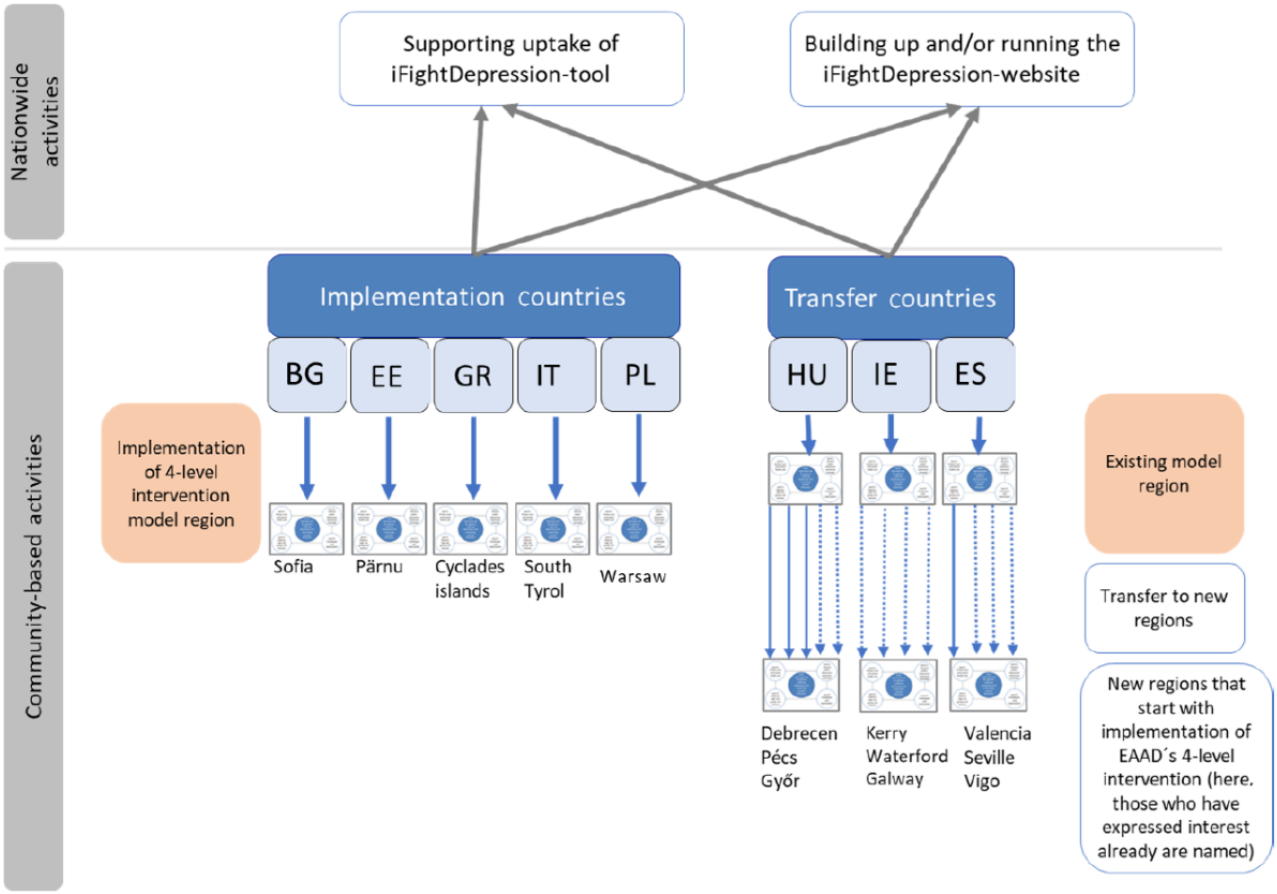
Overview of EAAD-Best Activities

Overview

The basic structure of EAAD-Best activities is illustrated in Figure 2.

The participating countries were chosen to represent the different regions of the EU. They differ not only in population and gross national income per inhabitant but also in their health care systems and national approaches to mental health, including the regional health care system facilities for patients with depression.

Figure 2. Basic structure of activities within EAAD-Best. *Due to the dropout of the Italian consortium member, Italy is no longer a full-fledged implementation country but focuses on the implementation of the iFightDepression tool and awareness website. BG: Bulgaria; EAAD: European Alliance Against Depression; EE: Estonia; ES: Spain; GR: Greece; HU: Hungary; IE: Ireland; IT: Italy; PL: Poland.



Implementation Countries

In 4 countries, the 4-level intervention was implemented for the first time: Bulgaria, Poland, Estonia, and Greece. Italy was named as another implementation country in the initial EAAD-Best proposal, but the Italian partner changed during the project duration and therefore could only participate in the implementation of the nationwide uptake of the iFightDepression tool.

Model regions were Sofia (Bulgaria), Warsaw central district (Poland), Pärnu (Estonia), and 2 regions in Greece (ie, North

Attica and Cyclades Islands). They were chosen based on accessibility for project partners and identified needs.

Transfer Countries

A total of 3 countries (Ireland, Spain, and Hungary) with previous experiences with the 4-level intervention and existing model regions offered the intervention to new regions. Ireland extended activities to Kerry and Cork. Spain targeted Valencia, Seville, Alcala la Real, and Vic, and Hungary focused on Szeged, Békéscsaba, Szentendre, and Baja. The regions were chosen based on accessibility for project partners, identified needs, and expressed interest.

The iFightDepression tool was promoted nationwide in all participating countries. It targets persons with mild-to-moderate forms of depression. Specific inclusion criteria are (1) age ≥15 years; (2) access to a computer, an internet connection, and an email account; and (3) mild-to-moderate forms of depression. Exclusion criteria are (1) age <15 years, (2) severe depression, (3) acute suicidality, and (4) current substance abuse.

Implementation Processes in EAAD-Best

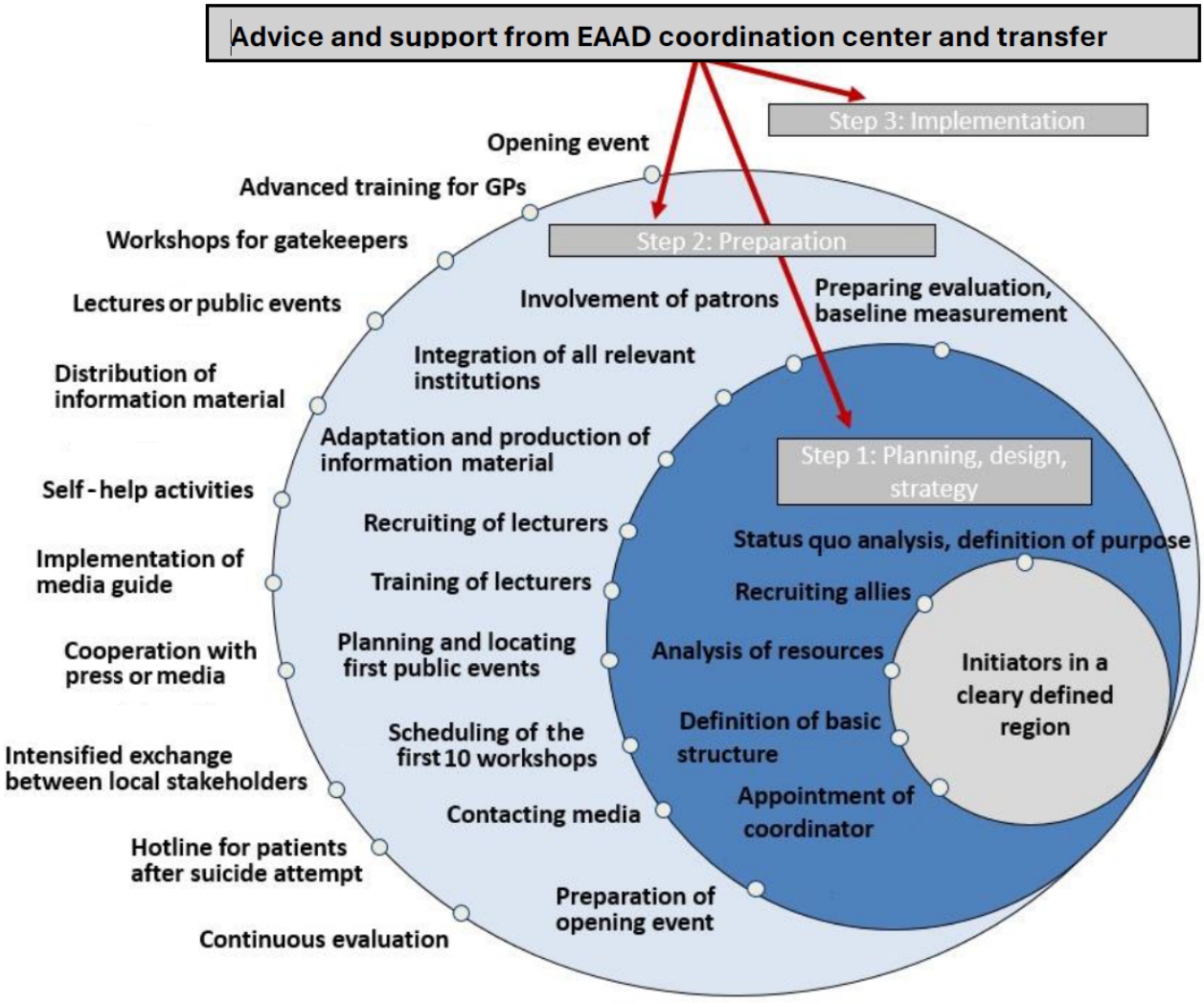
Initial Implementation of the 4-Level Concept in Implementation Countries

The process of implementing the 4-level intervention in implementation countries can be broken down into 3 steps:

- Step 1: Planning, design, and strategy
- Step 2: Preparation
- Step 3: Implementation

Within each step, there is a range of tasks and actions to consider (Figure 3).

Figure 3. Foreseen activities for planning, preparing, and implementing the European Alliance Against Depression's 4-level concept in the implementation countries. EAAD: European Alliance Against Depression; GP: general practitioner.



Step 1: Planning, Design, and Strategy

Status quo analyses in the model regions identify relevant stakeholders and institutions as well as potential gaps and limitations of the local care system (ie, "As Is" state). Next, the "To Be" state is defined (ie, what the local alliance seeks to achieve). Specific objectives can be derived by comparing the "As Is" state with the "To Be" state.

The identified network of stakeholders should be broad and include existing local health care initiatives and personal links

and partnerships. Stakeholders or potential sponsors should be involved in the preparation phase to increase their identification with the alliance.

Next, the alliance initiator is identified. It can be a person (eg, a psychiatrist), a small organization (eg, a self-help group), or an institution (eg, a psychiatric hospital). They should decide about the basic structure of the local alliance (eg, will it be part of an existing organization or will a nongovernmental organization be founded?). A small steering group (about 2-5 people) for leadership of the alliance should be formed and a local coordinator should be appointed.

Step 2: Preparation

In the preparation phase, the alliance is being formed and the interested institutions and stakeholders become integrated. Regular meetings are crucial, as most questions and fundamental decisions occur in this stage.

Materials required for activities on all 4 intervention levels must be translated and culturally adapted to regional needs (eg, public relation campaign materials, level-1 and -3 training materials, and iFightDepression awareness website). Templates are provided by the EAAD coordination center.

The professional groups that will receive training as part of intervention activities on levels 1 and 3 are defined and recruited as lecturers to run training sessions for other GPs, MHCPs, and community facilitators or gatekeepers. The first of these train-the-trainer training sessions take place and further ones are scheduled, so that respective dates can be announced at the opening ceremony and activities can start immediately afterward. A train-the-trainer information package including the referral of patients to the iFightDepression tool is provided by the EAAD.

A large public opening ceremony and further public events are prepared. Many types of public events are possible, such as public talks, podium discussions, theme nights, information booths, school projects, art exhibitions, or religious services. A range of events that are best suited to maximize contact with the target group is advisable.

A prominent and broadly respected person in the region should be involved as a patron. They do not need to have any connection with depression or suicide but should be willing to publicly support the alliance and its aims. A prominent patron will help gain support and cooperation from many partners, including the media.

The media are contacted actively, for example, by offering press releases on events or interviews on depression-related topics to journalists. The use of social media is also advised. It is recommended to appoint a person within the alliance responsible for all social media activities and "marketing" of the campaign.

Step 3: Implementation

During the implementation phase, different activities will be run simultaneously at the 4 levels. EAAD-Best partners focus on maintaining effective and frequent channels of communication with all alliance partners in this phase. Regular project meetings are essential to evaluate the status of all work, determine the next steps, and monitor the financial resources and compliance with an agreed timeline. Alliance partners receive feedback on their work to ensure high motivation and quality of work. If necessary, they are reminded of their responsibilities.

One key activity is the opening ceremony with all the stakeholders and patrons. Holding a press conference at the opening ceremony is advisable and is a good opportunity to provide local media with a press kit and media guidelines on reporting on suicides. A leaflet about the regional alliance against depression with basic information about depression and a map of contacts where to get help locally and ways to support the alliance (by donating, as a volunteer) should be distributed at the event. Setting up a public newsletter is a good way to promote the alliance and attendees at the opening ceremony can be invited to sign up for it. A range of material templates for the opening ceremony are provided by EAAD.

The main activities during the implementation phase are the recruitment and training of health professionals (level 1) and community facilitators or gatekeepers (level 3). The training can be delivered in person or through videoconferences.

Other activities concern an ongoing involvement with the media and the distribution of informative materials (especially flyers and posters) as a crucial aspect of the public awareness campaign (level 2). Talks and public events should take place continuously during the intervention period, as this not only benefits the dissemination of alliance activities but also indirectly raises awareness about depression as a health problem. Patients and relatives should be included as speakers at the events, as this will help fight stigma.

Dissemination of the 4-Level Concept to New Regions in Transfer Countries

In the 3 transfer countries, the goal was to expand the 4-level intervention activities from an existing model project to new regions. To achieve this goal, the following intervention steps were taken:

- Through press releases and other media activities, national and regional health politicians and stakeholders as well as nongovernmental organizations and self-help organizations were informed about the 4-level intervention concept. These activities should raise interest and motivation to start their own local alliances against depression and suicidal behavior in different communities.
- Those who were interested in starting a new regional alliance were supported in several ways: (1) financial support (ie, with a start-up budget of €3.800 [US $4.02]), (2) train-the-trainer sessions, (3) access to EAAD implementation materials and help with their local adaptation, and (4) continuous advice by the EAAD coordination center.
- The existing National Coordination Centre established a national learning and dissemination network of regional alliances by inviting all interested stakeholders (those implementing or interested in implementing regional 4-level interventions) to regular meetings. These allowed us to exchange experiences and best practices but also involved

workshops on topics such as fundraising, involving volunteers, or organizing press conferences.

Nationwide Uptake of the iFightDepression Tool in All Participating Countries

In order to make the iFightDepression tool available nationwide in all participating countries (ie, implementation and transfer countries), the following intervention steps have been implemented: (1) translation and cultural adaptation of the tool for all countries as needed; (2) in Greece, Italy, Hungary, and Spain, the iFightDepression tool was already implemented, and in all other intervention countries (Estonia, Bulgaria, Poland, and Ireland), a coordination site was appointed to manage the use of the iFightDepression tool; (3) advertised the tool to the general public and health professionals (GPs, MHCPs) through press releases, other media activities, and approaching professional organizations for GPs and MHCPs; and (4) trained health professionals to become guides and give patients access to the tool. The trainings were delivered in person or through videoconferences. e-Learning materials for GPs have been developed that allow them to complete the training at their convenience. It is followed by a test assessing correct understanding.

Evaluation of the Implementation of the 4-Level Concept in Implementation and Transfer Countries

Overview

Our evaluation approach considered monitoring and outcome measures. The monitoring evaluation involved process indicators addressing the extent to which planned activities took place in implementation and transfer countries. It also considered output indicators assessing the quantity and quality of the implemented activities. The outcome evaluation will test to what extent the 4-level intervention generated the expected positive effects in health professionals, community facilitators, and iFightDepression tool users.

Evaluation activities in implementation and transfer countries use the same materials and procedures described below.

Monitoring Evaluation

Process and output indicators were collected through a monitoring instrument twice per year. It presented a selection of core indicators of the 4-level intervention activities (eg, occurrence of the opening event and the number of attendees) to track whether planned activities took place and to assess their quantity and quality.

Outcome Evaluation

Given the limited time frame of this project, it was not feasible to evaluate whether the intended long-term outcomes of the 4-level concept (ie, reduction of suicidal behavior and improvements in the care of patients with depression) were achieved. Therefore, intermediate outcome indicators that are more directly linked to the operational goals of the 4-level intervention were selected. These are changes in self-judgment of the performance, importance, and competence of treating persons with depression and suicidal ideation. They were measured in health professionals and community facilitators participating in the level-1 and level-3 training sessions using self-developed questionnaires.

Data were collected at 2 measurement time points: before and immediately after the level-1 and -3 trainings. Informed consent was obtained before the first training session.

Evaluation of the iFightDepression Tool in All Participating Countries

To evaluate the iFightDepression tool and its effects, users were asked to complete 2 outcome measures. Their informed consent was obtained when registering for the iFightDepression tool, and all data were directly collected within the application. First, after their registration, users were asked to complete a self-developed survey measuring initial expectations regarding the tool. Then, over the following 8 weeks, mental well-being was assessed on a weekly basis with the Patient Health Questionnaire (PHQ-9) [20].

Ethical Considerations

Participating in any evaluation activity will require informed consent. Ethical approval has been obtained in all implementation and transfer countries before the start of data collection. The names of the ethics committees that approved the study are as follows: (1) Bulgaria: Central Ethics Committee of the Ministry of Health Republic of Bulgaria; (2) Estonia: Tervise Arengu Instituudi inimuuringute eetikakomitee, Research Ethics Committee of the National Institute for Health Development; (3) Greece: Department of Education, Research and Documentation Association of Regional Development and Mental Health; (4) Poland: ethics committee of the Maria Grzegorzewska University; (5) Hungary: Egészségügyi Tudományos Tanács, Tudományos és Kutatásetikai Bizottság; (6) Ireland: Clinical Research Ethics Committee of the Cork Teaching Hospitals; and (7) Spain: Comité Ético de Investigación Clínica de Galicia; Comité Ético de Investigación del Hospital Clínico de Valencia; and Comité de Ética de Investigación de los Hospitales Universitarios Virgen Macarena.

Results

Data collection was completed in March 2024. Data processing and analyses commenced in the autumn of 2023 and are expected to be completed by the end of 2024. Results are expected to be published in 2025.

Discussion

Principal Outcomes

EAAD-Best had three main objectives: (1) implementation of the 4-level intervention in model regions of EU countries in which the intervention had not yet been established, (2) dissemination of the 4-level intervention to new regions in EU countries in which it had already been implemented, and (3) nationwide promotion of the iFightDepression tool in participating countries. In general, all these objectives have been successfully achieved, as alliances against depression were established in all participating countries, iFightDepression guides were trained, and increasing numbers of people started using the tool. Analyses of the collected monitoring data

(currently ongoing, results expected to be published in 2025) will allow a more fine-grained conclusion regarding the quantity and quality of intervention activities. In line with previous studies (eg, [8,14]), we anticipate that the outcome evaluation (results expected to be published in 2025) will show that training of GPs, MHCPs, and gatekeepers will increase their subjective competence and their willingness to treat persons with depression and suicidal ideation in the future. Furthermore, iFightDepression tool users are expected to report a decrease in depressive symptoms. The anticipated results will add to the scarce literature on suicide prevention interventions [8] and, most importantly, will extend existing evidence on the effectiveness of the 4-level intervention and the iFightDepression tool to new regions and countries across Europe.

The following sections will discuss some practical issues involved in implementing and evaluating the 4-level concept and the iFightDepression tool and will highlight not only some of the challenges but also the strengths of the approach.

Participation of Professionals in EAAD Training

Participation in EAAD training sessions is completely voluntary. Professionals will not be remunerated for their participation. Recruiting GPs can be especially challenging due to time constraints and high workloads. Accordingly, trainings focus on practical materials for GPs and their patients, and are delivered in a convenient fashion (eg, in the evenings and online). The introduction of e-learning materials to allow GPs to complete the iFightDepression guide training has been very well received. It has also proven helpful to be able to award Continuing Medical Education points for training completion.

Training professionals will strengthen both their expertise in recognizing mental health issues and their ability to offer support. It is important to stress those benefits in communications. In particular, becoming a guide for the iFightDepression tool enables GPs to provide self-management support based on cognitive behavioral therapy to their patients.

Potential Risks and Benefits of Using the iFightDepression Tool

Previous studies have shown that the iFightDepression tool has beneficial effects on mental health without causing any adverse effects [14,15]. Therefore, the benefits of participation are expected to outweigh any potential risks (eg, suicidal crises can be overlooked) and unwanted effects (eg, an increase in rumination and somatization due to self-monitoring). In addition, all participants will remain within the usual care of their GPs or MHCPs while using the iFightDepression tool.

The expected benefits of the iFightDepression tool include increased uptake of treatment as online self-help tools are more accessible than traditional forms of psychological support. Hence, the iFightDepression tool has the potential to close the gap between people with depression seeking help and the limited immediate access to psychotherapy [1]. Furthermore, there will be a lower threshold to engage certain people who may be reluctant toward traditional mental health services. Given that the iFightDepression tool is used online and anonymously, users face no risk of stigmatization. The early detection of suicidal ideation and severe symptoms of depression through the inclusion of the PHQ-9 within the tool will help prevent attempted and completed suicides. In particular, the PHQ-9 contains 1 item that directly addresses suicidal ideation. If participants choose a response option indicating that they are experiencing suicidal thoughts or obtain a total score of 15 or above (indicating moderate-to-vigorous symptoms of depression), they will receive an automatic message suggesting contacting their health care professional, GP, or a quality-assured support service. Finally, the tool will strengthen the coping skills of participants, enabling them to manage current and future experiences of depression better.

Sustainability

The ultimate goal of EAAD-Best is that activities will continue to run and expand from model projects to national networks of alliances against depression upon project completion. In general, sustainability is a key aspect of the 4-level intervention. It has been considered in its development, for example, by making it as cost-effective as possible, flexible, and adaptive to various contexts and encouraging activities leading to an ownership feeling in the communities. Sustainability is further considered within implementation activities by asking partners after a defined intervention phase (2-3 years) to reflect on previous and ongoing activities, their main partners and stakeholders, experienced challenges, and facilitators so on. EAAD further recommends partners to create a national coordinator position that, on the basis of the experiences from the model project, can support and coordinate the dissemination of the approach in further cities and regions to make it efficient, cost-effective, and impactful.

Evaluation Challenges

Performing applied research like the presented implementation science project can pose challenges such as variability in implementation fidelity. This project tried to minimize such risks by implementing certain measures or processes. In general, questionnaires were always kept to a minimum to avoid overburdening project partners, professionals involved in trainings, and patients using the iFightDepression tool. The dedicated work package running evaluation activities in EAAD-Best provided templates for all assessments and reported completion rates at consortium meetings so that potential difficulties in certain countries could be identified and addressed right away. The training evaluations could be completed online or through paper and pencil to suit the local preferences and increase data completion. To match repeated assessments of training participants, a subject-generated identification code was used to allow correct matching while ensuring anonymity. Future publications on the results of the EAAD-Best project will discuss identified challenges and the chosen solutions in more depth.

Conclusion

The EAAD-Best project will contribute to improved depression care and prevention of suicidal behavior in Europe by extending the application of the 4-level intervention and the uptake of the iFightDepression tool. Besides supporting the implementation of best practices in mental health promotion and treatment,

EAAD-Best will also add to the implementation research evidence base in the area of mental health interventions. Implementing and evaluating a multilevel intervention, such as the 4-level intervention, bears certain risks and challenges, for example, convincing health professionals to join level-1 trainings, establishing wide and consistent networks of stakeholders, and finding funding opportunities to maintain and extend activities upon project completion, and so on. Lessons learned and identified pitfalls will be shared once the monitoring and outcome analyses have been completed (expected by the end of 2024 with resulting publications in 2025), to avoid costly mistakes and ensure an efficient implementation process with a wide and enduring impact beyond the EAAD-Best project in the future.

Acknowledgments

The authors acknowledge the EAAD-Best consortium. The present project received funding from the European Union's Third Health Program (HP-PJ-2020; grant 101018325). Although the described activities were cofunded by the European Union's Third Health Program, the views and opinions expressed are, however, those of the authors only and do not necessarily reflect those of the European Union or the European Health and Digital Executive Agency (HADEA). Neither the European Union nor the granting authority can be held responsible for them.

Data Availability

The datasets generated and analyzed during this study are available from the corresponding author on reasonable request.

Authors' Contributions

KMS and KA wrote the original draft. UH provided supervision, especially with editing and conceptualization. All authors reviewed the original draft and the final manuscript.

Conflicts of Interest

VPS reports the following: grants from CIBERSAM, ISCiii, UE H2020, EAAD, Compass, Novartis, Lundbeck, and Janssen; honoraria or consulting fees from Janssen, Otsuka, and Esteve; and participation in the speakers bureau for Janssen, Otsuka, GSK, Exeltis, ABBVIE, Abbot, Lundbeck, Esteve, Novartis, and Angelini.

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Abbreviations

EAAD: European Alliance Against Depression
EU: European Union
GP: general practitioner
MHCP: mental health care professional
PHQ-9: Patient Health Questionnaire

Edited by T Leung; submitted 12.07.24; this is a non–peer-reviewed article;accepted 28.09.24; published 10.01.25.

Please cite as:
Schnitzspahn K, Abdulla K, Arensman E, Van Audenhove C, Mere R, Pérez Sola V, Sisask M, Székely A, Toczyski P, Hegerl U Community-Based 4-Level Intervention Targeting Depression and Suicidal Behavior in Europe: Protocol for an Implementation Project
JMIR Res Protoc 2025;14:e64218
URL: https://www.researchprotocols.org/2025/1/e64218
doi:10.2196/64218
PMID:

Protocol

Examining Weight Suppression, Leptin Levels, Glucagon-Like Peptide 1 Response, and Reward-Related Constructs in Severity and Maintenance of Bulimic Syndromes: Protocol and Sample Characteristics for a Cross-Sectional and Longitudinal Study

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Abstract

Background: Bulimia nervosa and related syndromes (BN-S) characterized by binge eating vary considerably in illness severity and course. Using the Research Domain Criteria framework of the National Institute of Mental Health, we developed a model positing that the same set of physiological consequences of weight suppression (WS; defined as the difference between the highest and current adult body weight) contribute to binge-eating severity and maintenance by (1) increasing the drive or motivation to consume food (reward valuation effort [RVE]) and (2) decreasing the ability for food consumption to lead to a state of satiation or satisfaction (reward satiation).

Objective: Our funded project aimed to test concurrent associations among WS, physiological factors (leptin concentrations and postprandial glucagon-like peptide 1 [GLP-1] response), behavioral indicators of RVE (breakpoint on progressive ratio tasks) and reward satiation (ad-lib test meal intake), self-report of these core constructs, and binge-eating severity in BN-S (aim 1); test prospective associations to determine whether WS predicts BN-S maintenance in longitudinal models and whether posited mediators also predict BN-S maintenance (aim 2); and determine whether associations between WS and BN-S severity and maintenance are mediated by alterations in leptin levels, GLP-1 response, RVE, and reward satiation (aim 3).

Methods: We aimed to recruit a sample of 320 women with BN-S or noneating disorder controls, with BMI from 16 kg/m^2 to 35 kg/m^2, for our study. The study included diagnostic interviews; questionnaires; height, weight, and percentage of body fat measurements; weight history; fasting leptin level; postprandial GLP-1 and insulin responses to a fixed meal; and ad-lib meal and progressive ratio tasks to behaviorally measure reward satiation and RVE, respectively, at baseline, with at least 78.1% (250/320) of the participants providing data at 6- and 12-month follow-up visits. Data will be analyzed using structural equation models to test posited pathways.

Results: Data collection began in November 2016 and ended in April 2023, pausing in-person data collection from March 2020 to February 2021 due to the COVID-19 pandemic. Of 399 eligible women enrolled, 290 (72.7%) provided clinical, behavioral, and biological data at baseline, and 249 (62.4%) provided follow-up data. Measures demonstrated strong psychometric properties.

Conclusions: We seek to identify biobehavioral predictors to inform treatments that target key factors influencing the severity and course of binge eating. These data, supported solely through federal funding, can inform questions emerging from recent interest and controversy surrounding the use of GLP-1 agonists for binge eating.

International Registered Report Identifier (IRRID): RR1-10.2196/66554

(JMIR Res Protoc 2025;14:e66554) doi:10.2196/66554

KEYWORDS

binge eating; weight suppression; leptin; glucagon-like peptide 1; insulin; reward; satiation; longitudinal; behavior; Research Domain Criteria

Introduction

Background

On March 6, 2013, the National Institute of Mental Health (NIMH) released a request for applications titled "Advancing Eating Disorders Research through Dimensional Studies of Biology and Behavior (R01)" to stimulate research using the Research Domain Criteria (RDoC) framework to identify mechanisms underlying eating disorders. In response, our team submitted an application that addressed key requirements. Specifically, we proposed a model that (1) was transdiagnostic, bridging categories in the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (*DSM-5*) that involve recurrent binge eating; (2) was based on 2 RDoC positive valence domain constructs to explain the 2 defining features of binge eating in the *DSM-5*, including overconsumption of food and loss of control (LOC) over eating; (3) measured constructs and clinical features dimensionally, from a state of health to disease; and (4) used 3 units of analysis, including self-report via interview and questionnaire and biological and behavioral measurement. Our model translated work emerging from basic neuroscience studies of ingestive behavior in rodents to understand the severity and maintenance of bulimia nervosa (BN) and related syndromes (BN-S). This report provides an overview of our explanatory model, supporting literature informing our aims and hypotheses; our protocol for testing hypotheses and adjustments required by the onset of the COVID-19 pandemic; our data analytic plan; our timeline, including recruitment and retention over follow-up; a description of our sample; and psychometric properties of our measures. With data collection completed, this report addresses the feasibility of our approach to testing our model, and our discussion focuses on the implications of potential findings for the assessment, diagnosis, and treatment of eating disorders characterized by binge eating.

Explanatory Model

A comprehensive review of our explanatory model, including background literature and preliminary data, is available in an open-access article [1]. We proposed that weight suppression (WS), originally defined as the difference between the lifetime highest adult weight and current weight [2], represented a dimensional, transdiagnostic risk and maintenance factor for binge eating in eating disorders. Furthermore, we proposed that WS, independent of current adiposity, contributed to reduced circulating leptin levels, which contributed to a blunted glucagon-like peptide 1 (GLP-1) response to food intake, and that these reductions contributed to alternations in 2 RDoC constructs, reward valuation and reward satiation. Reward valuation represents "benefits of a prospective outcome [...] by reference to external information, social context (eg, group input), and prior experience" [3], and reward valuation effort (RVE) can be measured as the amount of work a reward is worth [4]. In contrast, reward satiation represents "the change in incentive value of a reinforcer over time as that reinforcer is consumed or experienced" [3], and reward satiation can be measured as the termination of reward consumption when it is freely available [4]. Disrupted RVE explains excessive appetitive drive to consume a reward, despite its costs, leading to LOC while eating. Perturbed reward satiation explains the diminished ability to reach a state of completion or satisfaction during consumption, leading to excessive food intake. LOC and excessive food intake represent the defining features of binge-eating episodes, and our model sought to explain both the severity and maintenance of BN-S defined by binge-eating episodes across *DSM-5* eating disorder diagnoses.

Supporting Literature

Women with BN often have a BMI within the range considered healthy [5], belying an average WS of 7.8 kg [6-14]. Cross-sectional and prospective studies support significant associations between greater WS and BN-S severity [9,14,15] and maintenance [6,8,9], controlling for age, BMI, body image disturbance, and dietary restraint [9,14]. In addition, robust evidence supports that greater WS predicts future weight gain [7,10,16-19]. This last point underscores how WS represents a state resulting from weight loss, which is difficult to maintain due to biological consequences known to influence ingestive behaviors. Our literature review focused on findings translated from basic neuroscience into clinical research that contribute to weight gain and may also impact the risk for binge-eating episodes.

Biological Consequences of Weight Loss

Weight loss includes loss of white adipose tissue, the primary source of the hormone leptin [20]. Leptin crosses the blood-brain barrier, providing a signal of stored energy to neural regions influencing ingestive behavior [20]. In addition to significant and large (r>0.90) positive associations between fat mass and circulating leptin levels [21], weight loss impacts leptin levels

independently of BMI [21,22]. Our previous work supported a significant association between greater WS and lower leptin levels, controlling for BMI [23,24] and body fat percentage [23].

Importantly, although WS and leptin levels represent states rather than traits, both demonstrate relative stability throughout the day and are unlikely to directly influence eating onset and termination. Instead, leptin modulates peripherally released meal-related signals that dynamically respond to changes in nutritional intake and impact ingestive behavior [25]. These signals include ghrelin, cholecystokinin, insulin, glucose-dependent insulinotropic polypeptide, secretin, peptide tyrosine tyrosine, insulin-like peptide 5, neurotensin, substance P, and GLP-1. The hormones relay information to the brain about acute changes in energy needs via stimulation of the vagus nerve, with some signals crossing the blood-brain barrier to bind to receptors in neural circuits that impact feeding [25]. Among these, our model focused on GLP-1 based on emerging research on its role in both reward valuation and reward satiation led by one of our investigators [26-30].

GLP-1 is released by L cells in the intestine, and research in rats suggested that leptin potently stimulated postprandial GLP-1 release via leptin receptors on intestinal L cells [31,32]. Thus, our model posits that lower leptin level is associated with blunted postprandial GLP-1 response. Supporting this prediction, individuals with higher leptin levels have demonstrated more robust GLP-1 responses to food intake [33]. These cross-sectional associations appear to reflect the influence of leptin on GLP-1 levels, rather than the reverse, as neither meal-induced increases in GLP-1 nor exogenous GLP-1 administration influence leptin levels in healthy volunteers [34,35]. Thus, our model predicts associations among greater WS, lower leptin levels, and blunted GLP-1 response to food intake, which then influence food intake via alternations in RVE and reward satiation.

Impact of Peripheral Leptin Levels and GLP-1 Response on Reward Valuation and Reward Satiation

Circulating leptin crosses the blood-brain barrier and binds to leptin receptors in many brain regions, including those involved in reward valuation (ventral tegmental area [VTA] and nucleus accumbens [NAc] [36] and reward satiation (several regions of the hypothalamus and the hindbrain) [37]. Peripherally administered leptin inhibits dopamine projections from the VTA to the NAc [36]. In the arcuate nucleus (Arc) of the hypothalamus, leptin inhibits neurons containing neuropeptide Y and agouti-related protein (NPY/AgRP) and activates neurons containing pro-opiomelanocortin and cocaine- and amphetamine-regulated transcript (CART) [37]. Mesolimbic dopamine signaling impacts many aspects of reward responsiveness [4,38], including RVE, measured as greater effort (breakpoint) in a progressive ratio (PR) task for reinforcers (eg, food, drugs of abuse, and intracranial self-stimulation) [39-42]. Manipulation of leptin receptor function in the VTA supports leptin's role in reward valuation. In a PR task for food reward, breakpoint was increased by knockdown of leptin receptor expression in the midbrain, including the VTA, but not the hypothalamus [43] and directly in the VTA, but not the substantia nigra [44].

Leptin activation of pro-opiomelanocortin/CART neurons decreases food intake in ad-lib meals across species, including humans [45]. In contrast, NPY/AgRP potently stimulate increased food intake [37]. Thus, when an organism loses adipose tissue (a state marked by WS), leptin levels decrease, activation of pro-opiomelanocortin/CART neurons decreases, and NPY/AgRP neurons remain active and increase ad-lib intake to return the organism to a state of energy balance [37]. Leptin infusions in the Arc [46] decrease ad-lib food intake in rats, and selective deletion of leptin receptors in pro-opiomelanocortin and AgRP neurons increased meal size in mice [47]. Thus, lower leptin levels contribute to diminished responsiveness to satiating signals during food intake. However, the clear causal effects of acute leptin administration in animal models may not reflect the physiological role of leptin in humans, given the noted within-day stability of both WS and circulating leptin levels. That is, an organism cannot lose and gain sufficient white adipose tissue from one meal to the next or within one meal to account for meal initiation or termination via physiological changes in leptin levels. Moreover, our previous work supported significant associations between greater WS and both lower leptin levels and a higher breakpoint on a PR task, and it also found a small negative association between leptin levels and breakpoint [23], further supporting a potential intermediary role for GLP-1.

Peripheral GLP-1 stimulates the vagus nerve, causing activation of the nucleus of the solitary tract (NTS), where central GLP-1 preproglucagon neurons are located [48]. Similar to the effect of leptin levels on GLP-1 release in the periphery, central leptin administration enhances GLP-1 release from preproglucagon neurons of the NTS [49,50]. GLP-1 neurons of the NTS project to multiple brain regions, including the VTA and NAc, where GLP-1 influences RVE [26,31,50-52], as well as to the Arc, paraventricular nucleus of the hypothalamus, and hindbrain, where it contributes to reward satiation [31,52]. In rats, 50% of VTA dopamine neurons express GLP-1 receptors [51], 30% of GLP-1 neurons in the NTS project to the VTA [53], and 40% project to the NAc [26,53]. This positions GLP-1 as a prime candidate for examining how *acute* changes in food intake influence reward pathways in the brain. Infusion of the potent GLP-1 agonist Exendin 4 in the VTA and NAc reduced breakpoint on a food PR task [54], and peripheral administration of a GLP-1 receptor antagonist blunted gastrointestinal nutrient-induced suppression of breakpoint on a food PR task [28]. Exendin 4 diminished conditioned place preference for cocaine [55], implicating GLP-1 signaling in reward responsiveness to a nonfood, noncaloric reinforcer. In healthy humans, meal-induced increases in GLP-1 levels reduced willingness to work for food rewards [56]. Thus, similar to leptin, GLP-1 appears to reduce RVE; however, work in humans has not clearly dissociated the effect of GLP-1 on reward valuation from its clear impact on reward satiation.

Similar to leptin, GLP-1 agonist treatment activates pro-opiomelanocortin and CART neurons [57], and peripheral or central GLP-1 administration suppresses ad-lib food intake and meal size in rodents [58-60]. In humans, peripheral GLP-1

infusion increased satiation and decreased food intake [61], and a meal pattern that increased GLP-1 response was associated with a 10% reduction in food intake during a subsequent ad-lib meal [56]. Moreover, since we initiated data collection to test our model, a plethora of research has emerged demonstrating the effects of GLP-1 agonists on weight via changes in food intake [25,62], and peripherally administered GLP-1 agonists cross the blood-brain barrier where they exert central effects on ingestive behaviors [63].

To summarize, animal-based studies show that leptin and GLP-1 reduce RVE through inhibitory effects in the mesolimbic dopamine pathway and increase reward satiation through a combination of inhibitory and excitatory actions in the Arc. We predicted that lower leptin levels would contribute to blunted postprandial GLP-1 release, which in turn would contribute to both increased RVE and decreased reward satiation. These behavioral consequences increase weight gain and increase the risk of experiencing large, out-of-control binge-eating episodes. We predicted that increased reward valuation would be associated with, and predict, increased frequency of LOC over eating, while decreased reward satiation would be associated with, and predict, consuming unusually large amounts of food.

Although no previous study has examined posited associations dimensionally and prospectively in humans, eating disorders characterized by binge-eating episodes are associated with lower leptin levels [23,64]; reduced GLP-1 response [65,66]; increased RVE, as measured by breakpoint on PR tasks [23,67-70]; and decreased satiation via greater food intake in ad-lib meals [71-77] compared to controls. Our laboratory was able to demonstrate hypothesized differences between women with BN and noneating disorder controls on each of these factors [23,66,78] and extended evidence of blunted GLP-1 response [66] and decreased satiation [78] in women with BN compared to those with purging disorder, which is a condition characterized by purging in the absence of binge-eating episodes [5]. This last finding addresses model specificity to eating disorders characterized by binge eating defined by LOC while eating an unusually large amount of food [5]. Finally, our cross-sectional analyses found that leptin levels statistically mediated the association between WS and reported duration of illness in BN-S [24].

Aims

Our funded project included the following aims. Aim 1 was to test concurrent associations among WS, physiological factors (leptin concentrations and postprandial GLP-1 response), behavioral indicators of RV-E (breakpoint on PR tasks) and reward satiation (ad-lib test meal intake), self-report of these core constructs, and binge-eating severity in BN-S. Aim 2 was to test prospective associations to determine whether WS predicts BN-S maintenance in longitudinal models and whether posited mediators also predict BN-S maintenance. Aim 3 was to determine whether associations between WS and BN-S severity and maintenance are mediated by alterations in leptin levels, GLP-1 response, RVE, and reward satiation.

Hypotheses

For examining BN-S severity using cross-sectional data, we hypothesized that greater WS would be associated with lower leptin levels, and lower leptin levels would be associated with lower postprandial GLP-1 response. We hypothesized that lower postprandial GLP-1 response would be associated with greater reward valuation and lower reward satiation. We predicted that greater reward valuation would be associated with a higher frequency of LOC over eating. We predicted that lower reward satiation would be associated with larger eating episode sizes, extending from eating episodes that were not large in control participants to objectively large binge-eating episodes in participants with BN-S across the full severity range (“eating/binge-eating episode size”). We also predicted a significant indirect pathway from WS to LOC frequency via leptin levels, GLP-1 response, and reward valuation. We predicted a significant indirect pathway from WS to eating/binge-eating episode size via leptin levels, GLP-1 response, and reward satiation. If supported, findings would demonstrate that biological concomitants of WS explain differences in the severity of binge eating via alterations in reward valuation and reward satiation.

For examining BN-S maintenance using longitudinal data, we hypothesized prospective associations in which greater WS would prospectively predict lower leptin levels, which would be associated with lower postprandial GLP-1 response. We hypothesized that lower postprandial GLP-1 response would be associated with greater reward valuation and lower reward satiation. We predicted that greater reward valuation would prospectively predict a higher frequency of LOC over eating. We also predicted that lower reward satiation would prospectively predict larger eating episode sizes.

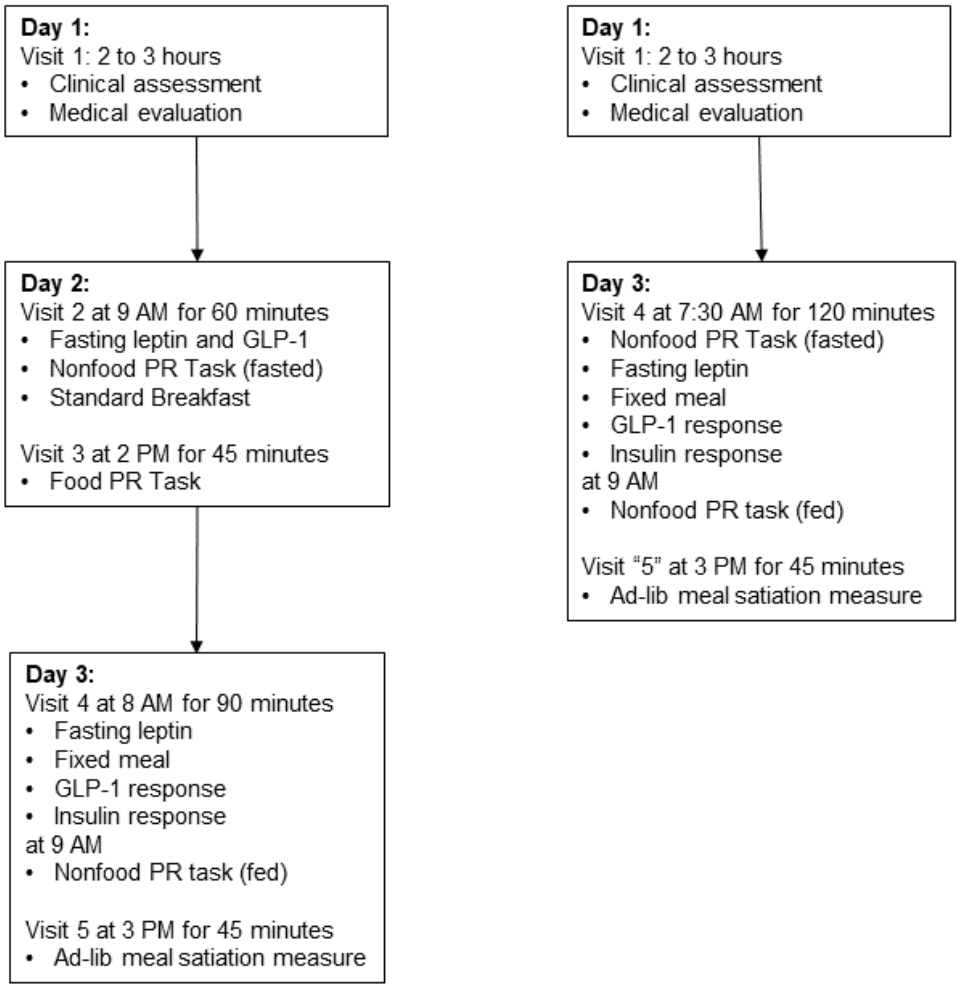
To examine the mediation of the association between WS and BN-S severity and maintenance via biobehavioral alterations, we predicted that reward valuation and reward satiation would mediate associations between WS and changes in LOC frequency and eating/binge-eating episode size. If supported, findings would translate findings from animal models in neuroscience to clinical outcomes in humans and identify GLP-1 as a potential target in future treatment studies of eating disorders characterized by binge eating, including BN-S.

Methods

Protocol

All data and sample collections, as well as assays, were conducted in a clinical research laboratory at Florida State University (FSU). Figure 1 presents an overview of study visits for participants enrolled before and after the onset of the COVID-19 pandemic.

Figure 1. Study protocol for participants enrolled before (left) and after (right) the onset of the COVID-19 pandemic. GLP-1: glucagon-like peptide 1; PR: progressive ratio.



Day 1 or Visit 1: Psychological and Medical Evaluation

At baseline, all participants completed in-person structured clinical interviews with clinical doctoral students and questionnaires on a laboratory computer (Measures section); a pregnancy test; an objective assessment of height, weight, percentage of body fat, and vital signs; and a medical screening. At baseline, participants also played Angry Birds (Rovio Entertainment) for 2 minutes, tasted M&M's (Mars, Inc) and frozen yogurt, and consumed the fixed meal used in visit 4 to ensure the ability to follow instructions in subsequent visits. After the onset of the COVID-19 pandemic, remote follow-up clinical assessments were offered via a Zoom (Zoom Communications) link, which complies with the Health Insurance Portability and Accountability Act (HIPAA), for interviews and a secure web-based link for questionnaires.

Days 2 and 3 Visits

The original protocol included 2 visits on day 2 at 9 AM (visit 2) and 2 PM (visit 3) and day 3 at 8 AM (visit 4) and 3 PM (visit 5). Start times were adjusted by up to 1 hour before or after indicated times, and any adjustment was held constant across a participant's visit. Participants were asked to abstain from eating or drinking anything except water and from purging or exercising after 11 PM before and between visits on both days. Participants were required to leave personal belongings, including mobile phones, books, and other items, in a bin outside the testing rooms. At the beginning of the morning visits, height, weight, body fat percentage, and vital signs were objectively measured, and a screening confirmed compliance with instructions and captured the past week's eating patterns and eating disorder symptoms. Task instructions were presented in print and via audio recording. We used digital video monitoring to detect technical problems and participant noncompliance during behavioral tasks. The revised protocol eliminated the day 2 visit but retained visit 2 tasks (Visit 2: Leptin, GLP-1, RVE for a Nonfood Reinforcer in Fasted State state).

Visit 2: Leptin, GLP-1, and RVE for a Nonfood Reinforcer in Fasted State

Participants had 5 ml of blood drawn by a registered nurse and completed momentary assessments before and after a PR task to play Angry Birds [79]. Briefly, participants were instructed that they could earn 1 minute of playtime in Angry Birds by pressing the space bar; the task consisted of up to 10 trials for up to 10 minutes of playtime, with the number of required presses increasing across trials (50 presses for trial 1, 250 presses for trial 2, 450 presses for trial 3, and so on up to 1850 presses

for trial 10). Participants were instructed that they should continue for as long as they wanted to play the game; they could stop at any time, and there were no right or wrong answers. When participants reached the criterion for a trial, a window opened, and they could play the game for 1 minute. After 1 minute, the screen automatically closed, and the participants were returned to the PR task, where they could work to gain access to continue the game. RVE was operationalized as a breakpoint, defined as the number of key presses in the last completed trial [80]. At 10 AM, participants consumed a standardized breakfast (300 kcal of yogurt parfait and juice) [23].

Visit 3: RVE for a Food Reinforcer

Participants completed momentary ratings before and after a PR task for M&M's [23], using the same design, instructions, and PR schedule as the nonfood task, to earn 10 M&M's per trial, with the potential to earn up to 100 M&M's over 10 trials. When participants reached the criterion for a trial, 10 M&M's dropped into a cup, and they were instructed to consume all M&M's before continuing to work for additional M&M's. The revised protocol eliminated the food PR task and associated momentary ratings.

Visit 4: GLP-1 Response to a Fixed Meal and RVE for a Nonfood Reinforcer in Fed State

A registered nurse placed an indwelling catheter into the participant's arm and allowed the participant to rest for 5 minutes. Participants completed momentary ratings before the nurse drew a fasting blood sample (5 ml) at –5 minutes for leptin, GLP-1, and insulin. Then, participants consumed a fixed liquid meal (Ensure Plus, Abbott Nutrition; 900 kcal in 660 g of fluid: 30% fat, 15% protein, and 55% carbohydrate) from –5 to 0 minutes. To capture GLP-1 and insulin responses to the fixed meal, 2 ml blood samples were drawn at +5, +15, and +30 minutes. Momentary ratings were completed immediately before each blood draw. After the last blood draw, participants had their intravenous catheter removed, rested for 5 minutes, and completed momentary ratings before and after the nonfood PR task (fed state). In the revised protocol, the fasted nonfood PR task and associated momentary ratings were completed before the first fasting blood draw, such that blood samples were drawn shortly after, rather than before, the fasted nonfood PR task.

Breakpoint on the nonfood PR task demonstrated excellent test-retest reliability (intraclass correlation [ICC]=0.91; 95% CI 0.80-0.96) over 2 weeks and convergent validity with the food PR task (r=0.51; P<.001) [79]. Consistent with animal models, breakpoint was lower in fed compared to fasted states across tasks (B=321.01, SE 552.40; P<.001). Finally, the nonfood task demonstrated discriminant validity from the measurement of satiation [79].

Visit 5: Ad-Lib Meal Assessment of Reward Satiation

Participants completed momentary ratings immediately before and after an ad-lib meal comprising 1.5 quarts (1420 g) of vanilla frozen yogurt (1.5 kcal/g) served at an individual place setting. Participants were presented with instructions in print and audio recorded to eat until they felt full or satisfied. Yogurt was weighed twice both before and after the meal using a top-loading, self-calibrated electronic balance, and the total intake was calculated in grams and kilocalories [81].

Training and Interrater Reliability

PKK provided all training and supervision for structured clinical interviewers and held biweekly assessment meetings. Interrater reliability (IRR) was examined via independent coding of audio recordings from 127 (16.5%) out of 769 interviews, randomly selected from each interviewer's assessments annually.

Participants

Textbox 1 presents the inclusion and exclusion criteria. Local recruitment was conducted via advertisements on social media platforms (eg, Instagram; Meta Platforms, Inc), billboards, pamphlets distributed to clinics, posters, outreach to college-based student organizations for ethnic or racial minority groups and churches, and emails to students at local universities with a link to a web-based eligibility screening. We received permission to send the mass email to female students aged 18 to 35 years once per academic term for all terms in which we recruited new participants at FSU and for one of the terms at a local Historically Black College and University. The mass email was the most effective recruitment tool, yielding the largest response. All prospective participants underwent telephone screenings to assess potential eligibility. Full eligibility was determined during the in-person assessment at baseline. The NIMH Data Archive (NDA) collection includes data from all eligible participants (N=399) and a small number of participants (n=6, 1.5%) who were later determined not to meet full eligibility criteria (details present in the Data Availability section).

Textbox 1. Eligibility criteria for participants.

Inclusion criteria

- Sex: female
- Age: 18 to 35 years
- BMI: 16 to 35 kg/m^2
- Free of psychotropic medications or stable dose of selective serotonin reuptake inhibitors for 8 weeks
- Free of alcohol, illicit drugs, and medications for 72 hours before reward valuation effort, reward satiation, and fixed meal tasks

Additional inclusion criteria for bulimia nervosa and related syndromes

- Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (*DSM-5*), binge episodes
  - ≥1,000 kcal within a 2-hour period and larger than what most people would eat in a similar context
  - Loss of control over eating during the episode
- More than 12 episodes of behavioral eating disorder symptoms (including binge, purging, and nonpurging behaviors) over the past 12 weeks
- Undue influence of weight or shape on self-evaluation, intense fear of gaining weight or becoming fat, or marked distress regarding binge eating
- *DSM-5* criteria for anorexia nervosa binge-purging, bulimia nervosa, binge eating disorder, or other specified feeding or eating disorder using the past 12 weeks as a measure of the past 3 months
- For current other specified feeding or eating disorder, score >16 on the Clinical Impairment Assessment; marked distress regarding binge eating; or impairment in one or more areas of life on the Structured Clinical Interview for DSM-5
- For atypical anorexia nervosa, BMI ≥18.5 to <19 kg/^{2} or >5% BMI reduction over a 1-month period

Exclusion criteria

- Medical condition or other treatment that could influence appetite, weight, or ability to participate
- Currently pregnant, nursing, or planning to become pregnant within the next year
- Planning to move >2 hours away from the laboratory within the next year
- Current blood, injection, or injury phobia

Additional exclusion criteria for noneating disorder controls

- Current eating disorder symptoms on the Eating Disorder Examination
- Current dietary restriction to lose weight on the Eating Disorder Examination (dietary restriction to prevent weight gain was permitted)
- History of any eating disorder symptoms on the Structured Clinical Interview for *DSM-5*
- Three-Factor Eating Questionnaire cognitive restraint subscale score ≥10
- Clinical Impairment Assessment score ≥16

To measure the severity of BN-S dimensionally from a state of health to disease, we included noneating disorder controls and participants with BN-S ranging from mild to severe. We deliberately recruited more participants with BN-S than controls to collect data appropriate for parametric analyses by minimizing variables with a modal value of 0. This strategy also prioritized the recruitment of participants with BN-S at baseline, as predictors of illness maintenance and the examination of GLP-1 dysfunction as a potential treatment target were most relevant for this group. Finally, this strategy reflected our previous research experience and the expectation that controls would demonstrate limited variance at baseline, when they were required to be free of eating pathology, and over the course of follow-up when the incidence of eating disorders would be rare. With reduced variability, a smaller number was expected to provide sufficiently narrow CIs on any secondary group-based analyses comparing controls to participants with BN-S.

Participants provided multiple and preferred methods of contact (phone calls, SMS text messages, and email). Participants also provided the name and contact information for at least 1 individual who would know how to reach them if the participant could not be contacted by their mobile number and gave permission for us to contact that individual if we lost contact. We used several strategies to enhance retention. First, we offered financial incentives to participants prorated by visit and a bonus for completing all visits as scheduled (details present in the Ethical Considerations section). Second, we provided written and verbal reminders and instructions for subsequent visits via calls, SMS text messages, and emails for 3 days and 1 day before visits and wake-up calls for morning visits. Third, we established clear participation policies: participants who missed 2 scheduled visits without prior notification were discontinued, and we limited rescheduled visits to 3 per sequence. Fourth, if ≥12 weeks passed between the day 1 interview and the final visit,

we required confirmation of continued eligibility via reassessment. Finally, a 6-month follow-up could begin 4 to 8 months after baseline, a 12-month follow-up could begin ≥10 months after baseline, and 6-month participation was not required to complete a 12-month follow-up. Assessment dates are included in the NDA collection.

Measures

BMI, WS, and Body Fat Percentage

Current weight and height were measured each day using a digital scale and stadiometer to calculate BMI (kg/m^2). We observed stability in BMI across days (r>0.95; P<.001), with no significant changes between days 1 and 2 (Cohen d=0.09), 2 and 3 (Cohen d=–0.07), and 1 and 3 (Cohen d=–0.007). WS was calculated as a percentage of BMI loss from the highest previous BMI, using self-reported highest adult weight at current height to calculate the highest BMI. At 6- and 12-month follow-up visits, we again asked about the highest adult weight to capture possible changes over time. Body fat percentage was measured using bioelectrical impedance analysis (Tanita Corporation of America), which demonstrates high correlations (r=0.88 to 0.94) with dual x-ray absorptiometry scans [82], supporting its feasibility (lower cost) and safety (no radiation exposure) in longitudinal studies with larger samples. We measured duration at current weight, time since highest weight, and duration of highest weight via self-report. WS represents our exposure variable, and BMI and body fat percentage represent covariates.

Interviews

The *Eating Disorder Examination* (EDE) *17.0D* [83] was selected due to previous evidence of good discriminant validity [84-87], IRR (0.83 to 0.99) [88,89], and good internal consistency of the restraint and body image subscales (Cronbach α>0.70) [90]. The EDE provided 3D outcome variables of eating disorder severity and maintenance, each with high IRR in the current project determined through ICC: LOC frequency (ICC>0.99), size of largest eating/binge-eating episode (in kcal; ICC=0.82), and the Global Scale score (ICC>0.99). LOC frequency represented the total number of eating episodes during the previous 12 weeks during which participants did not feel in control of their eating, regardless of the amount of food consumed. The size of the largest eating/binge-eating episode was captured by asking participants to report the largest amount of food they had eaten during the previous 12 weeks and recording the types and amounts of food consumed within 2 hours and converting these to kilocalories as described previously [78,91]. The EDE also provided scores with high IRR for restraint (ICC>0.99); eating concern (ICC=0.98); weight (ICC=0.99) and shape concerns (ICC>0.99); and symptoms for algorithms to diagnose current *DSM-5* anorexia nervosa (AN), BN, and binge-eating disorder (BED) in combination with objectively measured BMI. EDE symptom frequencies and durations permitted differential diagnoses of other specified feeding or eating disorder (OSFED) proposed by Keel [92]. IRR for symptom frequency or severity (ICC) and associated diagnostic thresholds over 3 months (κ) were good: objective binge episode size (κ=0.71), objective binge episode and inappropriate compensatory behavior frequency (ICC=0.97 and κ=0.93; ICC=0.96 and κ=0.91, respectively), fear of gaining weight or becoming fat (ICC=0.99 and κ=0.91), behavior to prevent weight gain (ICC=0.96 and κ=0.96), weight misperception (ICC=0.98 and κ=0.95), self-evaluation unduly influenced by weight (ICC=0.87) or shape (ICC=0.89 and κ=0.90), characteristics associated with binge episodes (ICC=0.78 and κ=0.73), and marked distress regarding binge eating (ICC=0.91 and κ=0.91). Marked distress regarding binge eating on the EDE was 1 of the 3 indicators of clinical significance for OSFED. The EDE was administered at baseline and 6- and 12-month follow-up assessments.

The Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (SCID-5) [93] captured eating (lifetime) and related disorder diagnoses (lifetime and current). Previous work supported good IRR for SCID diagnoses, with κ=0.92 for major depressive disorder, κ=0.75 for dysthymic disorder, κ=0.81 for any substance use disorder, κ=0.85 for panic disorder, κ=0.91 for social phobia, κ=0.73 for specific phobia, κ=1.00 for obsessive-compulsive disorder, and κ=0.90 for posttraumatic stress disorder [94]. We confirmed the absence of lifetime eating disorder symptoms in noneating disorder controls by ignoring skip rules [95]. The OSFED addendum provided a second indicator of clinical significance. The overview covered current and past treatment, including medication use, to confirm eligibility. At follow-up, we evaluated but did not exclude based on the use, type, dose, and duration of medication, and information may be included as covariates. Follow-up assessments focused on the period since the previous interview (eg, the past 6 months) to reduce participant burden. Current depressive and substance use disorders are covariates.

Self-Reported Questionnaires

C*linical Impairment Assessment* [96] established impairment and distress specifically linked to eating disorder symptoms in the domains of personal, social, and cognitive function. Previous work supported high internal consistency (>0.90), test-retest reliability (0.86), and concurrent and discriminant validity [96,97]. A score ≥16 was a third indicator of clinical significance for OSFED [96].

The *Three-Factor Eating Questionnaire* [98] comprises scales for cognitive restraint, which has successfully differentiated dieters from nondieters for our study's threshold for determining eligibility of controls, and disinhibition and hunger, which distinguish between purging women based on binge episode size [89,91]. Previous work supported good 1-month test-retest reliabilities for cognitive restraint, disinhibition, and hunger subscales of >0.90, 0.80, and 0.83, and internal reliabilities of >0.90, 0.91, and 0.85, respectively [98].

The *Visual Analog Scales* (VAS) assessed momentary states by presenting a single item on each page of a booklet with a 100-mm horizontal line anchored from "none or not at all" to "extreme or extremely." These provided self-reported levels of reward valuation and reward satiation during behavioral tasks. Participants marked the line to record how they felt "Right Now," regarding hunger, fullness, satiation, how much they wanted M&M's and to play the game, how much they liked M&M's and the game, and how rewarding they found M&M's

and gameplay, urge to binge, urge to vomit, nausea, stomach discomfort, sadness, anxiety, tension, and preoccupation with weight and shape. VAS dimensional scores are sensitive to momentary changes associated with postprandial gut peptide responses to a fixed meal, and responses to an ad-lib and fixed meal differ significantly between controls and participants with eating disorders [78,99].

The following measures were included to supplement the clinical description of participants based on the measures described earlier for determining eligibility, exposure, and outcome variables; in response to comments provided during the grant review (Multimedia Appendix 1); and in anticipation of potential questions that may emerge during the review of manuscripts presenting tests of our model.

The *Body Shape Questionnaire* [84] measured feelings and attitudes about body shape and weight as a possible covariate, based on previous evidence of its high test-retest (0.88) [100], high internal reliability (>0.98) [100,101], and good discriminant and concurrent validity.

The *Positive and Negative Affect Scale* [102] assessed trait levels during visit 1 and state levels of positive and negative affect before and after biobehavioral assessments in visits 2 to 5 to examine these as possible covariates of RVE and reward satiation. The Positive and Negative Affect Scale is a widely used measure due to its high internal consistency, test-retest reliability, and construct validity [102,103].

The *Behavioral Inhibition and Behavioral Activation Scales* [104] and the *Sensitivity to Punishment and Sensitivity to Reward Questionnaire* [105] measure reward-related traits. The former measure has demonstrated high internal consistency (0.82) in previous work [104] and concurrent and discriminant validity with the latter measure in eating disorder samples [105].

Leptin, GLP-1, and Insulin Assessments

Enzyme-linked immunosorbent assays (MilliporeSigma) of plasma samples were used to measure leptin (EZHL-80SK) [106], active GLP-1 (EZGLPHS-35K [107], total GLP-1 [EZGLP1T-36K] [108]), and insulin (EZHI-14K) [109] levels. Insulin was added to the protocol in response to grant reviewers' (Multimedia Appendix 1) concerns about the narrow focus on GLP-1 and the evidence that insulin, similar to GLP-1, might influence reward valuation, in addition to its already defined role in satiation [63]. Blood samples were collected into prechilled K2 EDTA vacutainers, following protocol instructions, including the preparation of vacutainers with DPP-IV inhibitor (10 µl/ml of blood) for active GLP-1, before centrifuging at 2000 revolutions per minute for 15 minutes at 4 °C. Plasma was then pipetted into prechilled, aliquot tubes labeled by participant number, analyte, visit, date, and sample number, and immediately placed on ice and transferred to a –80 °C freezer. We extracted up to 4 aliquots, providing up to 3 backup samples for each analyte.

DLW supervised all assays and approved results without knowledge of the participant's clinical status. All participant samples were run in duplicate in 1 assay (eg, baseline leptin from visits 2 and 4) and batched to ensure a balanced representation of control and BN-S participants across assays. When results were outside the detection limits or the intra-assay coefficient of variation (CV) exceeded 10%, backup aliquots were run in subsequent assays to ensure reliable estimates. Preliminary analyses indicated low stability of fasting active GLP-1 levels from visit 2 to 4 (r_{191}=0.18, P=.01) at baseline, raising concerns about fasting active GLP-1 as a sole measure of individual differences in GLP-1 function across visits. We added assays of total GLP-1 in backup samples to the protocol, which had been proposed in our grant application in the section on potential pitfalls and solutions in response to grant reviewers' (Multimedia Appendix 1) concerns about measuring active GLP-1. Total GLP-1 demonstrated adequate stability for fasting concentrations from visit 2 to 4 (r_{193}=0.70; P<.001). The NDA collection includes both active and total GLP-1 values. For participants enrolled after the onset of the COVID-19 pandemic, all GLP-1 values represented total GLP-1 and came from visit 4. Importantly, multilevel model analyses demonstrate that visit 4 VAS fullness ratings were significantly predicted by changes in active GLP-1 (B=0.83, 95% CI 0.65-1.01; t_{734}=9.06; P<.001) and total GLP-1 (B=0.40, 95% CI 0.27-0.54; 2-tailed t_{708}=5.91; P<.001) values, with greater effect size for active GLP-1 level. Thus, both provide valid indicators of GLP-1 function, with total GLP-1 providing more stable, "trait"-like information and active GLP-1 value providing more sensitive, "state"-like information.

The kit user guides and information published on the MilliporeSigma (Merck Group) website and included in assay kits reported the following upper limits of interassay and intra-assay CVs, respectively: 6.2% and 4.6% for leptin [106], <15% and <10% for active GLP-1 [107], <12% and <5% for total GLP-1 [108], and 11.4% to 6.95% for insulin [109]. In our project, mean intraassay and interassay CVs, respectively, were 4.3% and 9% for leptin, 7.4% and 9.5% for active GLP-1, 2.9% and 10.3% for total GLP-1, and 3.9% and 8.9% for insulin. We observed comparable or better CVs compared to published estimates, except for the higher interassay CV for leptin. Date and assay (numbered consecutively) are included in the NDA collection so that future users can control for interassay variability.

Data Structure and Missing Data

NDA data are organized by measure and stored in long form. Variable names indicate visits via the "_#" naming convention. Regardless of when participants were enrolled, variable names retained their original designations. The "_2" suffix reflects variables collected before, during, and after the fasted nonfood RVE task. Similarly, data collected from the fixed meal assessment of GLP-1 and insulin responses are identified by the "_4" suffix, and data collected from the ad-lib meal assessment are identified by the "_5" suffix. Each visit has a "Notes" column to indicate protocol deviations that may impact data quality. In addition to attrition, participants skipping questions, experimenter error, and equipment failures contributed to missing values. Technical problems included M&M's jamming the dispenser and not dispensing the reward after participants reached the criterion (the apparatus was redesigned part way through the project to minimize this problem) and the computer program freezing. When a

participant's effort for reward exceeds the planned ratio, data from the session are included in the data collection but will not be included in planned analyses. Refer to the study by Keel et al [79] for an example of main analyses, which excluded values from sessions with noted problems and sensitivity analyses, including all available data. The NDA collection includes all available data; several variables must be calculated (eg, breakpoint).

Data Analytic Plan

For concurrent tests of severity, we plan to use structural equation models (SEM) in MPlus (version 8; Muthén & Muthén) to obtain estimates of overall model fit; account for shared variance; and provide path estimates within the model, including tests of indirect effects using bias-corrected bootstrapped CIs with 10,000 samples to include all available data in the model from the 399 eligible participants enrolled in the study. This strategy includes running correlations between all variables in the model as a first step, followed by SEM with WS as the sole exogenous variable and the remaining variables as endogenous variables. Both RVE and reward satiation will be modeled as latent variables, with pathways from both behavioral tasks and self-reported states from VAS ratings. For prospective associations and temporal mediation predicting illness maintenance, we proposed cross-lagged SEM with bootstrapping methods for testing indirect effects [110]. Model fit will be evaluated with common fit indices, with the following thresholds for interpreting good fit: root mean square error of approximation, comparative fit index, and Tucker-Lewis Index ≥0.90; root mean square error of approximation value ≤0.05, 95% CI >0.00 to ≤0.08; and standardized root mean square residual ≤0.08 [111-116]. Coefficients and their 95% CIs will be used to evaluate the significance of hypothesized direct and indirect pathways, and only direct pathways that are in the predicted direction, with 95% CIs that do not include 0, will be interpreted as supporting the a priori hypotheses generated by our model.

Sensitivity analyses will evaluate the impact of adding covariates with pathways to each endogenous variable in the model on overall model fit and parameter estimates. Covariates include age, BMI, body fat percentage, enrollment before and after the onset of the COVID-19 pandemic, hormonal contraceptive use, selective serotonin reuptake inhibitors use, current depressive disorder diagnosis, and current substance use disorder diagnosis. Because sensitivity analyses involve nonnested models, we will evaluate whether there is a qualitative change in the adequacy of model fit, from inadequate to adequate or from adequate to good. When there is no qualitative change in model fit, lower values on the Akaike information criterion and Bayesian information criterion will be interpreted as evidence of improved fit.

Power Analyses

We conducted power analyses in R (R Foundation for Statistical Computing) with PowMedR for mediation as our least-powered analyses. Across the posited indirect effects (eg, GLP-1 mediates the association between WS and reward satiation), a sample size of n=195 provides 80% power with path coefficients ≥0.22 from the initial variable to the mediator and from the mediator to the outcome variable, while controlling for the initial variable. Analyses on multiple imputed datasets indicated 80% power with path coefficients ≥0.20 to test indirect effects. We aimed for longitudinal data from 250 participants to permit exploratory moderation analyses for potentially weaker effects at higher BMIs, where leptin levels might be high despite high WS and high food consumption [1].

Ethical Considerations

The FSU Institutional Review Board Human Subjects Committee reviewed and approved the study protocol and materials (HSC 2016.15338/STUDY00000353). Written informed consent was obtained from all study participants before their participation. All data have been deidentified and only a study-generated ID number and a globally unique identifier number in the NDA have been retained. For the original protocol, participants were paid US $75 for day 1, US $50 for day 2, US $100 for day 3, and a US $35 bonus for a total potential compensation of US $780 for baseline and 6- and 12-month follow-up visits. For the revised protocol, participants were paid US $75 for day 1, US $110 for day 3, and a US $15 bonus for a total of US $400 for baseline and 6-month follow-up.

Results

Overview

The project was funded as an investigator-initiated R01 in August 2016, and data collection began in November 2016. Data collection from participants was completed in April 2023, and assays of analytes were completed in June 2023. Information presented on recruitment and retention addresses the feasibility of our design and provides context on information reported on the reliability of measures in the current sample.

Timeline and Recruitment

We aimed to recruit 320 women over a 5-year period to provide clinical, biological, and behavioral data. We estimated that 250 (78.1%) out of 320 women would complete 6- and 12-month follow-up visits, including approximately 78% (200/256) with BN-S and 78% (50/64) control participants. By March 2020, we had recruited 301 eligible participants. Due to the COVID-19 pandemic, the laboratory closed that month for in-person assessments. To retain participants with baseline data who had not completed 12-month follow-up, institutional review board (IRB)–approved, NIMH-approved, and HIPAA-compliant remote clinical assessments were added to our protocol.

On February 19, 2021, we reopened the laboratory for in-person follow-up visits for those who had completed all baseline visits before laboratory closure, implementing IRB-approved safety precautions. The precautions included (1) a screening checklist for symptoms, potential COVID-19 exposure, and a temperature check completed with the participant outside the laboratory before admitting them into the laboratory; (2) allowing only 1 participant into the laboratory at a time; (3) reducing study staff to the minimum required to complete a visit; (4) following masking and social distancing guidelines; (5) sanitizing all surfaces before and after running each participant; and (6) continuing to allow participants to complete follow-up clinical assessments via remote means. The final precaution reflected

evidence of minimal differences between in-person versus remote follow-up assessments conducted among those enrolled before the onset of the COVID-19 pandemic [117]. We adjusted pandemic-related precautions as needed, including periodically pausing in-person assessments in response to spikes in new variants and relaxing precautions with growing community immunity.

On October 8, 2021, we enrolled our first new participant since laboratory closure, supported by 2 no-cost extensions of our NIMH-funded grant and a US Department of Education Higher Education Emergency Relief Fund awarded to FSU. Before enrolling new participants, and with prior approval from the FSU IRB and the NIMH, we revised the protocol to reduce the number of in-person visits to conserve remaining funds and further minimize the risk of COVID-19 exposures. Changes were also informed by evidence of the reliability and the convergent and discriminant validity of our task for measuring RVE for a nonfood reward [79]. We completed data collection in April 2023. We experienced no known incidents of COVID-19 exposure in our laboratory during the project.

Retention

Figures 2 and 3 show retention across study visits and follow-up for participants enrolled before and after the onset of the COVID-19 pandemic, respectively. Among those 399 eligible, 321 (80.5%) had a current BN-S, 78 (19.5%) were noneating disorder controls. A total of 290 (72.7%) out of 399 women completed all baseline assessments, including 226 (70.4%) out of 321 with BN-S and 64 (82.1%) out of 78 controls (χ^2_1=4.3; P=.04; ϕ=0.10). Given the uncertainty surrounding the duration of the COVID-19 pandemic–related closures and concerns for participant safety, participants (91/399, 22.8%) without complete baseline assessments were considered ineligible to continue (n=83, 91% with BN-S and n=8, 9% controls). We estimate that the COVID-19 pandemic impacted 3.3% (13/399) participants' ability to complete baseline assessments, all of whom had BN-S. The mean time between days 1 and 2 was 17.7 (SD 15.1) days, between days 2 and 3 was 16.5 (SD 17.3) days, and between days 1 and 3 was 28.1 (SD 19.3) days. There was no significant difference between groups in days between study visits (P values ranged from .72 to .07, and effect sizes were small; Cohen d=–0.09 to 0.29).

Among the 290 women eligible for follow-up, 249 (85.9%) provided follow-up data, including 96 (33.1%) with 6-month, 123 (42.4%) with 6- and 12-month, and 30 (10.3%) with 12-month data. Groups did not differ in participation at 6-month (χ^2_1=3.5; P=.06; ϕ=0.11) or 12-month follow-up (χ^2_1=0.0; P=.95; ϕ==0.004). The mean time between baseline to 6-month follow-up was 6.0 (SD 2.2) months, 6- to 12-month follow-up was 8.5 (SD 7.8) months, and baseline to 12-month follow-up was 14.6 (SD 5.6) months and did not differ significantly between groups (P values ranged from .82 to .30, and effect sizes were small; Cohen d=–0.09 to 0.29).

Figure 2. Participant flow through the study for participants recruited before the onset of the COVID-19 pandemic. At the 6-month follow-up, 2 additional participants with BN-S completed questionnaire assessments but did not complete interviews for study visit 1. Participants who completed all visits at baseline were recruited to participate at the 12-month follow-up, whether or not they had completed 6-month follow-up. BN-S: bulimia nervosa and related syndromes.

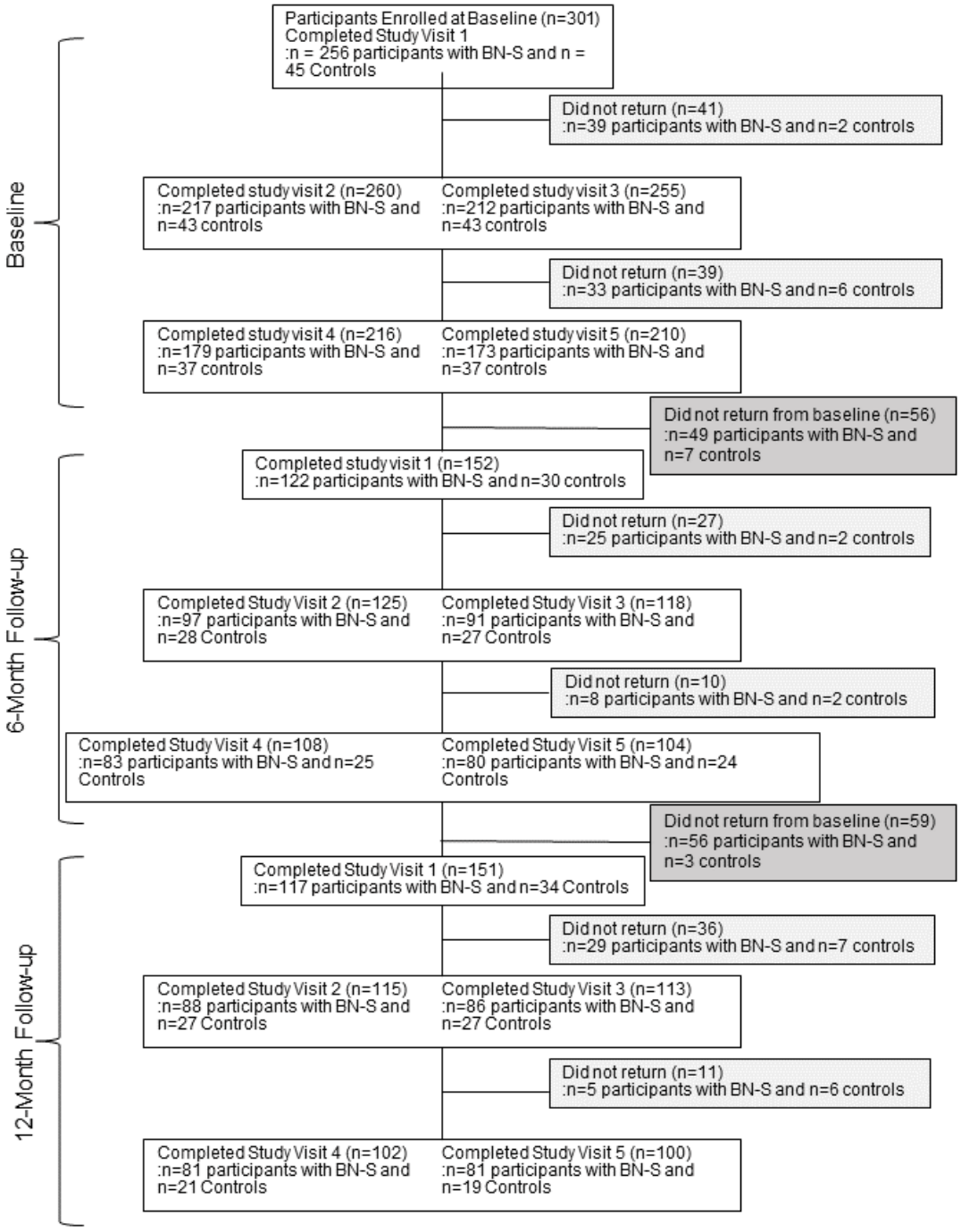
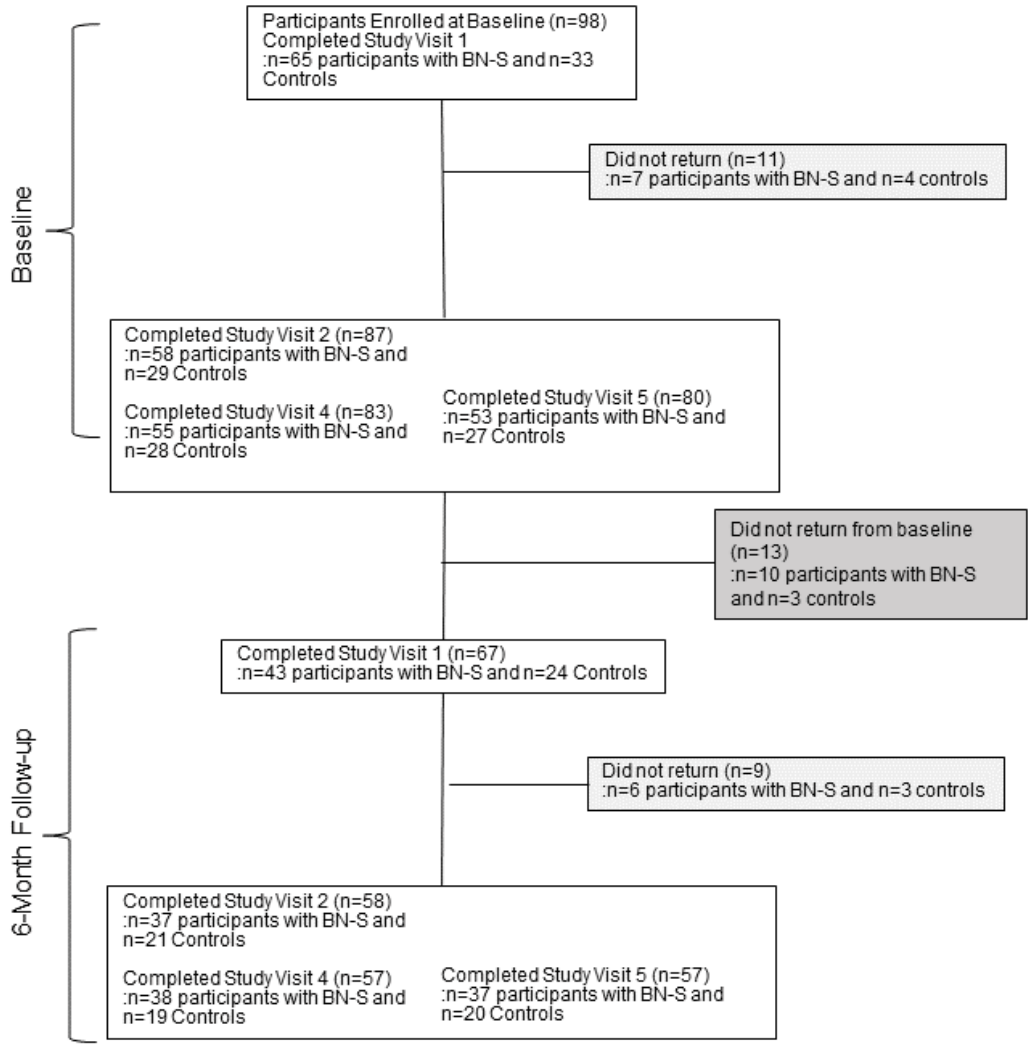


Figure 3. Participant flow through the study for participants recruited after the onset of the COVID-19 pandemic. BN-S: bulimia nervosa and related syndromes.



Sample Descriptors

Table 1 describes sample characteristics. Biological sex as female at birth was required for all participants (Textbox 1), and almost all endorsed being cisgender individuals. We did not assess sexual orientation. According to 2020 US Census data [118], the racial or ethnic composition of Leon County, Florida, was 0.4% American Indian or Alaska Native, 3.8% Asian, 32.1% Black or African American, 8.3% Hispanic or Latino, 0.1% Native Hawaiian or other Pacific Islander, 61% White (54.1% non-Hispanic and non-Latino), and 2.6% multiracial. Racial or ethnic composition of the sample differed from the county population (χ^2_5=91.9; P<.001; Cramer V=0.008), with lower participation among individuals identifying as Black or African American (χ^2_1=72.2; P<.001; ϕ=0.02) and greater participation among those identifying as Native Hawaiian or other Pacific Islander (χ^2_1=4.3; P=.04; ϕ=0.004) or multiracial (χ^2_1=6.7; P=.01; ϕ=0.005) relative to those identifying as White individuals. Furthermore, we observed greater participation among individuals identifying as Hispanic or Latinx compared to non-Hispanic or Latinx (χ^2_1=193.8; P<.001; ϕ=0.03).

There was no significant association between racial or ethnic identity and whether or not participants completed baseline visits (χ^2_5=2.1; P=.84 and χ^2_1=0.0; P=.99) and 6-month (χ^2_5=0.6; P=.99 and χ^2_1=1.3; P=.72) or 12-month (χ^2_5=1.6; P=.90 and χ^2_1=0.1; P=.79) follow-up (all effect sizes for all associations; η^2<0.01). Table 2 presents 6-month sample characteristics, and Table 3 presents 12-month sample characteristics.

Table 1. Characteristics of the sample at baseline for all eligible participants (N=399).

Characteristic	Total, n (%)	Bulimic syndrome group (n=321), n (%)	Control group (n=78), n (%)
Female	399 (100)	321 (100)	78 (100)
Gender			
Woman	397 (99.5)	320 (99.7)	77 (98.7)
Nonbinary	1 (0.2)	0 (0)	1 (1.3)
Not reported	1 (0.2)	1 (0.3)	0 (0)
Ethnicity			
Hispanic or Latino	110 (27.6)	91 (28.3)	19 (24.4)
Not Hispanic or Latino	289 (72.4)	230 (71.7)	59 (75.6)
Race			
American Indian or Alaska Native	2 (0.5)	2 (0.6)	0 (0)
Asian	14 (3.5)	8 (2.5)	6 (7.7)
Black	47 (11.8)	36 (11.2)	11 (14.1)
Hawaiian or other Pacific Islander	2 (0.5)	2 (0.6)	0 (0)
Multiracial	23 (5.8)	20 (6.2)	3 (3.8)
White	311 (77.9)	253 (78.8)	58 (74.4)
Educational level			
Part college	346 (86.7)	284 (88.5)	62 (79.5)
Associate degree	10 (2.5)	6 (1.9)	4 (5.1)
Bachelor degree	10 (2.5)	6 (1.9)	4 (5.1)
Part graduate school	30 (7.5)	24 (7.5)	6 (7.7)
Graduate degree	3 (0.8)	1 (0.3)	2 (2.6)
Relationship status			
Married or having a partner	33 (8.3)	25 (7.8)	8 (10.2)
Divorced or annulled	1 (0.3)	0 (0)	1 (1.3)
Single	241 (60.4)	198 (61.7)	43 (55.1)
In relationship	122 (30.6)	96 (29.9)	26 (33.3)
Other	2 (0.5)	2 (0.6)	0 (0)
Age (y), mean (SD; range)	20.3 (2.6; 18-35)	20.2 (2.5; 18-35)	20.4 (2.5; 18-34)
BMI (kg/m^2), mean (SD; range)	24.6 (4.2; 16.6-35.6)	25.2 (4.2; 16.9-35.6)	22.2 (3.2; 16.6-33.2)
Percentage of body fat, mean (SD; range)	30 (8.2; 6.1-48.7)	31.1 (8; 11.4-48.7)	25.5 (7.4; 6.1-45.8)
Highest BMI (kg/m^2), mean (SD; range)	26.2 (4.8; 17-45.0)	27.0 (4.8; 17.5-45.0)	23.1 (3.6; 17-37.9)
Highest BMI duration (d), mean (SD; range)	202 (276; 0-1825)	189 (256; 0-1460)	253 (340; 2-1825)
Days since highest BMI, mean (SD; range)	461 (642; 0-5110)	467 (649; 0-5110)	434 (614; 0-3650)
Current BMI duration (d), mean (SD; range)	237 (421; 1-5475)	191 (392; 1-5475)	429 (485; 1-2555)

Table 2. Characteristics of the sample at 6-month follow-up (n=221).

Characteristic	Total, n (%)	Bulimic syndrome group (n=167), n (%)	Control group (n=54), n (%)
Female	221 (100)	167 (100)	54 (100)
Gender			
Woman	221 (100)	167 (100)	54 (100)
Ethnicity			
Hispanic or Latino	64 (29)	50 (29.9)	14 (25.9)
Not Hispanic or Latino	157 (71)	117 (70.1)	40 (74.1)
Race			
American Indian or Alaska Native	1 (0.4)	1 (0.6)	0 (0)
Asian	9 (4.1)	5 (3)	4 (7.4)
Black	27 (12.2)	19 (11.4)	8 (14.8)
Hawaiian or other Pacific Islander	1 (0.4)	1 (0.6)	0 (0)
Multiracial	12 (5.4)	10 (6)	2 (3.7)
White	171 (77.4)	131 (78.4)	40 (74.1)
Educational level			
Part college	170 (76.9)	131 (78.4)	39 (72.2)
Associate degree	8 (3.6)	4 (2.4)	4 (7.4)
Bachelor degree	10 (4.5)	6 (3.6)	4 (7.4)
Part graduate school	19 (8.6)	16 (9.6)	3 (5.6)
Graduate degree	2 (0.9)	0 (0)	2 (3.7)
Relationship status			
Married or having a partner	15 (6.8)	11 (6.6)	4 (7.4)
Divorced or annulled	0 (0)	0 (0)	0 (0)
Single	136 (61.5)	103 (61.7)	33 (61.1)
In relationship	63 (28.5)	48 (28.7)	15 (27.8)
Other	2 (0.9)	2 (1.2)	0 (0)
Age (y), mean (SD; range)	20.9 (2.8; 18-35)	20.9 (2.8; 18-33)	20.9 (2.9; 18-35)
BMI (kg/m^2), mean (SD; range)	24.7 (4.4; 17.4-37.7)	25.4 (4.5; 17.4-37.7)	22.5 (3.3; 17.5-35.0)
Percentage of body fat, mean (SD; range)	30.1 (8.0; 11.3-48.6)	31.1 (8.2; 11.3-48.6)	27.2 (6.7; 17.7-45.9)
Highest BMI (kg/m^2), mean (SD; range)	26.4 (5.1; 18-45.2)	27.4 (5.2; 18-45.2)	23.1 (2.9; 18.2-31.3)
Highest BMI duration (d), mean (SD; range)	196 (294; 1-1825)	162 (212; 1-1095)	302 (452; 1-1825)
Days since highest BMI, mean (SD; range)	460 (683; 0-4380)	513 (739; 0-4380)	294 (431; 0-1460)
Current BMI duration (d), mean (SD; range)	192 (298; 1-1825)	142 (190; 1-730)	351 (472; 7-1825)

Participants' mean age did not differ between groups, and BMI was significantly higher in BN-S than control participants ($t_{141.92}$=6.73; P<.001; Cohen d=0.85). Neither age nor BMI was associated with completing baseline or 6-month follow-up (P values ranged from .76 to .19, and Cohen d ranged from –0.13 to 0.03). However, older age (mean 20.6, SD 3.1 vs mean 20.0, SD 2.2 years; $t_{250.04}$=2.12; P=.04; Cohen d=0.24) and lower BMI (mean 23.9, SD 3.9 vs mean 25.0, SD 4.4; $t_{350.24}$=–2.53; P=.01; Cohen d=–0.25) at baseline predicted 12-month follow-up participation. WS was significantly greater in the BN-S group compared to control participants ($t_{157.57}$=4.08; P<.001; Cohen d=0.52) and was not significantly associated with completing baseline or 6- or 12-month follow-up (P values ranged from .31 to .93, and Cohen d ranged from –0.11 to 0.01).

Table 3. Characteristics of the sample at 12-month follow-up (n=153).

Characteristic	Total, n (%)	Bulimic syndrome group (n=119), n (%)	Control group (n=34), n (%)
Female	153 (100)	119 (100)	34 (100)
Gender			
Woman	153 (100)	119 (100)	34 (100)
Ethnicity			
Hispanic or Latino	41 (26.8)	35 (29.4)	6 (17.6)
Not Hispanic or Latino	112 (73.2)	84 (70.6)	28 (82.4)
Race			
American Indian or Alaska Native	1 (0.7)	1 (0.8)	0 (0)
Asian	6 (3.9)	3 (2.5)	3 (8.8)
Black	16 (10.5)	11 (9.2)	5 (14.7)
Hawaiian or other Pacific Islander	1 (0.6)	1 (0.8)	0 (0)
Multiracial	11 (7.2)	8 (6.7)	3 (8.8)
White	118 (77.1)	95 (79.8)	23 (67.6)
Educational level			
Part college	110 (71.9)	88 (73.9)	22 (64.7)
Associate degree	5 (3.3)	4 (3.4)	1 (2.9)
Bachelor degree	12 (7.8)	8 (6.7)	4 (11.8)
Part graduate school	15 (9.8)	13 (10.9)	2 (5.9)
Graduate degree	5 (3.3)	2 (1.7)	3 (8.8)
Relationship status			
Married or having a partner	14 (9.2)	13 (10.9)	1 (2.9)
Divorced or annulled	0 (0)	0 (0)	0 (0)
Single	76 (49.7)	60 (50.4)	16 (47)
In relationship	57 (37.2)	42 (35.3)	15 (44.1)
Other	0 (0)	0 (0)	0 (0)
Age (y), mean (SD; range)	21.9 (3.0; 19-35)	21.8 (2.9; 19-34)	22.5 (3.4; 20-35)
BMI (kg/m^2), mean (SD; range)	24.4 (4.4; 16.7-39.8)	25.0 (4.6; 16.7-39.8)	22.5 (3.1; 17.6-33.4)
Percentage of body fat, mean (SD; range)	28.3 (7.9; 11-50.9)	29.3 (8.1; 11.0-50.9)	24.9 (6.1; 15.2-42.5)
Highest BMI (kg/m^2), mean (SD; range)	25.9 (4.7; 17.7-45.0)	26.7 (4.8; 18.9-45)	23.0 (2.8; 17.7-32.6)
Highest BMI duration (d), mean (SD; range)	216 (363; 1-3650)	177 (196; 1-1095)	375 (702; 14-3650)
Days since highest BMI, mean (SD; range)	490 (648; 0-2555)	511 (649; 0-2555)	413 (651; 0-2190)
Current BMI duration (d), mean (SD; range)	230 (412; 0-3650)	171 (222; 0-1095)	467 (772; 7-3650)

Eating Disorder and Psychiatric Diagnoses and Treatment

Table 4 presents *DSM-5* eating disorder and other psychiatric diagnoses and features at baseline. BN was the most common diagnosis, followed by OSFED-BN of low frequency or duration, with few participants meeting the criteria for current AN, BED, or their related OSFED. Diagnosis was significantly associated with completing baseline visits (χ^2_3=8.9; P=.03; ϕ=0.10), occurring in 7 (88%) out of 8 participants with AN binge-purging, 118 (77.1%) out of 153 participants with BN, 2 (50%) out of 4 participants with BED, and 99 (63.5%) out of 156 participants with OSFED diagnoses.

Table 4. Lifetime and current eating disorder and other psychiatric diagnoses and treatment at baseline (N=399).

	Total, n (%)	Bulimic syndrome group (n=321), n (%)	Control group (n=78), n (%)
EDE[a] current diagnosis			
AN[b] binge-purging	—[c]	8 (2.5)	—
BN[d]	—	153 (47.7)	—
BED[e]	—	4 (1.2)	—
OSFED[f]	—	156 (48.6)	—
OSFED subtypes[g]			
Atypical AN[h]			
Broad	—	11 (3.4)	—
Narrow	—	9 (2.8)	—
BN low frequency or duration			
Broad	—	136 (42.3)	—
Narrow	—	118 (36.8)	—
BED low frequency or duration			
Broad	—	4 (1.2)	—
Narrow	—	3 (0.9)	—
Other or unspecified			
Broad	—	5 (1.6)	—
Narrow	—	26 (8.1)	—
SCID-5[i] lifetime ED[j] diagnosis			
AN (κ=0.93)	—	42 (13.1)	—
BN (κ=0.92)	—	230 (71.7)	—
BED (κ=0.88)	—	62 (19.3)	—
OSFED[k] (κ=0.92)	—	159 (49.5)	—
Atypical AN	—	14 (4.4)	—
BN low frequency or duration	—	124 (38.6)	—
BED low frequency or duration	—	11 (3.4)	—
PD[l]	—	2 (0.6)	—
NES[m]	—	0 (0)	—
Other or unspecified	—	8 (2.5)	—
SCID-5 diagnoses (κ)			
Major depressive disorder			
Lifetime (κ=0.85)	183 (45.9)	175 (54.5)	8 (10)
Current (κ=0.74)	46 (11.5)	46 (14.3)	0 (0)
Persistent depressive disorder			
Lifetime (κ=0.87)	118 (29.6)	113 (35.2)	5 (6)
Current (κ=0.94)	73 (18.3)	71 (22.1)	2 (3)
Any mood disorder			
Lifetime (κ=0.98)	270 (67.7)	256 (79.8)	14 (18)
Current (κ=0.95)	121 (30.3)	118 (36.8)	3 (4)

	Total, n (%)	Bulimic syndrome group (n=321), n (%)	Control group (n=78), n (%)
Alcohol use disorder			
Lifetime (κ=0.92)	149 (37.3)	139 (43.3)	10 (13)
Current (κ=0.81)	96 (24.1)	90 (28)	6 (8)
Cannabis use disorder			
Lifetime (κ=0.90)	113 (28.3)	107 (33.3)	6 (8)
Current (κ=1.00)	74 (18.5)	71 (22.1)	3 (4)
Any substance use disorder			
Lifetime (κ=0.90)	197 (49.4)	183 (57)	14 (18)
Current (κ=0.83)	136 (34.1)	128 (39.9)	8 (10)
Any anxiety disorder			
Lifetime (κ=0.94)	213 (53.4)	203 (63.2)	10 (13)
Current (κ=0.97)	183 (45.9)	178 (55.5)	5 (6)
Obsessive-compulsive disorder			
Lifetime (κ=0.82)	55 (13.8)	53 (16.5)	2 (3)
Current (κ=0.85)	46 (11.5)	45 (14)	1 (1)
Posttraumatic stress disorder			
Lifetime (κ=0.91)	106 (26.6)	104 (32.4)	2 (3)
Current (κ=0.68)	49 (12.3)	49 (15.3)	0 (0)
Any trauma-related disorder			
Lifetime (κ=0.98)	115 (28.8)	111 (34.6)	4 (5)
Current (κ=0.73)	63 (15.8)	62 (19.3)	1 (1)
Suicide-related variables			
Lifetime ideation	177 (44.4)	167 (52)	10 (13)
Past week ideation	19 (4.8)	19 (5.9)	0 (0)
Lifetime suicide attempt	43 (10.8)	42 (13.1)	1 (1)
Psychological treatment			
Inpatient: lifetime	23 (5.8)	21 (6.5)	2 (3)
Any treatment: lifetime	226 (56.6)	200 (62.3)	26 (33)
Current outpatient	64 (16)	57 (17.8)	7 (9)
Current medications			
Stable SSRI[n] over 8 wk	38 (9.5)	34 (10.6)	4 (5)

	Total, n (%)	Bulimic syndrome group (n=321), n (%)	Control group (n=78), n (%)
Hormonal contraceptive	183 (45.9)	146 (45.5)	37 (47)

[a]EDE: Eating Disorder Examination.

[b]AN: anorexia nervosa.

[c]Not applicable.

[d]BN: bulimia nervosa.

[e]BED: binge-eating disorder.

[f]OSFED: other specified feeding or eating disorder.

[g]Guidelines presented by Keel [92] were followed for differential diagnosis of OSFED. There were no cases of current purging disorder due to the requirement of recurrent objectively large binge episodes as an inclusion criterion for participants with BN and related syndromes. In addition, 2 sets of criteria were used. Broad criteria were based on the key features that distinguish among the OSFEDs, such as significant weight loss of atypical AN, the presence of binge eating and inappropriate compensatory behaviors for BN of subthreshold duration or frequency, and the presence of binge eating and absence of recurrent inappropriate compensatory behavior for BED of subthreshold duration or frequency. Narrow criteria required the associated cognitive and affective features for each OSFED diagnosis so that narrow criteria for atypical AN indicated that all criteria for AN were met except for low weight, all criteria for BN were met except for duration or frequency of behavioral symptoms, and all criteria for BED were met except for duration or frequency of binge-eating episodes.

[h]Significant weight loss was defined as >5% reduction in BMI within 30 days or BMI <19 kg/m^2.

[i]SCID-5: Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition.

[j]ED: eating disorder.

[k]Lifetime OSFED diagnoses were based on clinical interviewer assessments in the SCID-5. Given the possibility of meeting a lifetime diagnosis for >1 OSFED, no diagnostic hierarchy was used; however, parsimony was applied in making lifetime OSFED diagnoses to avoid diagnosing a prodromal phase or period of partial remission as a separate diagnosis.

[l]PD: purging disorder.

[m]NES: night eating syndrome.

[n]SSRI: selective serotonin reuptake inhibitor.

Most BN-S participants had a lifetime mood (256/321, 79.8%), substance use (183/321, 57%), or anxiety disorder (203/321, 63.2%), whereas most noneating disorder controls did not (14/78, 18%; 14/78, 18%; 10/78, 13%). All suicide indicators were more common in BN-S participants compared to controls (lifetime suicidal ideation: χ^2_1=39.1; P<.001; ϕ=0.32; past week suicidal ideation: χ^2_1=4.4; P=.04; ϕ=0.11; and lifetime suicide attempt: χ^2_1=9.1; P=.003; ϕ=0.15). No suicide attempts were reported in the week before the interview. Reflecting group differences, lifetime treatment for mental health was twice as likely in BN-S compared to control participants (χ^2_1=21.5; P<.001; ϕ=0.23).

Eating disorder diagnosis was not associated with participation at 6- or 12-month follow-up (Table 5 outlines 6-month follow-up data and Table 6 outlines 12-month follow-up data). Participants with current or lifetime obsessive-compulsive disorder at baseline were significantly less likely to participate at 12-month follow-up (χ^2_1=4.6; P=.03; ϕ=0.11 and χ^2_1=5.7; P=.01; ϕ=0.12, respectively). There were no other significant associations between completing baseline or follow-up visits and current or lifetime psychiatric diagnoses, suicide-related variables, or treatment.

Table 5. Current eating disorder and other psychiatric diagnoses and treatment at 6-month follow-up (n=221).

	Total, n (%)	Bulimic syndrome group (n=167), n (%)	Control group (n=54), n (%)
EDE[a] current diagnosis			
No eating disorder	72 (32.6)	19 (11.4)	53 (98)
AN-bp[b]	5 (2.3)	5 (3)	0 (0)
BN[c]	38 (17.2)	38 (22.8)	0 (0)
BED[d]	2 (0.9)	2 (1.2)	0 (0)
OSFED[e]	102 (46.2)	101 (60.5)	1 (2)
OSFED subtypes			
Atypical AN[f]			
Broad	9 (4.1)	9 (5.4)	0 (0)
Narrow	5 (2.3)	5 (3)	0 (0)
BN low frequency or duration			
Broad	62 (28.1)	62 (37.1)	0 (0)
Narrow	49 (22.2)	49 (29.3)	0 (0)
BED low frequency or duration			
Broad	5 (2.3)	5 (3)	0 (0)
Narrow	2 (0.9)	2 (1.2)	0 (0)
Other or unspecified			
Broad	26 (11.8)	25 (15)	1 (2)
Narrow	46 (20.8)	45 (26.9)	1 (2)
SCID-5[g] current diagnoses			
Major depressive disorder	15 (6.8)	15 (9)	0 (0)
Persistent depressive disorder	29 (13.1)	27 (16.2)	2 (4)
Any mood disorder	47 (21.3)	45 (26.9)	2 (4)
Alcohol use disorder	38 (17.2)	34 (20.4)	4 (7)
Cannabis use disorder	27 (12.2)	24 (14.4)	3 (6)
Any substance use disorder	58 (26.2)	52 (31.1)	6 (11)
Any anxiety disorder	73 (33)	66 (39.5)	7 (13)
Obsessive-compulsive disorder	23 (10.4)	22 (13.2)	1 (2)
Posttraumatic stress disorder	20 (9)	18 (10.8)	2 (4)
Any trauma-related disorder	23 (10.4)	21 (12.6)	2 (4)
Suicidal ideation in the past week	9 (4.1)	9 (5.4)	0 (0)
Current treatment and medications			
Outpatient	31 (14)	28 (16.8)	3 (6)
SSRI[h]	16 (7.2)	15 (9)	1 (2)
Hormonal contraceptives	75 (33.9)	57 (34.1)	18 (33)

[a]EDE: Eating Disorder Examination.

[b]AN-bp: anorexia nervosa binge-purging.

[c]BN: bulimia nervosa.

[d]BED: binge-eating disorder.

[e]OSFED: other specified feeding or eating disorder.

[f]AN: anorexia nervosa.

[g]SCID-5: Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition.
[h]SSRI: selective serotonin reuptake inhibitor.

Table 6. Current eating disorder and other psychiatric diagnoses and treatment at 12-month follow-up (n=153).

	Total, n (%)	Bulimic syndrome group (n=119), n (%)	Control group (n=34), n (%)
EDE[a] current diagnosis			
No eating disorder	63 (41.1)	30 (25.2)	33 (97)
AN-bp[b]	3 (2)	3 (2.5)	0 (0)
BN[c]	16 (10.5)	16 (13.4)	0 (0)
BED[d]	0 (0)	0 (0)	0 (0)
OSFED[e]	69 (45.1)	68 (57.1)	1 (3)
OSFED subtypes			
Atypical AN[f]			
Broad	3 (2)	3 (2.5)	0 (0)
Narrow	3 (2)	3 (2.5)	0 (0)
BN low frequency or duration			
Broad	41 (26.8)	41 (34.5)	0 (0)
Narrow	31 (20.3)	31 (26.1)	0 (0)
BED low frequency or duration			
Broad	3 (2)	3 (2.5)	0 (0)
Narrow	3 (2)	3 (2.5)	0 (0)
Other or unspecified			
Broad	22 (14.4)	21 (17.6)	1 (3)
Narrow	32 (20.9)	31 (26.1)	1 (3)
SCID-5[g] current diagnoses			
Major depressive disorder	10 (6.5)	10 (8.4)	0 (0)
Persistent depressive disorder	24 (15.7)	23 (19.3)	1 (3)
Any mood disorder	33 (21.6)	32 (26.9)	1 (3)
Alcohol use disorder	25 (16.3)	24 (20.2)	1 (3)
Cannabis use disorder	17 (11.1)	16 (13.4)	1 (3)
Any substance use disorder	39 (25.5)	38 (31.9)	1 (3)
Any anxiety disorder	44 (28.8)	43 (36.1)	1 (3)
Obsessive-compulsive disorder	15 (9.8)	14 (11.8)	1 (3)
Posttraumatic stress disorder	11 (7.2)	11 (9.2)	0 (0)
Any trauma-related disorder	15 (9.8)	15 (12.6)	0 (0)
Suicidal ideation in the past week	2 (1.3)	2 (1.7)	0 (0)
Current treatment and medications			
Outpatient	27 (17.6)	26 (21.8)	1 (3)
SSRI[h]	4 (2.6)	4 (3.4)	0 (0)
Hormonal contraceptives	57 (37.3)	43 (36.1)	14 (41)

[a]EDE: Eating Disorder Examination.

[b]AN-bp: anorexia nervosa binge-purging.

[c]BN: bulimia nervosa.

[d]BED: binge-eating disorder.

[e]OSFED: other specified feeding or eating disorder.

[f]AN: anorexia nervosa.

[g]SCID-5: Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition.

[h]SSRI: selective serotonin reuptake inhibitor.

Psychometric Properties of Measures

IRR was excellent for all lifetime and substantial for current SCID-5 diagnoses [119,120]. Table 4 includes κ statistics for lifetime and current SCID-5 diagnoses based on IRR assessment from an independent review of 127 interviews across the full project, including baseline and follow-up assessments. Estimates include in-person and remote interviews.

Table 7 presents internal consistency and Table 8 provides test-retest reliability for EDE interview and questionnaire scales. Cronbach α exceeded thresholds for acceptability across all assessments and compared favorably to published estimates for all measures. Test-retest reliability was good and generally higher over shorter intervals, likely reflecting true change in constructs over time.

Table 7. Internal consistency reliability of measures at baseline and follow-up.

Measures	Cronbach α at baseline	Cronbach α at 6 mo	Cronbach α at 12 mo
Eating pathology			
Eating Disorder Examination interview			
Global	0.90	0.91	0.90
Restraint	0.83	0.81	0.81
Eating concern	0.76	0.77	0.81
Shape concern	0.92	0.91	0.91
Weight concern	0.86	0.87	0.82
Self-report			
Clinical impairment assessment	0.96	0.97	0.96
Body shape questionnaire	0.98	0.99	0.98
Three-Factor Eating Questionnaire			
Cognitive restraint	0.92	0.93	0.91
Disinhibition	0.90	0.89	0.90
Hunger	0.78	0.79	0.74
Reward or inhibition			
Behavioral inhibition scale	0.81	0.77	0.79
Behavioral Activation Scale	0.85	0.89	0.88
Drive	0.78	0.84	0.86
Fun seeking	0.73	0.74	0.79
Reward responsiveness	0.73	0.77	0.77
Sensitivity to Reward and Sensitivity to Punishment Questionnaire			
Sensitivity to reward	0.77	0.78	0.81
Sensitivity to punishment	0.89	0.88	0.89
Affect			
Positive and Negative Affect Schedule			
Positive affect	0.89	0.90	0.94
Negative affect	0.89	0.92	0.93

Table 8. Test-retest reliability of measures across assessment waves.

Measures	Baseline to 6 mo, *r*	6 to 12 mo, *r*	Baseline to 12 mo, *r*
Eating pathology			
Eating Disorder Examination interview			
Global	0.85	0.79	0.76
Restraint	0.74	0.64	0.67
Eating concern	0.65	0.60	0.53
Shape concern	0.84	0.79	0.76
Weight concern	0.79	0.78	0.70
Self-report			
Clinical impairment assessment	0.79	0.82	0.71
Body shape questionnaire	0.85	0.85	0.82
Three-Factor Eating Questionnaire			
Cognitive restraint	0.85	0.82	0.82
Disinhibition	0.84	0.78	0.78
Hunger	0.70	0.59	0.60
Reward or inhibition			
Behavioral Inhibition Scale	0.68	0.78	0.70
Behavioral Activation Scale	0.68	0.68	0.57
Drive	0.65	0.57	0.54
Fun seeking	0.65	0.68	0.58
Reward responsiveness	0.59	0.65	0.50
Sensitivity to Reward and Sensitivity to Punishment Questionnaire			
Sensitivity to reward	0.68	0.75	0.66
Sensitivity to punishment	0.83	0.90	0.82
Affect			
Positive and Negative Affect Schedule			
Positive affect	0.59	0.79	0.67
Negative affect	0.64	0.65	0.49

Discussion

Principal Findings

The study protocol is designed to test an explanatory biobehavioral model for the association between WS and severity and maintenance of BN and related eating disorders characterized by binge eating. For BN-S severity, we expect significant cross-sectional associations between greater WS, lower leptin levels, lower GLP-1 response, greater reward valuation, and lower reward satiation. We also anticipate that greater reward valuation will be significantly associated with higher LOC frequency and a significant indirect pathway from greater WS to higher LOC frequency via lower leptin levels, lower GLP-1 response, and greater reward valuation. Furthermore, we expect that lower reward satiation will be significantly associated with larger eating/binge-eating episode size and a significant indirect pathway from greater WS to larger eating/binge-eating episode size via lower leptin levels, lower GLP-1 response, and lower reward satiation. If supported, findings would demonstrate that biological concomitants of WS explain variance in binge-eating severity via alterations in reward valuation and reward satiation. For BN-S maintenance (vs remission), we hypothesized significant prospective associations between these variables, with reward valuation and reward satiation temporally mediating associations between WS as the exposure and changes in LOC frequency and eating/binge-eating episode size, respectively, as the outcomes. If supported, findings would have implications for the assessment, diagnosis, and future clinical trials of eating disorders characterized by binge eating.

Current standardized eating disorder assessments, including the SCID-5 [93] and the EDE 17.0D [83], secure information about current body weight and lowest body weight in relation to height. However, neither includes a question about the highest lifetime adult weight. If findings support hypotheses, then future assessments would benefit from including this question to calculate WS as a prognostic indicator.

Results may inform diagnostic criteria for eating disorders. The *DSM-5* currently uses BMI as a severity indicator for AN, frequency of inappropriate compensatory behaviors for BN, and frequency of binge-eating episodes for BED [5]. If our model supports WS as a marker of severity transdiagnostically, then WS could provide a common metric across eating disorders and potentially explain differences in outcomes among them. Beyond broad, transdiagnostic implications, findings may also refine the discrepancies between the *DSM-5* and *International Classification of Diseases, 11th Revision* (*ICD-11*) in the definition of a binge-eating episode for diagnosis of BN and BED. Our model focuses on the *DSM-5* definition, which requires the consumption of an objectively large amount of food in addition to LOC. The *ICD-11* requires a subjective LOC combined with eating either "notably more or differently than usual" [121]. If findings support posited pathways from WS to episode size and LOC, this would support the validity of the *DSM-5* definition over the *ICD-11* definition.

Finally, given recent interest and controversy surrounding the use of GLP-1 agonists for binge eating (eg, semaglutide in Wegovy and Ozempic) [122,123], these longitudinal data, funded solely by the NIMH and the US Department of Education, can elucidate mixed findings from early clinical trials [124-126] and inform the design of future investigations. Specifically, our model contextualizes the impact of GLP-1 function for those who have lost weight, predicting greater disruptions associated with greater WS. Previous studies supporting the potential efficacy of GLP-1 agonists have relied on secondary analyses of data collected in open trials [125-127] or a randomized controlled treatment trial for obesity without placebo control [128]. In the sole double-blind, randomized controlled trial testing a GLP-1 agonist against a placebo for the treatment of BED [124], no significant differences emerged in remission of binge eating or BED. Similar to other studies of GLP-1 agonists, weight loss was significantly greater in the active compared to the control condition. However, participants on placebo lost only 0.9 (SD 0.7) kg over 17 weeks. Comparing improvements in binge eating on a placebo without weight loss may not provide a valid comparison against those treated with liraglutide, who lost 4.7 (0.8) kg of weight and experienced decreases in binge eating [124]. If our hypotheses are supported, future evaluations of GLP-1 efficacy will examine WS at intake and relative changes in weight over treatment as covariates in predicting changes in binge-eating severity.

Strengths of the project include the large, diverse sample; inclusion of multiple units of analysis; and longitudinal design, with high retention across multiple visits at baseline and high retention over follow-up. We retained 290 (72.7%) out of 399 women for all clinical, behavioral, and biological assessments at baseline, and 249 (85.8%) of these 290 women provided longitudinal data. This supports the feasibility of our approach even in the face of unanticipated challenges encountered with the onset of the COVID-19 pandemic. Studies using laboratory-based feeding paradigms [81] have included anywhere from 7 to 103 participants in PR tasks and fixed or ad-lib meals. Our combination of all methods in 290 participants far exceeds these benchmarks. Furthermore, most biobehavioral studies were constrained by their cross-sectional design, limiting conclusions regarding the role of observed disruptions as correlates, consequences, or contributors to pathology. Our measures had strong psychometric properties that minimized random error, and initial analyses indicate that effect sizes will exceed original estimates. Thus, we will have sufficient power for prospective analyses.

Project weaknesses include the absence of sexual orientation information and the exclusion of male participants. Eating disorders, including AN binge-purging, BN, BED, and their OSFED variants, predominantly affect female individuals [129,130]. Although restricting recruitment to women limits generalizability to men due to potential biologically based differences in the influence of ovarian hormones on GLP-1 function [65], it was not feasible to recruit enough men to directly examine sex as a biological variable. This limitation was due to the large sample size required for adequately powered analyses and the low prevalence of eating disorders in men. Despite this limitation, findings may impact the assessment, diagnosis, and treatment of a majority of those with eating disorders characterized by binge eating, given the preponderance of these disorders in women [129,130]. Furthermore, the sample demonstrated limited diversity in socioeconomic status. Participation requirements were likely too high for most individuals with limited resources or full-time commitments at work or home. These factors will impact the generalizability of findings. Attrition was related to age, BMI, and the presence of a BN-S at baseline. Greater attrition in BN-S may reflect a higher participant burden in this group, including longer interview duration due to greater pathology and behavioral task duration due to higher RVE and lower reward satiation. BN-S participants endorsed greater impairment, which may extend to impaired ability to follow through with study participation. Among participants who provided full baseline data and were eligible for longitudinal follow-up, we did not observe significant differences between BN-S and control groups. We advise using all available data with imputation for missing values to minimize the influence of biased attrition.

Finally, in using the RDoC approach to participant recruitment, we did not set a priori goals for the recruitment of participants who would fall into specific *DSM-5* diagnostic groups, and this may have limited the extent to which our sample has a transdiagnostic representation of all eating disorders characterized by binge eating. The requirement that participants be medically healthy and free of medications that could influence weight or appetite was necessitated by our interest in biological factors underlying RVE and satiation, consistent with the RDoC approach. This may have restricted the number of participants who presented with AN or BED, given the associations between extreme BMI and medical conditions. This, combined with our age range, may explain the large number of participants with *DSM-5* BN and OSFED characterized as BN with low duration or frequency. The latter group could lead to misinterpretation of the sample as including participants with "subthreshold" eating disorders. However, all participants had a full-threshold *DSM-5* eating disorder. Further, the minimum behavioral symptom frequency ensured that all participants met the minimum symptom frequency required for a *DSM-5* diagnosis of BED. Many of our OSFED participants

were engaging in binge eating frequently enough for a diagnosis of BN or BED, but the frequency of inappropriate compensatory behaviors was too high for a diagnosis of BED and too low for a diagnosis of BN.

Conclusions

Preliminary data from subsets of participants in this project have been included in other reports [1,79,131-133]; however, this is the first report presenting data from all participants and all waves. Future papers will focus on testing our model to predict the severity and maintenance of BN-S. Beyond testing our RDoC-informed model, biological and behavioral variables will be examined in novel combinations as predictors of changes in eating disorder expression and comorbidity. A careful review of this paper will help researchers accessing data through the NDA identify which data are most relevant (eg, active vs total GLP-1), their context (eg, pre– vs post–COVID-19 pandemic), and other factors that may influence interpretations. Grounding analyses with a full understanding of methods will facilitate rigorous and reproducible research.

Acknowledgments

The authors would like to acknowledge the following individuals for their contributions to data collection: Alexandra Brockdorf, Annie Reynolds, Beatriz Varela, Blaise Huntley, Calyn Maske, Charlotte Grillot, Chelsea Lynch, Elizabeth Fitzgerald, Eunyoung Choi, Gabriela Aguilera Tovar, Grace Kennedy, Jean Forney, Jessica Bahorski, Joshua Paredes, Karin Fisher, Kathleen Hower, Kelly Klein, Kelsey Kaiser, Kimberly Martinez, Kimberly Sheldon, Lisa Anderson, Lisandra Alfaro, Madeline Wick, Maggie Walsh, Maria Gabriela Cucalón Cabarcos, Mariana Villarroel Rojas, Mariela Rodriguez, Megan Whitaker, Mia Newlin-Bradner, Molly Franklin, Morgan de Casenave-Patterson, Neha Shete, Nicole Lilly, Rachel Busby-Drewek, Rebecca Berhalter, Sophie Abber, and Tiffany Bradley.

Data Availability

The datasets generated or analyzed during this study are available in the National Institute of Mental Health Data Archive repository [134].

Conflicts of Interest

JA serves on the Advisory Board of EMD Serono on HIV-related research. All other authors declare no other conflicts of interest.

Multimedia Appendix 1
Peer-review report from the Center for Scientific Review Special Emphasis Panel Member Conflict: Sleep, Memory, Anxiety, and Reward (ZRG1 BBBP-Z [02]; National Institutes of Health).
[PDF File (Adobe PDF File), 137 KB - resprot_v14i1e66554_app1.pdf]

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Abbreviations

AN: anorexia nervosa
Arc: arcuate nucleus
BED: binge-eating disorder
BN: bulimia nervosa
BN-S: bulimia nervosa and related syndromes
CART: cocaine- and amphetamine-regulated transcript
CV: coefficient of variation
DSM-5: Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
EDE: Eating Disorder Examination
FSU: Florida State University
GLP-1: glucagon-like peptide 1
HIPAA: Health Insurance Portability and Accountability Act
ICC: intraclass correlation
ICD-11: International Classification of Diseases, 11th Revision
IRB: institutional review board
IRR: interrater reliability
LOC: loss of control
NAc: nucleus accumbens
NDA: National Institute of Mental Health Data Archive
NIMH: National Institute of Mental Health
NPY/AgRP: neuropeptide Y and agouti-related protein
NTS: nucleus of the solitary tract
OSFED: other specified feeding or eating disorder
PR: progressive ratio
RDoC: Research Domain Criteria
RVE: reward valuation effort
SCID-5: Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
SEM: structural equation model
VAS: Visual Analog Scale
VTA: ventral tegmental area
WS: weight suppression

Edited by A Schwartz; submitted 16.09.24; this is a non–peer-reviewed article;accepted 05.03.25; published 08.04.25.

Please cite as:
Keel PK, Bodell LP, Ali SI, Starkey A, Trotta J, Luxama JW, Halfhide C, Hill NG, Appelbaum J, Williams DL
Examining Weight Suppression, Leptin Levels, Glucagon-Like Peptide 1 Response, and Reward-Related Constructs in Severity and Maintenance of Bulimic Syndromes: Protocol and Sample Characteristics for a Cross-Sectional and Longitudinal Study
JMIR Res Protoc 2025;14:e66554
URL: https://www.researchprotocols.org/2025/1/e66554
doi:10.2196/66554
PMID:

Protocol

The Application of Machine Learning Algorithms to Predict HIV Testing in Repeated Adult Population–Based Surveys in South Africa: Protocol for a Multiwave Cross-Sectional Analysis

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Abstract

Background: HIV testing is the cornerstone of HIV prevention and a pivotal step in realizing the Joint United Nations Program on HIV/AIDS (UNAIDS) goal of ending AIDS by 2030. Despite the availability of relevant survey data, there exists a research gap in using machine learning (ML) to analyze and predict HIV testing among adults in South Africa. Further investigation is needed to bridge this knowledge gap and inform evidence-based interventions to improve HIV testing.

Objective: This study aims to determine consistent predictors of HIV testing by applying supervised ML algorithms in repeated adult population-based surveys in South Africa.

Methods: A retrospective analysis of multiwave cross-sectional survey data will be conducted to determine the predictors of HIV testing among South African adults aged 18 years and older. A supervised ML technique will be applied across the five cycles of the South African National HIV Prevalence, Incidence, Behavior, and Communication Survey (SABSSM) surveys. The Human Science Research Council (HSRC) conducted the SABSSM surveys in 2002, 2005, 2008, 2012, and 2017. The available SABSSM datasets will be imported to RStudio (version 4.3.2; Posit Software, PBC) to clean and remove outliers. A chi-square test will be conducted to select important predictors of HIV testing. Each dataset will be split into 80% training and 20% test samples. Logistic regression, support vector machines, random forests, and decision trees will be used. A cross-validation technique will be used to divide the training sample into k-folds, including a validation set, and models will be trained on each fold. The models' performance will be evaluated on the validation set using evaluation metrics such as accuracy, precision, recall, F_1-score, area under curve-receiver operating characteristics, and confusion matrix.

Results: The SABSSM datasets are open access datasets available on the HSRC database. Ethics approval for this study was obtained from the University of Johannesburg Research and Ethics Committee on April 23, 2024 (REC-2725-2024). The authors were given access to all five SABSSM datasets by the HSRC on August 20, 2024. The datasets were explored to identify the independent variables likely influencing HIV testing uptake. The findings of this study will determine consistent variables predicting HIV testing uptake among the South African adult population over the course of 20 years. Furthermore, this study will evaluate and compare the performance metrics of the 4 different ML algorithms, and the best model will be used to develop an HIV testing predictive model.

Conclusions: This study will contribute to existing knowledge and deepen understanding of factors linked to HIV testing beyond traditional methods. Consequently, the findings would inform evidence-based policy recommendations that can guide policy makers to formulate more effective and targeted public health approaches toward strengthening HIV testing.

International Registered Report Identifier (IRRID): DERR1-10.2196/59916

(JMIR Res Protoc 2025;14:e59916) doi:10.2196/59916

KEYWORDS

predictive modelling; testing; support vector machines; random forest; supervised machine learning; decision trees; adult; population-based; South Africa; protocol; HIV/AIDS; HIV testing; retrospective analysis; cross-sectional survey; chi-square test; logistic regression; public health; epidemiology; infectious disease

Introduction

HIV/AIDS remains a public health threat, affecting 39 million people globally, of whom 25.6 million are within the Sub-Saharan African region [1]. More than half of the global HIV prevalence is concentrated in East and Southern Africa, according to the World Health Organization and the Joint United Nations Program on HIV/AIDS (UNAIDS) [1,2]. HIV testing is a crucial component of the HIV prevention and care continuum [3] and a pivotal step in realizing the UNAIDS's goal of ending AIDS by 2030 [4]. It aims to diagnose and minimize HIV transmission rates while enabling early and effective treatment. Rolling out HIV testing coverage and accessibility to populations with low HIV testing prevalence could assist in improving HIV epidemic control and elimination efforts [3-7].

South Africa has made significant progress toward the UNAIDS 2030 target, ensuring 90% of people living with HIV are aware of their status by the end of 2022 [8,9]. However, the country remains behind schedule as the 90% attainment was set for 2020. Furthermore, there still exist numerous barriers to the uptake of HIV testing [10]. According to Simbayi et al [10], lack of HIV testing is one of the key drivers of HIV infections among the South African adult population.

Previous studies have identified sociodemographic factors, sociobehavioral factors, socioeconomic factors, sexual behaviors, knowledge, attitudes, and perceptions about HIV that could influence an individual's decision to undergo HIV testing [6,7,11,12]. The uptake of HIV testing was found to be very low (34.9%) among Ethiopian youth due to regional variations [11]. The study revealed that being a male, following a protestant religion or orthodox religion negatively influenced the uptake of HIV testing [11]. The same study [11] noted that Ethiopian youth might undergo HIV testing if they have a good knowledge of HIV, engage in risky sexual behavior, are married, are rich, and have access to media. A retrospective analysis of the 2017 South African National HIV Prevalence, Incidence, Behavior, and Communication Survey (SABSSM) survey by Jooste et al [12] highlighted geographic variations by districts and sex in HIV testing among individuals aged 15 years and older. The districts with the lowest HIV testing were uMkhanyakude (54.7%) and Ugu (61.4%) in KwaZulu-Natal and Vhembe (61%) in Limpopo [12]. On the other hand, the uptake of HIV testing was higher among women than men in most of the districts [12]. Probably stemming from the common perception that women are at the highest risk of HIV, numerous studies substantiated a greater hesitancy in HIV testing uptake among men compared to women [11,12]. Socioeconomic factors such as rural residence, low education, household income, and high alcohol consumption have also been associated with low HIV testing uptake [13].

Traditional statistical and testing approaches have been widely used to scale up HIV testing interventions worldwide; while they are effective, they can be subject to certain limitations, such as accuracy, precision, and privacy issues [14]. In contrast, machine learning (ML) models are designed to address these limitations, as they can analyze complex datasets to uncover latent variables associated with HIV testing beyond the reach of conventional methodologies [15,16]. ML refers to the use and development of computer systems that learn and adapt without following explicit instructions, and algorithms are used to analyze and draw conclusions from data patterns [17,18]. The algorithms rely on domain knowledge of the data to develop features that make them work [18]. Various disciplines, including health care, use 3 major types of ML, namely, supervised machine learning (SML), unsupervised machine learning, and reinforcement learning [17-19].

A growing number of studies are developing predictive models to classify HIV high-risk populations for improved HIV testing in a resource-efficient manner [20-24]. Ovalle et al [25] applied support vector machines (SVM), random forest, and logistic regression within a Gay Social Networking Analysis Program, an intelligent web-based health-promotion intervention framework. This study explored the link between social media messages and participants' offline sexual health and substance use outcomes, deriving HIV risk scores for targeted HIV testing [25]. Various SML algorithms such as logistic regression, SVM, random forest, and XGBoost were used to accurately predict HIV risk in South Africa, in which age, being a female, and condom use were significantly associated with HIV positivity [26].

Evidently, ML techniques facilitate the development of economically viable HIV testing methods that offer optimal value for resources invested [16]. Importantly [16], asserts that HIV risk prediction with ML techniques could increase the HIV-diagnosed fraction to 96.5% by 2030, compared to the current traditional method projection of a diagnosed fraction of 93.8% by the same year in South Africa.

Although a significant amount of survey data is available on the factors associated with HIV testing in South Africa, there has been limited research on using ML approaches to analyze

and forecast these factors. Thus, it is against this backdrop that this study is pioneering in using four SML algorithms (logistic regression, random forest, SVM, and decision trees) across all five cycles of the SABSSM surveys to provide new insights into the determinants of HIV-testing behavior in South Africa. The primary aim of this study is to determine consistent predictors of HIV testing and to compare the performance of the four SML models using repeated adult population-based surveys in South Africa to develop an evidence-based predictive model to enhance HIV testing.

Methods

Study Design

A retrospective analysis of data from multiple cross-sectional surveys will be used to predict factors associated with HIV testing across the five cycles of the SABSSM survey using SML algorithms. The analysis will involve four SML algorithms in developing an HIV testing predictive model for the South African adult population. This protocol followed several guidelines and checklists, such as the STROBE (Strengthening the Reporting of Observational Study in Epidemiology) checklist [27] (this can be found in Multimedia Appendix 1), the updated guidance for reporting clinical prediction models that use regression or ML [28] (this can be found in Multimedia Appendix 2), and the development and validation of observational and qualitative study protocol reporting checklists for novice researchers (ObsQual checklist) [29].

Data Source and Population

This secondary data analysis will make use of the 5 cycles of the SABSSM surveys conducted by the South African Human Science Research Council (HSRC). The SABSSM surveys are a series of nationally representative surveys conducted periodically in South Africa to assess the prevalence, incidence, behaviors, and communication related to HIV/AIDS [10]. The first SABSSM survey was conducted in 2002 with 9963 individuals interviewed, followed by SABSSM 2005 (n=23,275), SABSSM 2008 (n=20,826), SABSSM 2012 (n=38,431), and SABSSM 2017 (n=36,609) being the fifth survey [10,30-33]. All five cycles of the SABSSM datasets were made available to the research team on August 20, 2024, after filling and submitting the digital request form via the HSRC website [34]. This study's analysis will focus on adults aged 18 years and older, using data from the five cycles of the SABSSM survey—2002, 2005, 2008, 2012, and 2017. The final sample size for this study will be determined after cleaning and removing outliers from the datasets.

Inclusion and Exclusion Criteria

The SABSSM dataset is a combination of children's, adolescents', and adults' data. This analysis will only include male and female individuals aged 18 years and older from the SABSSM survey. Data outside the defined age bracket from the SABSSM survey data will be excluded from this analysis.

Study Variables

The outcome variable for this study will be HIV testing. The exposure variables are sociodemographic (age, sex, ethnicity or race, education level, marital status, employment, and rural and urban residence), socioeconomic (household income, financial status, and access and usage of health care facilities), sexual behaviors (history of sexually transmitted infections, knowledge of HIV transmission, number of sexual partners, and condom use), HIV knowledge and awareness (knowledge toward HIV prevention, testing and treatment services, and knowledge of HIV status), and perceptions and attitudes (attitudes toward HIV testing, perceived risk of infection, stigma, and discrimination related to HIV). Table 1 describes a few selected variables that are consistent across all the five SABSSM survey datasets. The complete list of the dependent and independent variables extracted from 2002, 2005, 2008, 2012, and 2017 SABSSM survey datasets can be found in Multimedia Appendix 3 (SABSSM 2002 variables), Multimedia Appendix 4 (SABSSM 2005 variables), Multimedia Appendix 5 (SABSSM 2008 variables), Multimedia Appendix 6 (SABSSM 2012 variables), and Multimedia Appendix 7 (SABSSM 2017 variables).

Table 1. Summary of variable and variable definitions from the SABSSM[a] dataset[b].

Variable name and variables	Variable descriptions	Variable recode
Outcome variable (HIV testing)		
HIV testing		
Ever had an HIV test	• Yes • No • No response	• Yes • No
Exposure variables		
Sociodemographic		
Age		
Respondent's age in years	Integer	• <20 • 20-24 • 25-29 • 30-34 • 35-39 • 40-44 • 45-49 • ≥50
Sex		
Sex of the respondent	• Male • Female	• Male • Female
Geotype		
Geographical location	• Urban formal • Urban informal • Rural formal • Rural informal	• Urban • Rural
Race		
Race	• African • White • Colored • Indian or Asian • Other	• African • Colored • Indian • White
Highest level of education		
Respondent's highest level of education obtained	• No schooling • Up to Std[c] 1/Gr[d] 3/ABET[e] 1 • Std 2-Std 3/Gr 4-Gr 5/ABET 2 • Std 4-Std 5/ Gr 6-Gr 7/ABET 3 • Std 6-Std 7/Gr 8-Gr 9/ABET 4 • Std 8/Gr 10/NTC[f] 1 • Std 9/Gr 11/NTC 2 • Std 10/Gr 12/Matric/NTC 3 • Certificate or diploma with Gr 12 • Bachelors degree • Postgraduate degree (HDE/Hons/Masters/PhD)	• No schooling • Primary • Secondary • Tertiary
Sociocultural		
Age at first marriage		
How old was the respondent when married for the first time	Integer	• <18 • 18-23 • 24-29 • 30-35 • >35
Male circumcision status		

Variable name and variables	Variable descriptions	Variable recode
Whether the male respondent is circumcised	• Yes • No	• Yes • No
Independent variable (socioeconomic)		
Employment status		
Employment status	• Unemployed • Sick or disabled and unable to work • Student or pupil or learner • Employed or self-employed • Other	• Unemployed • Sick or disabled and unable to work • Student or pupil or learner • Employed or self-employed • Other
Independent variable (sexual history, sexual behavior, and lifestyle)		
Ever had sexual intercourse		
Whether the respondent ever had sexual intercourse	• Yes • No • No Response	• Yes • No
Number of sexual partners in a lifetime		
Number of people the respondent had sexual intercourse within a lifetime	Integers	• 1 person • 2-5 • >5
Condom use decision		
Who suggested using a condom? The second most recent person	• Yourself • Your partner • Mutual agreement	• Yourself • Your partner • Mutual agreement
Independent variable (health status or pre-existing medical conditions or disabilities or stigma or violence)		
General well-being		
In general, would you say that your health is excellent, good, fair, or poor?	• Excellent • Good • Fair • Poor	• Excellent • Good • Fair • Poor
Independent variable (knowledge, awareness, and perception of HIV/AIDS)		
Knowledge of HIV/AIDS		
Can AIDS be cured?	• Yes • No • I don’t know	• Yes • No • I don’t know

[a]SABSSM: South African National HIV Prevalence, Incidence, Behavior, and Communication Survey.

[b]Only a few selected variables that are common across the five SABSSM surveys were included in Table 1. Please see Multimedia Appendices 1-5 for the complete list of dependent and independent variables.

[c]Std: standard.

[d]Gr: grade.

[e]ABET: adult basic education training.

[f]NTC: National Technical Certificate.

Data Extraction

A data extraction tool (Table 2) with headings such as study year, sample size, study population, age group study settings, and main variables was used to describe the characteristics of the available datasets of the SABSSM surveys. Each dataset was examined, and key variables that could influence HIV testing were identified using additional tools (Table 1, Multimedia Appendix 3 [SABSSM 2002 variables], Multimedia Appendix 4 [SABSSM 2005 variables], Multimedia Appendix 5 [SABSSM 2008 variables], Multimedia Appendix 6 [SABSSM 2012 variables], and Multimedia Appendix 7 [SABSSM 2017 variables]).

Table 2. Characteristics of the five SABSSM[a] survey datasets[b,c].

Study name and year	Sample size, n		Prevalence of HIV testing (reported), %
	Calculated	Individual Interview Response	
SABSSM 2002 [30]	14,450	9963	21.4
SABSSM 2005 [31]	24,236	23,275	30.5
SABSSM 2008 [32]	23,369	20,826	50.8
SABSSM 2012 [33]	42,950	38,431	65.5
SABSSM 2017 [10]	39,132	36,609	75.2

[a]SABSSM: South African National HIV Prevalence, Incidence, Behavior, and Communication Survey.

[b]The study is focused on the general population of South African adults aged 18 years and older.

[c]Study variables were extracted and redefined to guide the data cleaning and preprocessing, as detailed in the data preprocessing section.

Data Preprocessing and Feature Selection

The SABSSM survey datasets are open access data available upon request through the HSRC website [34]. All five cycles of the SABSSM datasets were accessed on August 20, 2024. We have explored them to understand the patterns and the nature of all the variables needed to develop an HIV testing predictive model. For this analysis, RStudio (version 4.3.2; Posit Software, PBC) will be used. The research team will first clean and process the available data to handle outliers and missing values and identify relevant dependent and independent variables in the five cycles of the SABSSM survey to be included in the predictive modeling. This will be followed by feature selection to eliminate redundant and irrelevant variables. Numerical features will be standardized to ensure consistency scaling, and the features will be analyzed to categorize those that will most likely influence HIV testing. We will conduct a chi-square test between the dependent variable (reported HIV testing status) and the independent variables (Table 1). Variables (features) with $P<.05$ will be considered important predictors and will be retained in the final model for predicting HIV testing status. Potential confounders and redundant variables will also be addressed during the feature selection, as detailed in the risk for bias assessment section. One-hot encoding will be used to encode the important HIV testing predictors based on the information available on the SABSSM surveys. One-hot encoding is the process of transforming categorical variables into binary variables, represented by values of 0 and 1, enabling their usage by ML algorithms [35]. This procedure will be accomplished by an R package known as “dplyr” [36].

Algorithms

This study will use four SML algorithms that are widely used in the field of health care, namely, logistic regression, decision trees, random forests, and SVM [37]. Logistic regression is a statistical method commonly used in ML for classification and predictive analytics tasks [38]. It solves classification problems by assigning multiple observations to a discrete set of categories or cases [38]. Another classifier that will be used in this analysis is SVM, a group of SML algorithms that can be applied to classification or regression [39]. The SVM can act as nonprobabilistic binary linear classifiers, depending on their configuration. For instance, a linear kernel function would make an SVM perform as a binary linear classifier. Moreover, SVM can also handle nonlinear classification tasks [39]. Similarly, a decision tree is also an SML classifier that categorizes or predicts depending on prior sets of questions [40]. According to Jo [19], a decision tree resembles a tree that classifies based on the branches of its root nodes. Random forest is also a very popular SML algorithm [22]. It is a robust SML algorithm well-suited for classification tasks involving complicated relationships between different features.

Training and Model Validation

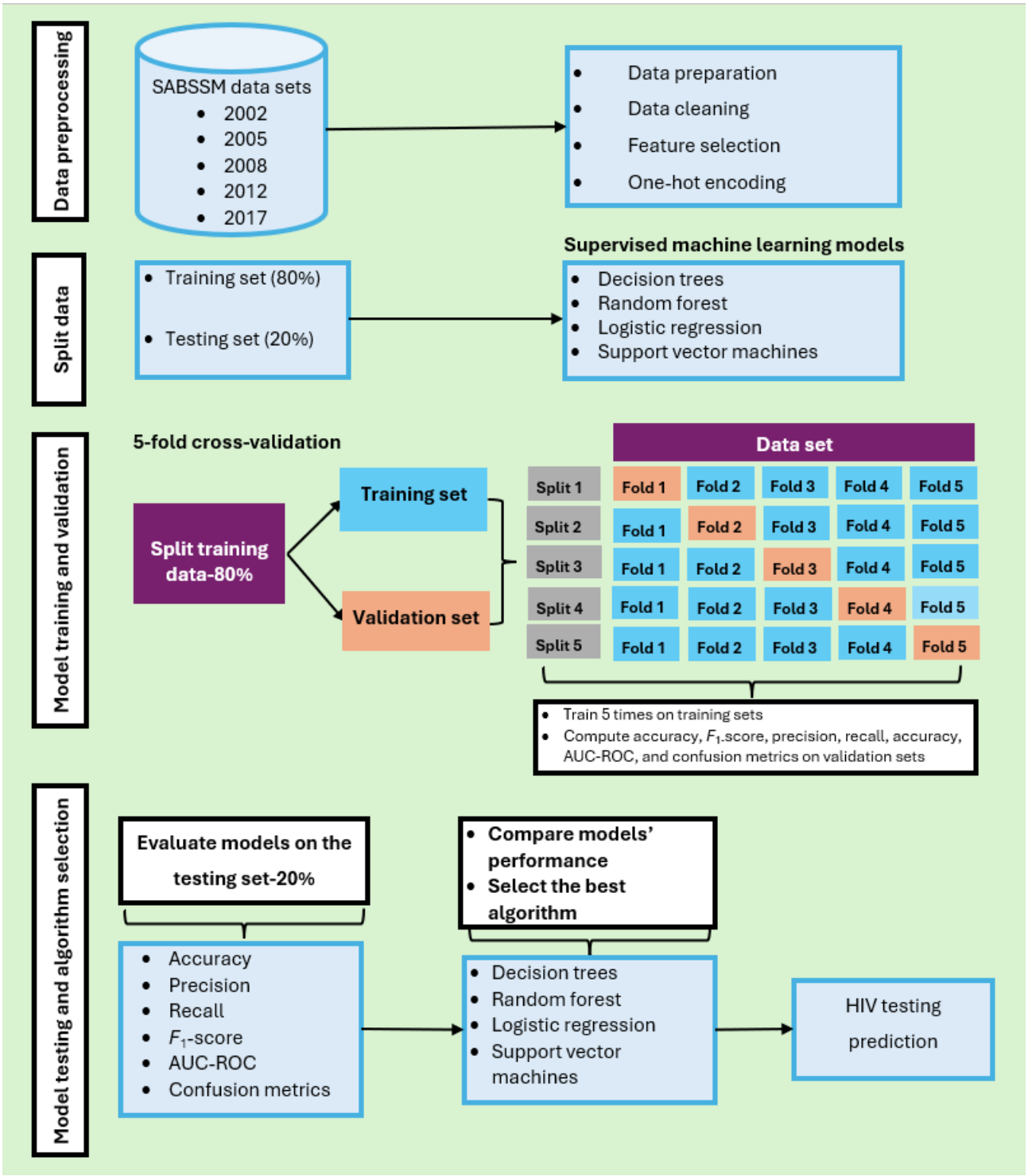
After the preprocessing and feature selection, each cleaned dataset will be split into 80% training and 20% testing samples. The 80/20 rule is the most used splitting ratio, and anecdotal evidence has supported it as being an effectively valid rule [41]. Training and validation will be done to set a probability threshold to predict those factors associated with HIV testing. Four standard SML algorithms will be applied to the training sample, such as logistic regression, decision trees, random forests, and SVM [37]. A cross-validation technique will be used, in which the training sample will be divided into k-folds, including a validation set, and models will be trained on each fold. Usually, k is taken to be 5 or 10, but may differ depending on the dataset size [42]. This study will use either a 5-fold or 10-fold cross-validation technique, depending on the compatibility with the available datasets. The models’ performance will be evaluated on the validation set using the following evaluation metrics: accuracy, precision, recall, F_1-score, area under curve-receiver operating characteristics, and confusion matrix.

Evaluation and Algorithms Selection for Predicting HIV Testing

Model evaluation involves selecting the best-performing model by providing an unbiased estimate of how well the models generalize on new or unseen data [18]. Upon completing the model development, the performance of the four SML models will be assessed on the testing sample using standardized performance evaluation metrics, including accuracy, precision, recall, F_1-score, area under curve-receiver operating characteristics, and confusion matrix [43]. This procedure will assess the performance of logistic regression, SMV, random forest, and decision trees in order to select the best-performing models in predicting HIV testing status using the five cycles of the SABSSM datasets. Figure 1 [21,43] depicts the data

processing stages, HIV testing predictive models to be used, and performance evaluation criteria.

Figure 1. Data preprocessing and HIV testing prediction modeling (created using PowerPoint [version 16.0.1; Microsoft Corp] diagram flow and concept guided by Mutai et al [21], Chingombe et al [38] and Chingombe et al [43]. AUC-ROC: area under curve-receiver operating characteristics; SABSSM: South African National HIV Prevalence, Incidence, Behavior, and Communication Survey.



Risk for Bias Assessment

Since the proposed study will analyze secondary data from multiple cross-sectional data, it is pertinent to assess and mitigate potential bias to ensure the validity and reliability of the results. The Joanna Briggs Institute Critical Appraisal Checklist for Analytical Cross-Sectional Studies (this can be found in the Multimedia Appendix 8) will be used to mitigate the risk of bias in this study. At first, the researchers reviewed published reports of the five SABSSM surveys to understand the study designs, study population, sample biases, study variables, and the data collection methods used in each survey by the HSRC. This process guided the development of the study design, eligibility criteria, and variable selection for this study. As of August 20, 2024, the authors have started exploring the SABSSM datasets to clean the data and treat missing values.

Imbalanced data occurs when one class has significantly more observations than the other, leading algorithms to be biased toward the majority class. In such cases, the researchers will use various techniques to address this and ensure fair model performance. Potential confounders of HIV testing will be identified based on consultations with the literature, as well as the use of statistical measures. Additionally, a variance inflation factor will be used to detect multicollinearity and remove redundant variables associated with HIV testing. This process will also inform the selection of features to be used for the HIV testing predictive modeling.

Data Management

This predictive modeling will use the SABSSM datasets sourced from the HSRC, with no personal information collected from the study participants. Following the data preprocessing and analysis, the preliminary results will be maintained securely using a memory stick that requires an access code. Only the researcher and the research team will be able to review these findings. The results to be published will not contain any identifying information. The electronic data will be stored in the Boloka data repository, password-protected with username access. The Boloka project aims to harness big heterogeneous data to evaluate the impact of HIV responses among key populations in generalized epidemic settings in Sub-Saharan Africa. All the data used in this study will be managed in compliance with the Protection of Public Information Act. The data generated from this study will be securely stored in the Boloka data repository for five years following the study's completion. It is important to note that the SABSSM datasets are governed by an End User License. As per the data-sharing conditions stipulated by the HSRC, the study's data cannot be duplicated, reshared, or sold without prior approval from the rights holder [34].

Ethical Considerations

This study protocol forms part of a doctoral study at the University of Johannesburg (UJ) by the first author (MJ), titled, "Integration of machine learning algorithms to predict HIV testing associations using repeated cross-sectional survey data in an adult South African population: an HIV testing predictive model." The study protocol was approved by the UJ Research and Ethics Committee on April 23, 2024; ethics approval REC-2725-2024 (this can be found in Multimedia Appendix 9). Further, the doctoral study falls under an umbrella project funded by the South African Medical Research Council under the South African Medical Research Council/UJ Pan African Centre for Epidemics Research Extramural Unit, titled: "Harnessing big heterogeneous data to evaluate the potential impact on HIV responses among the key populations in generalized epidemic settings in Sub-Saharan Africa" (ethics approval: REC-1504-2022). Since this study will analyze secondary data, a waiver of informed consent for secondary data use was obtained from the UJ Research and Ethics Committee (this can be found in Multimedia Appendix 9). According to Shisana and Simbayi [30], Shisana et al [31-33], and Simbayi et al [10], all the SABSSM surveys have been approved by the HSRC REC, and studies were conducted in accordance with international ethical standards, as well as the South African Children ACT 2007. Additionally, the SABSSM research team ensured that participants obtained voluntary informed consent. The authors of this study received the SABSSM datasets without any identifying information, and no further efforts will be made to reidentify the study participants during the analysis. The SABSSM datasets are open access data governed by an End User License that cannot be duplicated, reshared, or sold without prior approval from the rights holder (HSRC) [34]. This study will adhere to these data-sharing conditions and all the ethical standards governing the use of secondary data of human participants.

Results

The authors were given access to the SABSSM datasets for this retrospective analysis by the HSRC on August 20, 2024. All 5 datasets were downloaded from the HSCRC database and explored to identify the independent variables likely to influence HIV testing uptake as of September 30, 2024. The selected dependent (HIV testing status) and dependent variables (age, sex, province, marital status, knowing a place to test for HIV, male circumcision, condom use, sex debut, knowledge and perception of HIV, STI symptoms, visit a doctor, and contraceptive use) were recorded for each SABSSM dataset as similar to Table 1 (complete list of variables can be found in Multimedia Appendix 3 [SABSSM 2002 variables], Multimedia Appendix 4 [SABSSM 2005 variables], Multimedia Appendix 5 [SABSSM 2008 variables], Multimedia Appendix 6 [SABSSM 2012 variables], and Multimedia Appendix 7 [SABSSM 2017 variables]). The preprocessing and feature selection phase described in the methods section will determine which variables are to be used for the HIV testing predictive modeling. This process is expected to be completed by November 30, 2024.

The results of this study will be available by January 31, 2025, and each step of the analysis will be visualized and presented in tables and graphs. The anticipated date of publication for the proposed study is June 2025.

Discussion

Principal Findings

The proposed study seeks to identify intricate patterns and relationships among various sociodemographic, behavioral, and contextual variables that contribute to individuals' decisions to undergo HIV testing in South Africa. Since the first SABSSM survey in 2002, varying rates of HIV testing among South Africans have been reported by the HSRC, showing increased trends in each cycle until 2017 (Table 2). By applying SML learning techniques across the five cycles of the SABSSM survey datasets, the findings of this study will ascertain consistent variables predicting HIV testing uptake among the South African adult population over the 20-year period. Furthermore, the study will evaluate and compare the performance metrics of the four different SML algorithms, and the best model will be used to develop an evidence-based predictive model to enhance HIV testing among the South African adult population.

The emergence of ML applications in health care has demonstrated significant progress. However, predictive modeling in the context of HIV testing is relatively low in developing countries due to challenges such as usability issues, lack of expertise, and insufficient health care data [44]. Steadily, research institutions within specific African countries are increasingly expressing interest in this field.

A study conducted in Tanzania applied SML algorithms, including XGBost and random forest, to develop a model aimed at enhancing HIV index testing, with the recommendation that other health facilities use their model to simplify their work [18]. The study found that knowledge of HIV, age, sex, and marital were significantly associated with HIV index testing [18]. Likewise, a South African study by Majam et al [26] confirms that SML models can be built using digital surveys from low- and middle-income countries to predict high HIV groups for enhanced HIV testing. The models predicted, with over 80% accuracy, that female individuals hesitant to report condom use, and those who had not undergone HIV tests within the past year were at the highest risk of HIV [26]. In addition, an SML technique was used to assess the sociobehavioral predictors of HIV from Demographic and Health Survey data in 10 East and Southern African countries. According to the study, seven male and five female individuals would need to be tested to find one HIV-positive individual [37]. It is also important to consider HIV testing preferences for individuals undergoing HIV testing. Confidentiality, distance from the testing center, and method of data collection were identified as factors determining individual HIV testing preferences in South Africa [45].

The proposed study will expand on the existing knowledge of HIV testing predictors through the application of SML algorithms. Our choice of using SML is based on their heightened predictive accuracy, interpretability, efficiency, and adaptability. The proposed study aims to develop a predictive model to forecast HIV testing associations using repeated cross-sectional survey data in an adult South African population. The developed evidence-based model would assist relevant stakeholders in devising targeting HIV testing interventions in striving toward the UNAIDS 2030 goal of eradicating AIDS in South Africa.

Strengths and Limitations

To the best of our knowledge, this will be the first study to conduct HIV testing predictive modeling using all 5 cycles of the SABSSM surveys by applying SML algorithms. The large volume of data will be crucial for the generalizability of the developed models, as well as the major findings. It is also important to mention that the research involves a multidisciplinary team of experts across public health, epidemiology, biostatistics, and data science. The well-equipped team will devise a comprehensive methodological approach to developing an adaptable HIV testing predictive model.

However, this study is expected to face some limitations as the SABSSM surveys may contain missing values; proper imputation techniques will be used to address this issue. Since some ML models are not well developed, causing spatial and temporal variations, this could also be a limitation in our proposed study. Furthermore, because the analysis focuses on secondary datasets gathered using cross-sectional designs, the researchers are aware of potential limitations such as biases and lack of control over the variables included. The Joanna Briggs Institute Critical Appraisal Checklist will be used to mitigate the risk of bias in this study.

Conclusions

This study will contribute to knowledge and deepen understanding of factors linked to HIV testing beyond traditional methods. Consequently, the findings would inform evidence-based policy recommendations that can guide policy makers to formulate more effective and targeted public health approaches toward strengthening HIV testing in South Africa.

Acknowledgments

The study presented in this publication is within the scope of the Boloka Project and forms an essential part of a doctoral study by MJ conducted within the South African Medical Research Council/University of Johannesburg (SAMRC/UJ) Pan African Centre for Epidemics Research (PACER) Extramural Unit. The research outlined here was made possible through funding from SAMRC under its Division of Research Capacity Development, supported by the South African National Treasury (Project Code: 57035, SAMRC File ref: HDID8528/KR/202). The content of this paper remains the sole responsibility of the authors and does not necessarily represent the official views of SAMRC or UJ. Additionally, this paper forms an integral part of MJ's PhD study and is generously funded by the Global Excellence Stature (GES) 4.0 Scholarship at UJ. The authors express their gratitude to the SAMRC/UJ PACER and the UJ GES 4.0 for providing financial support for this study. We also extend our sincere appreciation to the Human Science Research Council and all the participants of the SABSSM surveys for providing the data used in this study.

Data Availability

The datasets to be analyzed in the proposed study are not publicly available due to the data-sharing conditions of the Human Science Research Council (HSRC; prohibition of the duplication, resharing, or selling of data without prior approval from the rights holder) but are available from the HSRC on reasonable request [32].

Authors' Contributions

MJ, RNP-M, EP, and YAS conceived and designed the study. MJ, RNP-M, and EP reviewed the literature. MJ wrote the first draft of the paper. MJ and YAS developed the methodology and identified machine learning models that will be used for predictive modeling of HIV testing. RNP-M, EP, and YAS reviewed and supervised the work. MJ, RNP-M, EP, and YAS edited the manuscript. All the authors contributed to this paper.

Conflicts of Interest

None declared.

Multimedia Appendix 1
STROBE (Strengthening the Reporting of Observational Study in Epidemiology) checklist.
[DOCX File , 41 KB - resprot_v14i1e59916_app1.docx]

Multimedia Appendix 2
TRIPOD+AI (Transparent Reporting of a multivariable prediction model of Individual Prognosis Or Diagnosis–Artificial Intelligence) checklist.
[PDF File (Adobe PDF File), 927 KB - resprot_v14i1e59916_app2.pdf]

Multimedia Appendix 3
SABSSM (South African National HIV Prevalence, Incidence, Behavior, and Communication Survey) 2002 variables.
[DOCX File , 42 KB - resprot_v14i1e59916_app3.docx]

Multimedia Appendix 4
SABSSM (South African National HIV Prevalence, Incidence, Behavior, and Communication Survey) 2005 variables.
[DOCX File , 42 KB - resprot_v14i1e59916_app4.docx]

Multimedia Appendix 5
SABSSM (South African National HIV Prevalence, Incidence, Behavior, and Communication Survey) 2008 variables.
[DOCX File , 42 KB - resprot_v14i1e59916_app5.docx]

Multimedia Appendix 6
SABSSM (South African National HIV Prevalence, Incidence, Behavior, and Communication Survey) 2012 variables.
[DOCX File , 43 KB - resprot_v14i1e59916_app6.docx]

Multimedia Appendix 7
SABSSM (South African National HIV Prevalence, Incidence, Behavior, and Communication Survey) 2017 variables.
[DOCX File , 45 KB - resprot_v14i1e59916_app7.docx]

Multimedia Appendix 8
JBI (Joanna Briggs Institute) checklist.
[PDF File (Adobe PDF File), 554 KB - resprot_v14i1e59916_app8.pdf]

Multimedia Appendix 9
Ethics Approval Letter.
[PDF File (Adobe PDF File), 88 KB - resprot_v14i1e59916_app9.pdf]

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Abbreviations

HSRC: Human Science Resource Council
ML: machine learning
SABSSM: South African National HIV Prevalence, Incidence, Behavior, and Communication Survey
SML: supervised machine learning
STROBE: Strengthening the Reporting of Observational Study in Epidemiology
SVM: support vector machine
UJ: University of Johannesburg
UNAIDS: Joint United Nations Program on HIV/AIDS

Edited by A Schwartz; submitted 26.04.24; peer-reviewed by AC Voetsch; comments to author 11.07.24; revised version received 28.08.24; accepted 18.10.24; published 27.01.25.

Please cite as:
Jaiteh M, Phalane E, Shiferaw YA, Phaswana-Mafuya RN
The Application of Machine Learning Algorithms to Predict HIV Testing in Repeated Adult Population–Based Surveys in South Africa: Protocol for a Multiwave Cross-Sectional Analysis
JMIR Res Protoc 2025;14:e59916
URL: https://www.researchprotocols.org/2025/1/e59916
doi:10.2196/59916
PMID:

Protocol

Feasibility of a Mobile App–Based Cognitive-Behavioral Perinatal Skills Program: Protocol for Nonrandomized Pilot Trial

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Abstract

Background: Mental illness is one of the top causes of preventable pregnancy-related deaths in the United States. There are many barriers that interfere with the ability of perinatal individuals to access traditional mental health care. Digital health interventions, including app-based programs, have the potential to increase access to useful tools for these individuals. Although numerous mental health apps exist, there is little research on developing programs to address the unique needs of perinatal individuals. In an effort to fill this gap, a multidisciplinary team of experts in psychology, psychiatry, obstetrics, and pediatric primary care collaborated to develop the novel Perinatal Skills Program within Maya, a flexible and customizable cognitive-behavioral skills app. Maya-Perinatal Skills Program (M-PSP) uses evidence-based strategies to help individuals manage their mood and anxiety symptoms during pregnancy and post partum.

Objective: This pilot study aims to assess the feasibility, acceptability, and usability of M-PSP and explore links between program use and symptoms of anxiety and low mood.

Methods: This single-arm trial will recruit 50 pregnant or postpartum individuals with mild-to-moderate anxiety or mood symptoms. Participants will be recruited from a variety of public and private insurance-based psychiatry, obstetrics, and primary care clinics at a large academic medical center located in New York City. Participants will complete all sessions of M-PSP and provide feedback. Outcome measures will include qualitative and quantitative assessments of feasibility, acceptability, and usability, passively collected program usage data, and symptom measures assessing mood, anxiety, and trauma. Planned data analysis includes the use of the grounded theory approach to identify common themes in qualitative feedback, as well as an exploration of possible associations between quantitative data regarding program use and symptoms.

Results: The recruitment began on August 2023. As of October 2024, a total of 32 participants have been enrolled. The recruitment will continue until 50 participants have been enrolled.

Conclusions: Digital health interventions, like M-PSP, have the potential to create new pathways to reach individuals struggling with their mental health. The results of this study will be the groundwork for future iterations of M-PSP in the hopes of providing an accessible and helpful tool for pregnant and postpartum individuals.

Trial Registration: ClinicalTrials.gov NCT05897619; https://classic.clinicaltrials.gov/ct2/show/NCT05897619

International Registered Report Identifier (IRRID): PRR1-10.2196/59461

(JMIR Res Protoc 2025;14:e59461) doi:10.2196/59461

KEYWORDS

perinatal mood and anxiety disorders; apps; smartphones; digital intervention; cognitive behavioral therapy; feasibility; pilot trial; mobile phones

Introduction

Maternal mental health plays a pivotal role in influencing the health and well-being of both mothers and their children. In the United States, there is a growing maternal health crisis, in which mental health conditions rank among the top causes of preventable pregnancy-related deaths for mothers [1,2]. During pregnancy and the postpartum period, perinatal mood and anxiety disorders (PMADs) significantly influence a mother's ability to function, care for, and bond with their newborn, which can have an impact on the child's subsequent socioemotional developmental trajectory [3-5].

Though PMADs remain prevalent, with global perinatal depression rates at 26.3%, there is a serious lack of effective, accessible, and affordable mental health care for individuals in the perinatal period [6]. This is particularly true in low- and middle-income communities and countries. In these areas, a general scarcity of maternal mental health services is further exacerbated by stigma, fewer financial resources, and logistical barriers that interfere with connecting to care [7]. As such, many struggling individuals suffer in silence, without appropriate recognition or intervention for their pressing maternal mental health needs [8].

Fortunately, the digital age offers a beacon of hope in bridging the divide between growing community needs and barriers to care, and digital health interventions have the potential to improve maternal mental health outcomes [9]. Specifically, smartphone apps may be able to offer accessible and user-friendly platforms that teach useful coping strategies, which may be especially beneficial for mothers who have difficulty accessing traditional mental health services [10]. However, the landscape of mobile health apps using evidence-based information or psychological interventions is relatively sparse, and efforts to tailor these tools to meet the unique needs of the perinatal population are in the early stages of the field [11,12]. There are numerous mobile health apps targeting this population, with a range of tools for prevention, screening, and treatment, and varying content that includes psychoeducation, symptom monitoring, cognitive behavioral therapy (CBT), mindfulness, and attention bias modification training. Thus far, evidence regarding the effectiveness of existing mobile health interventions is mixed. Recent meta-analyses and systematic reviews demonstrate that app-based interventions are effective for individuals with mild-to-moderate symptoms of perinatal depression and anxiety and may be effective at preventing and treating postpartum depression compared to control groups [12,13]. Few of the existing apps use both evidence-based strategies and provide psychoeducation, as well as target both pregnant and postpartum individuals and both depression and anxiety. More research is needed to aid in the development of technology that is feasible, acceptable, and effective for pregnant and postpartum individuals who need tools to support their mental health.

To help address the critical gap in care needs, this study will present a protocol to assess the feasibility and acceptability of the novel Perinatal Skills Program within Maya, a cognitive-behavioral skills app. Maya-Perinatal Skills Program (M-PSP) is a 12-session mobile app–based program teaching evidence-based strategies to manage mood and anxiety symptoms for perinatal individuals. Following a community-based participatory research model, the study team is seeking feedback from users throughout the early stages of program development. User input will help inform future iterations of the app-based program in hopes of creating a tool that can effectively meet the needs of this population. This protocol represents the first step in the development of a tool designed to increase access to evidence-based skills for individuals with PMADs.

Methods

Aims

The primary aim of this study is to assess the feasibility and acceptability of M-PSP. Specifically, the team will evaluate the mobile app–based program in terms of user satisfaction, perceived use of the program, and engagement with the program. A secondary aim of the study is to look for any associations between program completion and engagement with mental health symptoms.

Design

This study is a mixed methods open pilot trial assessing the feasibility, usability, and acceptability of M-PSP in a perinatal population. There are no comparison arms in the trial. Outcomes will include a combination of quantitative and qualitative data gathered via self-report questionnaires, interviews, and data passively collected through the app. This methodology will allow for the collection of symptom data, participant perceptions and feedback on their experience using the app, and information on app use and engagement. Results will provide information on the potential use of this program in helping pregnant and postpartum individuals manage mood and anxiety symptoms, as well as future directions for program development.

Setting

The study is being conducted through a large academic medical center in New York City. Participants will be recruited through various departments within the medical center, including a psychiatry specialty center, primary care and pediatric settings, and obstetrics and gynecology clinics. These sites range in providing services through private pay, private insurance, or public insurance.

Participants

The study is currently open to recruitment, with the aim to recruit 50 pregnant or postpartum individuals across all sites. In prior studies, feasibility studies often include a sample size of approximately 50 participants, which is deemed appropriate to ensure robust findings and comprehensive insights into app usability and effectiveness, balancing the need for inclusivity and accurate representation while accounting for potential participant attrition in digital mediums [14,15]. The inclusion criteria for study participation include (1) aged 18 years or older; (2) pregnant or up to 12 months post partum; (3) scoring 8-16 on the Edinburgh Postnatal Depression Scale (EPDS) [16] or 5-14 on the Generalized Anxiety Disorder-7 Scale (GAD-7) [17]; (4) able to read and speak English; (5) have access to a smartphone or mobile device capable of receiving SMS pushes and supporting Qualtrics Surveys and App (Weill Cornell Medicine); and (6) available to speak by phone or secure videoconference. The exclusion criteria include (2) safety concerns at the time of enrollment; (2) current substance use disorder; (3) current symptoms of psychosis or mania; and (4) history of bipolar or psychotic disorder.

M-PSP is designed to address mild-to-moderate anxiety and depression symptoms and may not be appropriate for more severely impaired individuals. In order to secure feedback from participants matching the app's target population, the inclusion criteria include those scoring in the mild-to-moderate range on anxiety and depression ratings. Participants with safety concerns at the time of intake, including recent suicidal ideation or self-harm, are excluded as they are at higher risk for heightened symptoms and risk in the perinatal period. Eligibility is not impacted by receipt of clinical care outside of the study, and participants are not excluded if they are receiving concurrent treatment for depression or anxiety.

Study participants may be disenrolled from the study if they are nonresponsive to 16 outreach attempts across 4 consecutive weeks or if their pregnancy ends.

Outcome Measures

Primary Outcome Measures

Feedback Interviews

Feedback interviews, led by staff via phone or video calls, include open-ended questions aimed to elicit qualitative feedback on program content, structure, and functionality, as well as user engagement and satisfaction. Questions such as "What ways could the app have been better tailored to help expectant or postpartum individuals?" will be asked to have a better gauge of acceptability, while questions like "What suggestions or comments do you have about the total number of sessions?" help address the feasibility of an intervention during and after pregnancy.

In-App Surveys

Weekly in-app feedback surveys are self-report measures that include Likert-scale questions regarding participant experience with specific session-by-session app-based content and structure (eg, "How helpful was Cognitive Practice [TINTED or Thinking Like a Lawyer]?"; "How likely are you to review any part of Session 3 again [eg, video, exercises, or quiz]?"). In particular, questions such as "How helpful was the content for you as an individual who is pregnant or postpartum?" and "How easy was it to fit using the app into your day-to-day life?" inform us of the acceptability and feasibility of the app, respectively, throughout the study.

User Version of the Mobile Application Rating Scale

Whereas the in-app surveys elicit session-by-session feedback, the user version of the Mobile Application Rating Scale (uMARS) elicits more global feedback on the overall app experience. The uMARS [18] is a validated 27-item self-report questionnaire evaluating engagement, functionality, aesthetics, information, subjective quality, and perceived impact of the app-based program. In particular, engagement, aesthetics, and information subscores will be used to measure acceptability and the functionality subscale will reflect the app's usability.

Mean scores are derived for each of these subsections, which can then be averaged to determine an overall App Quality Score. Responses are rated between 1 and 5, with 5 indicating higher levels of satisfaction. Stoyanov et al [18] found that uMARS exhibited satisfactory internal consistency (α=.90).

Passive Data Collection

M-PSP passively collects data, encompassing information captured without active user input, such as when sessions were completed, frequency of program usage, and program completion. These data points will serve as measures of program feasibility and user engagement.

Secondary Outcome Measures

Intake Survey

Participants will complete an intake questionnaire comprising questions related to demographics, health, mental health, and pregnancy history.

Edinburgh Postnatal Depression Scale

The EPDS [16,19] is a 10-item self-report measure of mood symptoms in perinatal individuals. Responses are coded on a scale of 0=lowest severity to 3=highest severity, with 30 being the highest score possible. Cutoffs are as follows: scores 7 and below indicate depression is unlikely, scores 8-13 indicate mild depression, 14-18 indicate moderate depression, and 19 and higher indicate severe depression [20]. Cox et al [21] found that the EPDS is a valid screening scale for depression and has satisfactory sensitivity (79%) and specificity (85%).

The Edinburgh Anxiety Subscale

The Edinburgh Anxiety Subscale [22] uses items 3, 4, and 5 from the EPDS to assess levels of anxiety among perinatal individuals. A score of 5 and above indicates the presence of anxiety [23].

Pregnancy Symptom Tracker

The daily Pregnancy Symptom Tracker (PST) is an ecological momentary assessment tool that aims to merge and consolidate gold-standard symptom measures into a format that is friendly and efficient for users, while also tracking information related to sleep, exercise, and daily behaviors. Developed by a group

of psychiatrists and reproductive psychiatrists, the measure takes 30-60 seconds to complete. Users use a sliding scale to indicate the degree of each symptom or behavior present within the last 24 hours.

GAD-7

The GAD-7 [17] is a 7-item self-report measure assessing symptoms of anxiety. Responders indicate the frequency of symptoms on a scale of 0=not at all to 3=nearly every day, with total scores running from 0 to 21. A score of 0-4 indicates minimal anxiety, 5-9 indicates mild anxiety, 10-14 indicates moderate anxiety, and 15-21 indicates severe anxiety. Spitzer et al [17] found that the GAD-7 exhibited reliable sensitivity (89%) and specificity (82%), validating its effectiveness as a screening tool for generalized anxiety disorder.

Patient Health Questionnaire-9

The Patient Health Questionnaire-9 (PHQ-9) [24] is a validated 9-item self-report measure assessing symptoms of depression. Responders indicate the frequency of symptoms on a scale of 0=not at all to 3=nearly every day. Scores can range from 0 to 27, with an additional qualitative question regarding the level of difficulty caused by symptoms ranging from no difficulty at all to extreme difficulty. Scoring interpretation is as follows: 1-4 (minimal depression), 5-9 (mild depression), 10-14 (moderate depression), 15-19 (moderately severe depression), and 20 and greater (severe depression). Kroenke et al [24] found that a PHQ-9 score ≥10 exhibited a satisfactory sensitivity of 88% and a specificity of 88% for major depressive disorder.

Perinatal-Post Traumatic Stress Disorder Questionnaire-II

The Perinatal-Post Traumatic Stress Disorder Questionnaire-II (PPQ-II) [25] is a validated 14-item self-report measure assessing symptoms of trauma among postpartum individuals. Frequency and duration of symptoms are rated on a 5-point Likert scale from 0=not at all to 4=often for more than a month, with total scores ranging from 0 to 56. Scores of 19 above indicate a clinical range of symptoms that would benefit from additional support. Komurcu Akik and Durak Batigun [25] found that the PPQ-II demonstrates validity and reliability as a scale for assessing the perinatal post-traumatic stress symptoms experienced by mothers.

The M-PSP Intervention

The Perinatal Skills Program was developed within Maya, a CBT skills app that is customizable and allows for the creation of individualized programs for multiple populations. M-PSP was adapted from one such program, Maya-Cognitive Behavioral Skills Program (M-CBT), which was a 12-session program that provided gold-standard, evidence-based strategies to help young adult users learn tools to manage anxiety and low mood. Preliminary data from a feasibility and acceptability trial of M-CBT suggest that the app is feasible and acceptable, and results showed a substantial decrease in both depression and anxiety from pre- to post-intervention [26]. In response to rising maternal mental health needs, an expert team of clinical psychologists specializing in CBT and reproductive psychiatrists with expertise in perinatal mental health adapted M-CBT into M-PSP. The team also consulted with physicians within pediatric primary care and obstetrics departments to better understand the needs of expectant and new parents. Changes to the original program included tailoring language and examples to address concerns that are common during and after pregnancy, as well as modifying skills as appropriate for the perinatal population. Several new skills were added, such as tools for managing communication and relationships as an expectant or new parent (Multimedia Appendix 1).

Users can work through each M-PSP session on their own schedule and are able to unlock up to 2 sessions per week. This pacing mirrors typical CBT session structure, allowing time for homework and practice between sessions, which is crucial for skill development and mastery [27,28], and acknowledges research showing that most people engage with apps for a limited duration, necessitating a structured yet flexible format to maximize engagement and effectiveness [29,30]. Each session in the program includes 3 main sections: learn (where new information and skills are shared), practice (where users can try out the skills they learned), and review (wrap-up of key lessons and takeaways). Users are introduced to a range of evidence-based tools throughout the 12 sessions (Table 1). There are also homework assignments for each session allowing users to practice what they have learned throughout the week. Users can individualize their experience by entering and tracking mood and anxiety ratings, planning for real-world skills use, personalizing examples, choosing preferred exercises to try, and reflecting on skill practice. The app has been programmed to help users see their progress through the app and track change toward self-identified goals. Users are also able to make use of tabs within the app for quick access to specific information, such as videos, skill practice, and favorite tools. Study staff have weekly meetings to ensure protocol is adhered to.

Table 1. M-PSP[a] session content.

Session	Session objectives and content
Session 1: Understanding symptoms and treatment	• Psychoeducation on perinatal anxiety and mood symptoms • Sleep tips for pregnancy and post partum. • Identifying common perinatal patterns of thoughts, feelings, and behaviors
Session 2: Facing challenges	• Identifying how emotions impact behavior during the perinatal period • Learning to gradually approach and overcome challenging tasks • "Face It!" exercise to craft an individualized goal ladder for daily practice
Session 3: Shifting thoughts	• Cognitive restructuring techniques to reframe unhelpful thinking • Guidance on effective communication and managing evolving relationships • Introduction of "TINTED Thoughts" exercises to recognize and correct cognitive distortions
Session 4: Relaxing your body and mind	• Introduction to relaxation exercises and audio-guided muscle relaxation meditation session. • Distress tolerance tips to manage stressful moments • "Face It!" exercise to craft an individualized goal ladder for daily practice
Sessions 5-10: Practice and use skills	• Revisiting the list of challenging situations and tracking progress • Continued practice of helpful thoughts and "Face It!" exercises • Introduction to problem-solving skills and additional distress tolerance exercises
Sessions 11-12: Maintenance and relapse prevention	• Guided selection of an exercise for ongoing skill practice • Skill review and reflection exercise • Guidance on next steps to support sustained mental health

[a]M-PSP: Maya-Perinatal Skills Program.

Procedure

As of October 2024, the study is open to recruitment. Recruitment strategies involve advertisements through listservs, clinician information sessions, and flyers within inpatient and outpatient departments. Interested individuals can complete a digital contact information form via a Health Insurance Portability and Accountability Act–compliant survey platform or have their providers complete the contact forms on their behalf.

Study staff reach out to individuals who have completed the form to screen for eligibility. Eligible participants are given further details about study involvement and complete informed consent. Study staff help participants download the app and provide an orientation, with recommendations to use the program for 10 minutes a day, 4 days a week. While it is recommended to complete the program within 6 weeks, sessions can be completed at the participant's convenience. All participants will be allowed up to 18 weeks for completion in order to account for delays or interruptions that may have occurred during pregnancy or after labor and delivery. Within 1 week of the study orientation, the research assistant will conduct a brief 5-minute phone check-in using a scripted protocol to ensure participants have been able to access and start the app, check on potential technical issues, and answer any questions related to app navigation.

Throughout participation, participants will be able to complete up to 2 sessions per week and will complete the in-app feedback surveys after each session. They will also be sent a text to their phone with a link to complete the daily PST. Additional assessments occur at midpoint (following completion of session 6), post (completion of session 12), and follow-up (6 weeks after post). These assessments include the staff-led feedback interviews via phone or videoconference, as well as the uMARS and all symptom measures. When risk items are endorsed on the daily PST, symptom measures, or during the assessments, study staff are notified and the participant is contacted by a licensed provider to conduct a formal risk assessment and safety plan as necessary.

To aid in retention and study completion, study staff monitor app completion progress and maintain contact with participants to schedule feedback interviews (Table 2). Through these methods, staff are able to problem-solve technical difficulties and other barriers to session completion as needed. Participants are encouraged to reach out via email or phone with any questions or concerns. Study staff follow institutional review board (IRB) guidelines to report any adverse events within the required timeline.

Table 2. SPIRIT[a] checklist.

	Prestudy	Intake	Weeks 1-6	Midpoint	Weeks 7-12	Post	6-week follow-up
Contact form	✓						
Eligibility screen		✓					
Informed consent		✓					
Download of Maya		✓					
Background questionnaire		✓					
App sessions			✓		✓		
In-app feedback			✓		✓		
Symptom measures		✓		✓		✓	✓
Daily symptom tracker			✓	✓	✓	✓	✓
Feedback interview and uMARS[b]				✓		✓	✓
Adverse event monitoring	✓	✓	✓	✓	✓	✓	✓

[a]SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials.

[b]uMARS: user version of the Mobile Application Rating Scale.

Data Analysis Plan

To analyze qualitative data from the feedback interviews, the grounded theory approach [31] will be used to review all responses and develop a consensus on existing themes. The data will then be systematically coded using these themes in order to identify core concepts and response patterns to derive meaningful interpretations of the feedback.

Data passively collected from the app will be transformed into practical means and ranges that will be used to understand user engagement and program feasibility. Means and SDs will be computed for demographic information and relevant symptom and acceptability questionnaires. Continuous scores from symptom scales and acceptability questionnaires will be analyzed in relation to app use and engagement. Correlations between these variables with be assessed using either Pearson or Spearman correlation depending on data distribution. For example, we will examine the correlation between EPDS symptom scores and app completion rates to explore whether postpartum depression symptoms are related to program feasibility. Hypothesis testing will be conducted with a *P* value=.05 as the threshold for statistical significance, and clinical significance will be considered for correlations that meet a meaningful cutoff (eg, 0.6 or 0.8). This analysis will help identify any demographic characteristics or symptoms that may require greater attention in future iterations of the program to ensure its effectiveness for a broad range of perinatal individuals. For participants who dropped out before study completion, all available data will be included, and any missing data will be handled using simple imputation. A correlation matrix will be generated to explore the relationships between symptom scales (eg, EPDS and GAD-7) and app engagement variables (eg, frequency of use, duration of use), allowing us to investigate possible associations without the need to correct for multiple testing in this exploratory pilot study.

Ethical Considerations

The study was granted approval through the Biomedical Research Alliance of New York IRB (BRANY #23-02-134-380) and the internal IRB within the academic medical center at which the trial is being conducted. The study has been registered at ClinicalTrials.gov (protocol number NCT05897619). This protocol was written in accordance with the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) guidelines (Multimedia Appendix 2) [32]. All participants provided informed consent and were made aware that they could withdraw from the study at any time without penalty. Participants are not compensated for their participation. All participants may continue to use the MAYA app following study completion if they so choose and will be given a list of resources, including referrals for clinical care.

While no individual data will be reported, the study team will report results via publication following trial completion. Health care providers within the Weill Cornell Medicine or NewYork-Presbyterian network may be given access to a summary of qualitative and quantitative outcomes. Every participant is given a unique study identifier. All data collected were confidential and safely stored per protocol approved by the IRB. As a small, unblinded study that does not involve invasive procedures or greater than minimal risk, there is no data monitoring committee. The study is internally sponsored, with no external funding organization involved in study design, management, monitoring, or analysis. The study is fully monitored by internal co-investigators, with IRB oversight through BRANY.

Results

The pilot trial received internal funding in August 2023 and data collection started in September 2023. As of October 2024, 32 participants have been enrolled in the study. It is anticipated that enrollment will continue throughout 2024, with projected

recruitment completion in December 2024. Data analysis will be completed upon study completion of the last participant.

Discussion

This study aims to assess the feasibility, usability, and acceptability of the M-PSP, a 12-session program teaching skills derived from CBT and adapted to suit the unique needs of a perinatal population. Regarding feasibility, it is anticipated that outcomes will indicate the program is able to be worked through by users, but that pacing and session length may need more flexibility in future versions of the app to account for the particular demands of this population. It is hypothesized that users will find the skills to be acceptable, but that some of the sample videos need revision to more directly reflect mood and anxiety concerns during and after pregnancy. Further, the study team anticipates that users will have input on specific content that could be added to improve their satisfaction with the app. Regarding usability, it is anticipated that the app will be user-friendly and easy to work through. As the secondary aims are exploratory, there are no specific hypotheses related to symptom measures as they are related to engagement. These outcomes will inform future iterations of the program in hopes of developing a widely accessible and useful tool for pregnant and postpartum individuals.

While the findings from this pilot study will provide valuable insights, several limitations must be acknowledged. This study relies on self-report data, which may introduce biases such as social desirability or recall errors. In future studies, clinician assessment of symptoms could help to mitigate these concerns. In this and future studies, the use of passively collected app usage data should provide some objective metrics regarding engagement and feasibility. A further limitation is the small sample size. As a pilot trial, this study is not powered to detect statistical significance, as the primary aim is to assess feasibility and acceptability rather than efficacy. Therefore, these findings should be interpreted as preliminary, and further research with larger samples will be necessary to assess the program's effectiveness in improving mental health outcomes.

Despite these limitations, this study is an important step in helping to fill the gap between an increasing maternal mental health crisis and barriers to appropriate support. By using a community-based-participatory research model, the development team has been able to consider input from researchers and clinicians across different specialties and will be able to incorporate feedback from end users through each stage of program development. Once feedback has been considered and incorporated into the program, the team will look to conduct future studies to assess the effectiveness of the tool in helping perinatal individuals manage anxiety and mood symptoms. Per guidelines on progressing from a pilot trial to a fully powered randomized controlled trial (RCT) [33], the research team has outlined a number of criteria that will influence the next steps. To ensure adequate participant numbers for an RCT, the pilot trial will need to demonstrate a 50% retention rate between screening and enrollment. The team will also move forward if 75% of participants complete primary outcome measures, which consist of feasibility, acceptability, and usability feedback interviews and surveys. While the study team will track adherence to the intervention (ie, completing M-PSP sessions), this will not be used as a criterion for progressing to a full RCT as nonadherence may be attributable to feasibility or acceptability concerns that the pilot study intends to illuminate so that future versions of the app can be modified prior to an RCT.

Acknowledgments

The study receives funding from the Weill Cornell Medicine Ritu Banga Healthcare Disparity Research Award and the Weill Cornell Medicine Children's Health Council. Dr Lara Baez receives funding through the National Institute of Mental Health training grant (T32 MH115882).

Data Availability

The datasets generated during this study will be available from the corresponding author on reasonable request.

Authors' Contributions

ATY led study conception and design, development of the intervention, and manuscript drafting. AH, SG, and SB made substantial contributions to study conception and design. LB, LO, and CG have contributed significantly to the study design. AA and EB have led data acquisition and drafted portions of this manuscript. AD, AO, ML, MS, and IS have drafted portions of this manuscript. MS and SZ contributed to the development of the intervention and design for data acquisition. AF led the development of the original intervention and conception of the overall app-based programming.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Sample screenshots of the MAYA Perinatal Skills Program.
[DOCX File , 521 KB - resprot_v14i1e59461_app1.docx]

Multimedia Appendix 2
SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) checklist.
[PDF File (Adobe PDF File), 1505 KB - resprot_v14i1e59461_app2.pdf]

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Abbreviations

CBT: cognitive behavioral therapy
EPDS: Edinburgh Postnatal Depression Scale
GAD-7: Generalized Anxiety Disorder-7 Scale
IRB: institutional review board
M-CBT: Maya-Cognitive Behavioral Skills Program
M-PSP: Maya-Perinatal Skills Program
PHQ-9: Patient Health Questionnaire-9
PMAD: perinatal mood and anxiety disorder
PPQ-II: Perinatal-Post Traumatic Stress Disorder Questionnaire-II
PST: pregnancy symptom tracker
RCT: randomized controlled trial
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials
uMARS: user version of the Mobile Application Rating Scale

Edited by A Schwartz; submitted 12.04.24; peer-reviewed by J R Pozuelo, AM Babker; comments to author 29.06.24; revised version received 29.08.24; accepted 25.10.24; published 28.01.25.

Please cite as:
Temkin-Yu AB, Ayaz A, Blicker E, Liu MX, Oh A, Siegel IE, Seewald MJ, Hermann AD, Givrad S, Baez LM, Osborne LM, Green CM, Schier MM, Davis AM, Zhu S, Falk A, Bennett SM
Feasibility of a Mobile App–Based Cognitive-Behavioral Perinatal Skills Program: Protocol for Nonrandomized Pilot Trial
JMIR Res Protoc 2025;14:e59461
URL: https://www.researchprotocols.org/2025/1/e59461
doi:10.2196/59461
PMID:

Protocol

Novel Procedures for Evaluating Autism Online in a Culturally Diverse Population of Children: Protocol for a Mixed Methods Pathway Development Study

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Abstract

Background: Current autism assessment procedures are costly and resource-intensive. The COVID-19 pandemic accelerated the adoption of telemedicine, highlighting the benefits of innovative diagnostic tools. Telemedicine-based pathways could enhance accessibility and equity in autism diagnostics.

Objective: The Children with Autism Technology Enabled Assessment (CHATA) project aims to develop and pilot an open-source autism diagnostic pathway for children up to 5 years old, delivered through telemedicine. The pathway is designed to be culturally and linguistically adaptable, increasing its applicability to diverse populations and integrating with existing National Health Service digital systems.

Methods: Initial pathway development was informed by systematic evidence reviews, coproduction, and mixed methods usability. CHATA comprises 2 key elements: online self-completed standardized autism questionnaires and a structured online interview and observation by a trained clinician. Out of 60 families near the top of the local waiting list will be invited to participate in the pilot evaluation, assessed using both the CHATA and usual assessment pathways. Sensitivity and specificity will be calculated by comparing the diagnosis of autism through CHATA with usual care. Quantitative usability assessment will be gathered from all families using the System Usability Scale (where a mean above 68 indicates above-average usability). A subset of CHATA assessments will be reviewed for interrater reliability (measured by the Cohen κ for categorical data [diagnosis present or absent], with values indicating the level of agreement; eg, <0 indicating no agreement, 0.61-0.80 indicating substantial agreement). Qualitative data on acceptability, feasibility, and usability will be gathered from semistructured interviews with a subset of families and health care providers. We will recruit 60 families for the main pilot study (including the usability testing) and 10-15 participants for the qualitative substudy. Data will estimate CHATA's diagnostic accuracy, validity, reliability, usability, and acceptability. Patient and public involvement will be integral throughout. The study will take place in a socio-economically deprived, ethnically diverse inner-London Borough within a community-based child health National health service responsible for the Autism assessment of children and young people up to the age of 13 years.

Results: Ethics approval was received in June 2023 (Research Ethics Committee reference 22/LO/0751; IRAS project ID 320499). Data collection commenced in April 2023 and completed in October 2024. Project end date is March 2025. As of November 2024, we had enrolled 57 participants to the pilot study and 12 to the qualitative substudy.

Conclusions: The CHATA project aims to establish a novel, culturally sensitive, equitable, and accurate online autism assessment pathway. By addressing geographical and linguistic barriers, this pathway seeks to reduce service costs, shorten waiting times, and promote equity in autism diagnosis. The procedures developed are expected to be generalized to other populations nationwide.

International Registered Report Identifier (IRRID): DERR1-10.2196/55741

(JMIR Res Protoc 2025;14:e55741) doi:10.2196/55741

KEYWORDS

autism; child; telehealth; co-development; feasibility; acceptability; assessment; diagnosis; online; evaluation; diagnostic; intervention; pilot implementation evaluation study

Introduction

Autism spectrum disorder (ASD) is a complex neurodevelopmental condition marked by difficulties in social communication, restricted and repetitive behaviors, and sensory sensitivities [1]. Despite a significant increase in autism prevalence in the United Kingdom among children aged 10-14 years, only about 1 in 190 children are diagnosed during the preschool years [2]. Consequently, many children are not identified or assessed until they have been in school for several years, leading to educational disadvantages. As of December 2023, over 170,000 people in England were awaiting an autism assessment, with 85% waiting beyond the recommended 13 weeks [3]. While data on waiting lists for older children in child and adolescent mental health services are available, equivalent data for preschool assessments is less reliable [4]. However, anecdotal evidence suggests lengthy waiting times of 36-42 months for preschool appointments, with some regions having no availability at all. Autism can be reliably identified by 24 months [5], but the average diagnosis age is >5 years in Europe and North America [6,7].

Structural inequity exists in autism assessment. Girls, and people from ethnic minorities or lower socioeconomic groups, receive support later than their peers, if at all. The 2024 Child of the North (UK) report found that ethnicity and associated language barriers play an important role in determining who gets assessed; overall, children of white heritage are substantially more likely to receive an autism diagnosis than children of Asian heritage [8,9].

Traditional autism evaluations involve developmental history, current behavior descriptions, and direct observation of social interaction skills. The COVID-19 pandemic has increased interest in using telehealth for preschool autism assessments. Various tools and methods are used in telehealth, including video-based observations, digital questionnaires, and online behavioral checklists. These tools can be used for both live (synchronous) and recorded (asynchronous) assessments, providing flexibility in how evaluations are conducted. Telehealth offers benefits like flexible scheduling, increased accessibility, fewer no-shows, optional audio and video recording, reduced travel and costs, fewer room bookings, and lower environmental impact [10]. Families in rural or underserved areas can now access diagnostic services more easily through remote assessments [11]. In addition, telehealth can significantly reduce wait times by enabling quicker initial screenings and follow-ups, which is especially beneficial given the high demand for autism assessments and the limited number of specialists available [11]. Our recent systematic review found that Telehealth assessments are as accurate as in-person assessments, with over 80% diagnostic agreement [12]. Online asynchronous parental reports and behavioral observation tools also show high validity and reliability, with agreement rates of 82%-88% compared with in-person assessments.

However, telehealth also faces several limitations. Technological barriers are a significant issue, as not all families have access to the necessary technology or reliable internet connections [13]. This can create disparities in who can benefit from telehealth services. In addition, there is a need for more training for clinicians to effectively use telehealth tools and ensure consistent and accurate assessments [14]. The standardization of telehealth procedures is still evolving, which can affect the reliability of these assessments. Equity issues are another concern. Telehealth may not be equally effective for all populations, as cultural and language differences can impact the accuracy of assessments. Moreover, telehealth tools may not be validated for diverse populations, potentially leading to biased outcomes.

We have developed a telemedicine assessment pathway - Children with Autism Technology Enabled Assessment (CHATA) that combines both asynchronous (parent online questionnaires) and synchronous (online clinical assessment) elements. Designed currently for children up to 5 years old, it has been developed to optimize linguistic and cultural accessibility. Given the potential limitations of the telemedicine approach, refining approaches such as CHATA and conducting pilot trials are crucial. These efforts can help improve the efficiency of autism screening and diagnosis by developing more reliable and user-friendly telehealth tools. They can also address disparities in telehealth access and effectiveness, ensuring that all children, regardless of their background, receive accurate, and timely diagnoses. Furthermore, refining CHATA can contribute to the standardization of telehealth procedures, making them more consistent and reliable across different settings. Ultimately, this study aims to enhance the efficiency and equity of autism assessments for children. Our objectives are to refine the pilot version of the CHATA diagnostic assessment for preschool children with suspected autism,

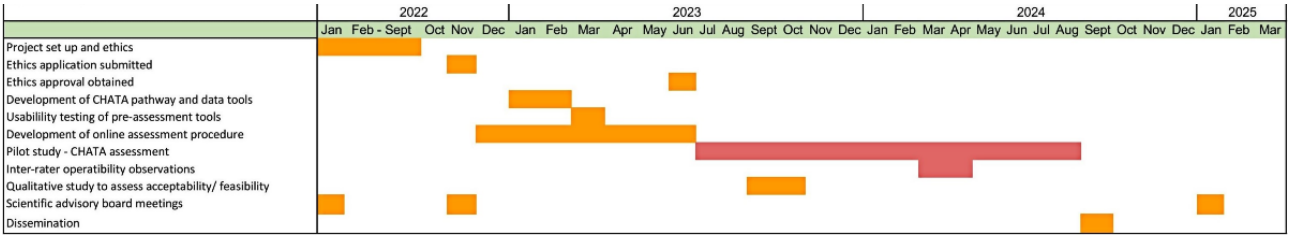
evaluate its usability, acceptability, feasibility, and interrater reliability, and estimate its sensitivity and specificity.

Methods

Study Design

This mixed methods study integrates pathway refinement, pilot evaluation, and implementation, using both qualitative and quantitative approaches. It focuses on usability, acceptability, feasibility, clinical validity, and reliability. The research framework is grounded in Behavioral Science and Participatory Action Research [15]. This approach captures diverse challenges and resilience factors among families, addressing the limitations of solely using survey questionnaires. Qualitative data will enrich quantitative findings, providing a comprehensive understanding of individual experiences. The study timeline is provided in Figure 1.

Figure 1. Study timeline. CHATA: Children with Autism Technology Enabled Assessment.



Study Setting

The study will take place in the London Borough of Newham (LBN), UK, known for its high ethnic and linguistic diversity, with approximately 78% of the population from ethnic minority groups and over 140 spoken languages. LBN is also among the most deprived areas in England, with over 50% child poverty. The East London National Health Service (NHS) Foundation Trust provides community child health services, including the Children with Autism in Newham–Diagnosis Service (CHAND) for children up to 13 years old. Due to underfunding and increased demand during the COVID-19 pandemic, over 1200 children are currently awaiting assessment by CHAND (personal communication as of June 14, 2024).

Patient and Public Involvement

To inform the initial development of CHATA and this pilot study protocol, 2 patient and public involvement (PPI) workshops were held with 8 parents of children who had online autism assessments during the COVID-19 pandemic. The group included 5 Asian or Asian British parents and 3 Black or Black British parents, 1 requiring an interpreter. While most preferred face-to-face appointments, they accepted online assessments for reduced waiting times. A “Parent Voice” representative, an Asian parent of children with autism is a named co-investigator, who will participate in regular meetings, assist with study design, and analysis, and provide ongoing feedback.

Stakeholder Engagement

A Scientific Advisory Board will guide the development of the online autism assessment pathway, meeting biannually with regular email updates. Additional engagement with the National Institute for Health and Care Excellence guideline stakeholders will explore novel provisions. Study outcomes will be disseminated through an event with local clinical service stakeholders, and key findings will be shared through the NHS Trust website. In addition to scientific manuscripts and presentations, a pamphlet will publicize the study’s outcomes and policy implications.

Usual Autism Pathway Procedures in Study Setting

The usual care pathway in LBN, referred to as the “CHAND reference pathway,” currently includes the following steps:

1. Referral: made to CHAND.
2. Triage: conducted by a multidisciplinary team (MDT) based on referral information, resulting in 1 of 3 outcomes: acceptance, request for additional information (eg, school report), or rejection.
3. Assessment decision: if accepted, the triage team determines whether the case is straightforward or complex based on demographics (eg, age) and clinical factors.
4. Assessment: straightforward cases are booked to see a pediatrician or senior speech and language therapist alone. Complex cases are booked for a multidisciplinary assessment involving at least 2 clinicians (eg, pediatricians, speech, and language therapists, psychologists, and occupational therapists). One clinician conducts an Autism Diagnostic Observation Schedule, Second Edition (ADOS-2) assessment [16], and the other takes a case history. If a diagnostic outcome is not reached, the case is discussed at a wider MDT meeting, including representatives from pediatrics, speech and language therapy, occupational therapy, and psychology. Additional assessments may include a school visit, a Diagnostic Interview for Social and Communication Disorders with parents [17], or an informal observational assessment to evaluate mental health difficulties or masking in girls.
5. Feedback and follow-up: diagnostic feedback and psychoeducation about autism and autism-specific supports are provided. Local signposting and invitations to postdiagnosis group workshops or one-to-one sessions with a parent connector are offered.

The service is diagnostic only and does not provide postdiagnosis support or interventions. Onward referrals for occupational or speech and language therapy are made with the family’s consent. All children under 5 undergo a face-to-face physical examination with a pediatrician, where blood and genetic testing may be considered.

CHATA Index Assessment Procedures

The CHATA index pathway, designed to be compatible with National Institute for Health and Care Excellence guidelines for autism assessment [18] and to replace, where appropriate, usual care CHAND assessment step 4 above, involves 2 steps:

1. Digital questionnaires: participants complete a series of self-administered questionnaires within 45 minutes on an NHS-compatible digital platform.
2. Online clinical observation: this is followed by a real-time, semistructured parent-child interaction through video conferencing, taking between 30 and 60 minutes depending on the need for interpreting.

Both the questionnaire and observational data are hosted on Drupal, a secure, open-source web application, locally hosted on an NHS server.

Digital Questionnaires

The questionnaire was developed by integrating items that effectively identified autistic behaviors in preschool children from the following sources:

1. 3di interview, a computerized diagnostic tool used by UK Autism assessment teams [19]. The full 3di comprises nearly 200 questions, applicable across the full range of children and adolescent ages. We developed a preschool version using data from 1,437 children referred to the Great Ormond Street Hospital Social Communication Disorder Clinic (2005-2023). Using a discriminant function analysis, we identified 41 questions that best discriminated preschool children (n=356) assigned an autism diagnosis by the multidisciplinary clinic. From nearly 200 questions, 41 were selected for their effectiveness in distinguishing autism in preschool children. These interview questions were reconfigured into questionnaire format for CHATA.
2. The Modified Checklist for Autism in Toddlers, a screening tool for children under 30 months, consisting of 20 questions for parents [20].
3. The Developmental Check-In, a brief ASD screening tool validated for Hispanic children aged 24-60 months, includes 26 questions with accompanying photographs to aid parents with limited literacy [21,22].

An audit of the CHAND waiting list identified Urdu and Bengali (Sylheti and Dakar dialects) as the most frequently spoken languages after English. Questionnaires were professionally translated and back-translated, with parent focus groups assessing their accuracy and acceptability. Audio descriptions were created for participants with low literacy and uploaded alongside the written questionnaires.

Five parents/carers of children under 5 years of age who had undergone autism assessment participated in usability testing using the “think aloud approach” and the quantitative System Usability Scale (SUS; Multimedia Appendix 1), standard usability assessments [23,24]. Usability feedback was broadly positive, with critical feedback focused on the need to ensure clear instructions for accessing the questionnaires.

Online Observations

The online observations will be conducted by an experienced clinician in preschool autism assessment, trained in the ADOS-2 autism assessment. Parents will use a broadband phone camera for the session, guided by the clinician through semistructured interactions with their child. This online observation was developed informed by the TELE-ASD-PEDS model, where the clinician remotely observes and instructs the caregiver in real-time tasks [25]. Scoring will align with the ADOS-2 methodology [16]. For the purposes of this pilot study sessions will be recorded for independent analysis to assess inter-rater reliability.

The assessment includes a 10- to 20-minute clinical interview, followed by a structured real-time observation. The clinician will review preassessment results to tailor the interview, focusing on specific concerns. During the observation, the child will perform activities with common household items and toys, guided by detailed instructions provided in advance. This will assess social communication, interaction, and restricted or repetitive behaviors. Interpreters will assist families who do not speak English as their first language, translating instructions and responses.

Recruitment to Pilot Study

Families receiving health services at an inner London clinic, specifically those on the autism assessment waiting list, will be recruited. Potential participants will be contacted through telephone or email and provided with detailed study information. Participants can discuss any questions with the research assistant through various communication methods. Cultural advocates will ensure cultural sensitivity during recruitment (see inclusion and exclusion criteria in Textbox 1).

Cultural advocates and trained research team members will ensure a supportive environment.

Textbox 1. Inclusion and exclusion criteria.

Inclusion criteria

- Parents and caregivers of children aged 5 or younger on the autism assessment waiting list in Newham, East London.
- Residents of Newham.
- Parents and caregivers aged 18 or older.

Exclusion criteria

- Inability to give consent.
- Known safeguarding concerns.
- Nonspeakers of English, Urdu, or Bengali.

Sample Size and Sample Size Justification

We will recruit 60 families for the main pilot study (including the usability testing) and 10-15 participants for the qualitative sub-study.

For clinical validation with approximately 80% power and an estimated 90% prevalence, a minimum sample size of 34 is needed to detect high sensitivity [26]. To detect high specificity with similar power, a minimum of 310 is required. A prestudy audit of the CHAND service showed a 90% autism diagnosis rate, like the 86% conversion rate in Bradford Autism Services [9]. Given the pilot nature of this study, we chose a pragmatic sample size of 50-60, prioritizing sensitivity assessment over specificity.

The sample size for quantitative usability testing is driven by the overall pilot sample size.

Approximately 15 participants are anticipated for the qualitative study, sufficient to reach thematic saturation and thoroughly explore core themes and patterns.

Estimated Diagnostic Accuracy

Families will complete both parts of the CHATA assessment, the online questionnaire and a structured videoconferencing clinical assessment, before their usual face-to-face CHAND clinical assessment. Following the CHATA assessment, children will proceed with the standard clinical assessment, including an in-person physical examination by a pediatrician and review at the MDT meeting for complex cases. This process (from the first CHATA assessment to the initial CHAND assessment) is expected to be finished within 6 weeks and will not affect their position on the clinical service waiting list.

Families will receive general autism information but no diagnosis from the CHATA assessment. The CHATA assessment results will be classified as autistic, nonautistic, or unsure by the research clinician but will not be shared with families or the clinical team to maintain blinding. The CHAND clinical team will record their own assessment outcomes and disclose them to the family as per usual processes. An independent researcher will compare the CHATA diagnostic outcome with the CHAND diagnostic outcomes from electronic health records to determine sensitivity and specificity.

Quantitative Usability

All families enrolled in the pilot will complete the SUS after completing the online questionnaires [24]. The SUS is a validated, widely used tool for measuring the usability of systems, with scores ranging from 0 to 100. The SUS consists of 10 items, with responses recorded on a 5-point Likert scale ranging from “Strongly Disagree” to “Strongly Agree.” Participants’ responses will be anonymized and collected into a database for analysis.

Qualitative Acceptability, Feasibility, and Usability Substudy

A qualitative study will include 10-15 families from the main study, chosen to represent diverse languages and experiences. This subset will help assess the acceptability and feasibility of the CHATA process, focusing on both positive aspects and areas for improvement. Recruitment will end when thematic saturation is reached, meaning no new themes emerge from the data. Data analysis will continue until no new codes appear, only recurring themes. In addition, 2-5 health care providers involved in autism assessments will be interviewed to gather their perspectives on the CHATA assessment, including its strengths and challenges. All interviews will be recorded with the participants’ consent.

Time Taken for Assessment

Informed by a recent study estimating the cost taken to undertake autism assessments in UK NHS services [27], we will estimate the time taken for each child to be seen under the usual care pathway, recording the grade of health care providers undertaking the assessments and compare that to the time taken to be seen under CHATA. We will then estimate costs associated with these using standard NHS outpatient costings.

Quantitative Data Analysis

Usability Data

The SUS score for each participant will be calculated using the standard method: for each of the 10 items, scores range from 0 to 4. Positive items (1,3,5,7,9) will have 1 subtracted from the response, while negative items (2,4,6,8,10) will have the response subtracted from 5. The total score will be multiplied by 2.5, resulting in a final SUS score ranging from 0 to 100.

To summarize the CHATA online questionnaire usability, we will compute the mean, median, and SD of SUS scores. Scores will be interpreted as follows: above 68 is considered above average, 50 to 68 is marginally acceptable, and below 50 may indicate usability issues. We will perform subgroup analyses to compare SUS scores across different demographics (eg, age, language, and education) using *t* tests or ANOVA, as appropriate. The mean SUS score, with a 95% CI, will provide a precise estimate of usability, and significant differences between groups will be reported. If the mean SUS score falls below the acceptable threshold of 68, we will conduct qualitative follow-up interviews to explore specific usability issues. The findings will inform any necessary revisions to improve the CHATA pathway’s usability.

Diagnostic Accuracy

To evaluate the diagnostic accuracy of the CHATA pathway, we will calculate sensitivity, specificity, and positive predictive value (PPV; Multimedia Appendix 2). Sensitivity measures the pathway’s ability to correctly identify autism, calculated as the number of true positives divided by the sum of true positives and false negatives. Specificity, reflecting the pathway’s ability to correctly identify nonautistic cases, is calculated as the number of true negatives divided by the sum of true negatives and false positives; however, we may not have sufficient power to calculate this. PPV, which indicates the likelihood that a positive result truly indicates autism, is determined by dividing the number of true positives by the total number of positive results. These metrics will be assessed using data from the pilot cohort to evaluate the CHATA pathway’s accuracy in diagnosing autism in young children from diverse backgrounds.

Interrater Reliability

A second clinician will review about 10% of the online pilot assessment recordings and compare their diagnostic decisions with those of the original clinician. For inter-rater reliability, we will analyze the consistency of ratings across independent reviewers who are blinded to the initial results. Out of 13 observations, randomly selected from 60, will be reviewed independently by a second clinician and supervised by a third senior clinician. All reviewers will be trained to ensure consistent understanding of the assessment criteria. The primary measure of inter-rater reliability will be Cohen κ for categorical data (diagnosis present or absent), with values indicating the level of agreement (eg, <0 as no agreement, 0.61-0.80 as substantial agreement). The analysis will determine the consistency of the CHATA pathway across different clinicians, with high reliability indicating reliable use of the pathway and lower reliability suggesting areas for improvement. Results will be reported with CIs, and significant discrepancies will prompt a follow-up review to address potential issues in training, criteria, or guidance.

Qualitative Analysis

We will transcribe and, if necessary, translate the interview data for analysis using reflexive thematic analysis with an inductive approach. This analysis will evaluate the acceptability, feasibility, usability, and barriers or enablers of the assessment tools. A feasibility study will gather insights from parents, caregivers, and clinicians on both online and in-person assessments to identify effective aspects and challenges.

Interviews will be conducted within 2 weeks of the online assessment, either in-person at Child Development Clinics or online based on participants' preferences. The interviews will be broad to capture diverse experiences, with topic guides (Multimedia Appendix 3) adjusted as new themes emerge. Qualitative data will be analyzed using NVivo [Lumivero] software, guided by the Theoretical Framework of Acceptability and the Theoretical Domains Framework [28,29]. The Theoretical Framework of Acceptability examines acceptability across 7 domains, including affective attitude and perceived effectiveness. The Theoretical Domains Framework integrates 33 behavior change theories and 14 domains to explore factors influencing behavior change, helping to identify barriers and enablers to implementation. We will use thematic analysis as outlined by Braun and Clarke [30], a widely used method for identifying, analyzing, and interpreting patterns of meaning within data. This approach is flexible and provides a detailed, nuanced understanding of the data, making it well-suited for the exploratory nature of this study. Since the study is qualitative and does not start with a pre-existing hypothesis, thematic analysis is particularly appropriate for uncovering insights.

The analysis will be reflexive, meaning it will involve continuous reflection and iteration by the research team. Out of 2 team members will independently familiarize themselves with the data, then regularly meet to discuss themes, resolve discrepancies, and finalize the themes and subthemes. The findings from this analysis will inform further iterations and refinements of the assessment tools to ensure they are as acceptable and effective as possible for both providers and recipients of the assessments.

Ethical Considerations

This study has been approved by the London Bloomsbury Research Ethics Committee (reference 22/LO/0751).

Measures to support participants include clear communication, confidentiality assurance, flexible scheduling, addressing recruitment barriers, providing interpreters, offering supporting letters for nursery absences, and incentives like vouchers.

Children flagged for concerns related to Adverse Childhood Experiences or safeguarding will be assessed using the standard pathway, following all ELFT safeguarding protocols.

Before participation, each participant will review the information sheet (Multimedia Appendix 4) and consent form with a research team member, who will address any questions. Consent can be provided in various formats: face-to-face, by post, email, video call, or telephone. Participants will indicate their preferred communication method and availability. Materials and consent forms will be translated into participants' preferred languages if needed. Non-English speakers will have the option to discuss the study with an interpreter through phone. Before the observation assessment, participants will receive detailed instructions and consent to record the session if desired. Researchers will be trained in consent processes, including assessing mental capacity. Parents will assess their child's willingness to participate; if a child shows discomfort or resistance, they will not be enrolled in the study.

Data will be anonymized once data collection is completed and before any analysis. Digital recordings from qualitative interviews will be securely transferred to a dedicated NHS server drive and permanently deleted from recording devices and video conferencing platforms once verified. Pseudonymized transcripts will be stored on this secure drive, separate from the original recordings, which will be kept in a password-protected folder. Participants' contact details will be stored in a separate, password-protected database on NHS servers. Hard copies of pseudonymized transcripts and research notes may be printed and kept in locked filing cabinets. Anonymized data will be retained on secure servers for 10 years before permanent deletion. All data handling will comply with the Data Protection Act 2018, with the participating NHS Trust as the Data Controller and Chief Investigators as data custodians.

Results

Chata project funding commenced in April 2021, ethics approval obtained in June 2022 pilot study data collection commenced in April 2023, and completed in Oct 2024. Pilot study end date is March 2025. As of Nov 2024, we had enrolled 57 participants in the pilot study and 12 in the qualitative substudy.

Discussion

Overview

This paper outlines our protocol for refining and evaluating a novel online autism assessment system tailored for children

under 5 within East London's culturally and linguistically diverse population. The primary goal is to address the limitations of traditional autism assessments, which include high costs, lengthy procedures, and extensive waiting lists that often exceed 2 years, as well as reduced applicability to non-White and non–English-speaking groups. By the end of this study, we anticipate being able to describe the sensitivity, specificity, quantitative and qualitative usability, interrater reliability, acceptability, and feasibility of the CHATA pathway.

Feasibility and Strategies

Conducting this trial presents inherent challenges due to the complexity of autism assessments in young children and the diverse needs of our target population. We are focusing on developing tools that are effective across diverse cultural and linguistic backgrounds. By integrating feedback from PPI and using non–English languagebased methods, we aim to ensure that the tools are culturally and linguistically appropriate. This approach is supported by previous research emphasizing the importance of cultural sensitivity in diagnostic tools [31,32]. To maximize the use of available clinical time, we are collecting parental information online before the assessment and ensuring that direct observations are concise. Literature supports this approach, noting that preassessment data collection and streamlined observations can significantly improve diagnostic efficiency [33].

We recognize the potential risks associated with implementing a novel assessment tool, including issues with engagement and the accuracy of online assessments. To mitigate these risks, we have designed a comprehensive evaluation process that includes both quantitative and qualitative assessments. This involves calculating sensitivity, specificity, and PPV to ensure diagnostic accuracy and conducting interrater reliability checks to maintain consistency [16,25].

We are taking several steps to minimize risks. All clinicians involved in the assessment process will undergo thorough training to ensure consistent application of the assessment criteria. This is critical for maintaining the reliability and validity of the assessments, as highlighted in previous research [33]. We have established robust protocols for data handling to ensure confidentiality and compliance with the Data Protection Act 2018. This includes secure storage of digital recordings and pseudonymized transcripts, as well as safeguarding participants' contact details. Adherence to these protocols is essential for protecting participant privacy and maintaining trust [34]. The study will incorporate iterative feedback from participants and clinicians to continuously refine the assessment tools. This iterative approach, supported by research on diagnostic tool development, emphasizes the importance of ongoing evaluation, and adjustment to effectively meet user needs [35].

Conclusion

Our study aims to develop a novel online autism assessment tool that addresses the limitations of traditional methods while being adaptable to diverse populations. By incorporating a range of assessment methods, ensuring rigorous training, and adhering to data protection standards, we strive to overcome the inherent challenges of this trial. Although the study is not designed to assess the cost-effectiveness of the assessment, it will focus on refining the tools and evaluation methods. Next steps include optimizing the efficiency of the questionnaire by reducing the redundancy of items and including visual content that has been created with ethnically diverse populations. Future research will need to assess sensitivity and specificity in a larger sample, address the long-term impact and cost-effectiveness of the online assessment system, and evaluate its applicability to a broader population, including those with lower digital literacy. The findings from this study will contribute valuable insights into autism diagnostics and provide a foundation for future trials aimed at improving assessment practices and reducing waiting times for autism services nationwide.

Acknowledgments

The authors thank the public and patient involvement participants involved in the development of the assessment tool and the study protocol and documents. This study is supported by the Patrick Paul Foundation (REC reference 22/LO/0751). PK was affiliated with the Great Ormond Street Institute of Child Health at University College London and East London NHS Foundation Trust at the time of the study and is currently affiliated with the School of Health and Well Being at the University of Glasgow and NHS Highland.

Conflicts of Interest

None declared.

Multimedia Appendix 1
System Usability Scale.
[DOCX File , 287 KB - resprot_v14i1e55741_app1.docx]

Multimedia Appendix 2
Calculator for sensitivity, specificity, and positive predictive value (PPV).
[DOCX File , 235 KB - resprot_v14i1e55741_app2.docx]

Multimedia Appendix 3
Topic guides for parents and clinicians.
[PDF File (Adobe PDF File), 1454 KB - resprot_v14i1e55741_app3.pdf]

Multimedia Appendix 4
Information sheets.
[PDF File (Adobe PDF File), 1748 KB - resprot_v14i1e55741_app4.pdf]

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Abbreviations

ADOS-2: Autism Diagnostic Observation Schedule, Second Edition
ASD: autism spectrum disorder
CHAND: Children with Autism in Newham – Diagnosis Service
CHATA: Children with Autism Technology Enabled Assessment
LBN: London Borough of Newham
MDT: multidisciplinary team
NHS: National Health Service
PPI: patient and public involvement
PPV: positive predictive value
SUS: System Usability Scale

Edited by A Schwartz; submitted 22.12.23; peer-reviewed by G Kernohan, R McConkey; comments to author 13.05.24; revised version received 06.09.24; accepted 09.12.24; published 11.02.25.

Please cite as:
Mirzaei V, Wolstencroft J, Lockwood Estrin G, Buckley E, Sayani S, Katakis P, Anand R, Squire T, Short E, Frankson P, Skuse D, Heys M
Novel Procedures for Evaluating Autism Online in a Culturally Diverse Population of Children: Protocol for a Mixed Methods Pathway Development Study
JMIR Res Protoc 2025;14:e55741
URL: https://www.researchprotocols.org/2025/1/e55741
doi:10.2196/55741
PMID:39932780

Protocol

Scaling Up Kangaroo Mother Care Through a Facility Delivery Model in Rural Districts of Pakistan: Protocol for a Mixed Methods Study

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Abstract

Background: The neonatal mortality rate in Pakistan is the third highest in Asia, with 8.6 million preterm babies. These newborns require warmth, nutrition, and infection protection, typically provided by incubators. However, the high maintenance and repair costs of incubators pose a barrier to accessibility for many premature and low birth weight neonates in low- and middle-income countries. This study aims to implement a context-specific kangaroo mother care (KMC) model in Sanghar within secondary health care facilities and catchment communities.

Objective: This study aims to achieve at least 80% KMC coverage for premature and low birth weight neonates.

Methods: This research uses a mixed methods design grounded in implementation science principles, with the goal of developing adaptive strategies tailored to district and facility managers, as well as health care workers, leveraging previous evidence on the benefits of KMC. The research is conducted in the district of Sanghar, Sindh with an emphasis on promoting KMC for infants weighing between 1200 and 2500 g in three facilities. It includes preimplementation data collection, training of health care providers and lady health workers, and intervention involving mother-baby skin-to-skin contact, breastfeeding initiation, and postdischarge follow-ups. Ethical considerations and data management are prioritized, to improve KMC coverage and neonatal health outcomes.

Results: This research will be implemented over a period of 18 months. The primary objective of this research is to achieve an 80% improvement in KMC coverage, with the secondary objective to promote optimal breastfeeding practices among postpartum mothers. Key indicators include the proportion of eligible infants enrolled in KMC, the percentage of mother-baby pairs receiving skin-to-skin care postdischarge, and the duration of KMC during the neonatal period. Additionally, the study will assess exclusive breastfeeding rates, neonatal weight gain, and neonatal deaths within the cohort. The data management team will evaluate the effectiveness of the model in achieving the targeted KMC coverage.

Conclusions: The integration of KMC into the health care system will provide valuable insights for policy makers regarding effective implementation and scaling strategies. The study's findings will highlight facilitators and barriers to KMC adoption, benefiting regions across Pakistan and globally. Additionally, these findings will offer valuable insights for the development of future newborn care programs.

International Registered Report Identifier (IRRID): DERR1-10.2196/56142

(JMIR Res Protoc 2025;14:e56142) doi:10.2196/56142

KEYWORDS

kangaroo mother care; scale up intervention; health facility; community; preterm infants

Introduction

Neonatal mortality continues to be a significant challenge for public health systems in low- and middle-income countries (LMICs), despite the global reduction in newborn deaths from 5 million in 1990 to 2.4 million in 2019. The majority of neonatal deaths occurred in India, Nigeria, and Pakistan [1]. Of these, 75% occurred during the first week of life, due to factors like preterm birth, intrapartum-related complications, low birth weight (LBW), birth asphyxia or lack of breathing at birth, infections, and congenital disabilities [2]. The leading cause of neonatal death is the preterm complication, defined as the live birth of a newborn before 37 weeks of gestation. An estimated 15 million babies are born prematurely every year, and approximately 1 million children die each year due to preterm birth complications. Additionally, many survivors face lifelong disabilities, including learning disabilities and visual and hearing impairments [3].

In Asia, Pakistan ranks third in neonatal mortality, with 8.6 million preterm babies. Premature and LBW neonates require warmth, adequate nutrition, and protection from infection [4]. Typically, these newborns are cared for using incubators, which are ventilated, sterile, moist, and oxygenated devices that provide life support by maintaining body temperature and ensuring a safe environment [5]. However, the maintenance and repair of incubators have significant financial implications, making this care modality challenging and inaccessible for most premature and LBW neonates in low- and middle-income countries, including Pakistan.

In Pakistan, 32% of neonates are born with LBW, representing one-third of all births in the country. In November 2015, the World Health Organization (WHO) identified kangaroo mother care (KMC) as the primary method of managing LBW and premature births [6]. The WHO has defined KMC as a practice of early, continuous, and prolonged skin-to-skin contact between mother and babies, in addition to exclusive breastfeeding or breastfeeding, early discharge after the onset of KMC in the hospital with continuation at home, and adequate support and follow-up for mothers at home [7].

The KMC strategy comprises three main components: thermal care by continuous skin-to-skin contact, support for exclusive breastfeeding or provision of other appropriate nutrition, and early detection and response to any complications that may arise. A systematic review has indicated that KMC is an effective and safe alternative to conventional neonatal care for LBW infants, especially in resource-limited settings [8]. For clinically stable LBW infants <2500 g, implementation of KMC has shown potential to reduce mortality, and if widely applied, could reduce premature deaths [9,10]. Globally, KMC has been recognized as an integral component of the newborn health initiative following the Every Newborn Action Plan [11]. WHO and the United Nations Children's Fund have advocated for facility-based KMC as a routine method of care for clinically stable LBW newborns [12]. However, recent data from the Pakistan Demographic and Health Survey 2017-2018 revealed that only 6.3% and 6.5% of skilled birth attendants (SBAs) in rural Sindh and Balochistan, respectively, conducted newborn care practices that involved placing the newborn in skin-to-skin contact with the mother during childbirth [13].

In a recent study conducted by the Saving Newborn Lives program and Maternal and Child Health Integration Program, a situational analysis of 5 Asian countries, including Pakistan, was carried out to evaluate facility-based KMC [14]. Findings from the Maternal and Child Health Integration Program project implementation in Pakistan suggested that ensuring facility readiness, improved capacity of service providers at facility and community, and focused community mobilization effectively help program planners implement KMC at both levels of care [9,10]. India, on the one hand, has demonstrated substantial improvement in newborn and infant survival using a community-based KMC implementation and interpreted that community-initiated KMC substantially improves newborn baby and infant survival [7]. In Pakistan, researchers in newborn health have recently highlighted KMC as a top preterm intervention as part of the Every Newborn Action Plan [9,11]. Despite KMC being recognized as a cost-effective intervention, its adoption in Pakistan, both at the community and facility level, has been minimal.

The primary objective of this scaleup project is to introduce a context-specific KMC model in Sanghar focusing on secondary health care facilities and catchment communities, with the aim of attaining a minimum of 80% KMC coverage for premature and LBW neonates. Following the implementation of the KMC model in the targeted facilities and communities, the study also aims to assess the impact of this low-cost intervention on reducing neonatal morbidity and mortality among premature and LBW newborns within the rural health system of Sindh, Pakistan. This project will involve and encourage the adoption of the low-cost KMC model by public health facility leadership and community. Additionally, an implementation model tailored to the local context will be developed and assessed to achieve enhanced coverage. The findings of this study will hold significant implications for the government and other stakeholders in implementing and scaling up KMC at the district, provincial, or national level.

Methods

Study Design

A mixed methods design will be used with the principles of implementation science to develop an adaptive strategy to help district managers, facility managers, and health workers both at the facility and the community to identify ways to improve implementation. Considering the evidence from prior studies in Sindh and Pakistan proven to reduce the risk of hypothermia,

improve the rate and duration of breastfeeding, improve early initiation of breastfeeding practices, improve mother-infant attachment and bonding, and reduce parental distress related to their infant's well-being due to constant attachment [15-18], we aim to scale up the current practices for reaching over 80% coverage of KMC from the baseline. In the preimplementation phase of formative research, we will gather data on components of the health system and the organization of services, knowledge and skills of health care providers, and the community perceptions, acceptance, and challenges. Findings will be used to inform the development of an initial implementation model, addressing facility and community challenges, improving provider's skills, and community acceptance, and improving service delivery to strengthen the health system services. This will be followed by regular assessments at different levels of KMC coverage.

We will implement the research in three facilities in District Sanghar. Our intervention promotes KMC for babies born weighing >1200 and <2500 g, both within the facility and its catchment area.

Setting

The study will be conducted in Sanghar, which is in central Sindh; the total population of the district is 47.9 million, with 71% of the population residing in rural areas and 29% residing in urban areas. The district has a strong primary care setup with 60 basic health units and 6 rural health centers. Sanghar has 6 Mother and Child Health Centers and 2 maternity homes. The district is comprised of 38.3% public health facilities and 32.4% private health facilities, which translates into 70.7% institutional deliveries. Regarding assistance during delivery, District Sanghar has 72.2% of deliveries with SBAs compared to 82.7% of deliveries with SBAs in Sindh. The district reports poor maternal and child health indicators and a high neonatal mortality rate at 33 per 1000 live births, followed by infant and under-5 mortality rates at 47 and 56 per 1000 live births, respectively.

The intervention period for the study will be 18 months (from January 2022 to June 2023). Three public health facilities will be selected to adopt the KMC model. The selection of these facilities will be based on the availability of Maternal, Newborn, and Child Health services, as well as logistical considerations, such as availability of Basic Emergency Obstetric and Neonatal Care services, immediate referral capabilities, availability of human resources, and the monthly turnover of women seeking outpatient care for maternal health services, including the average number of deliveries (approximately 80-120) during the finalization of study sites.

Study Population

Inclusion Exclusion Criteria

All stable newborns provided relevant consent of birth weight >1200 and <2500 g delivered at a targeted health facility or home in the catchment area of the correspondent health facility within District Sanghar will be considered for study. Newborns who are sick according to predefined criteria (ie, do not tolerate oral feeds, severe respiratory distress including respiratory rate of <20 breaths per minute, grunting, central cyanosis, very severe chest in-drawing, convulsions, unconsciousness, and severe hypothermia of <32 °C) will not be included. They will first be stabilized and referred to advanced care facilities. Newborns delivered outside the catchment area and those whose families did not provide consent will not be included.

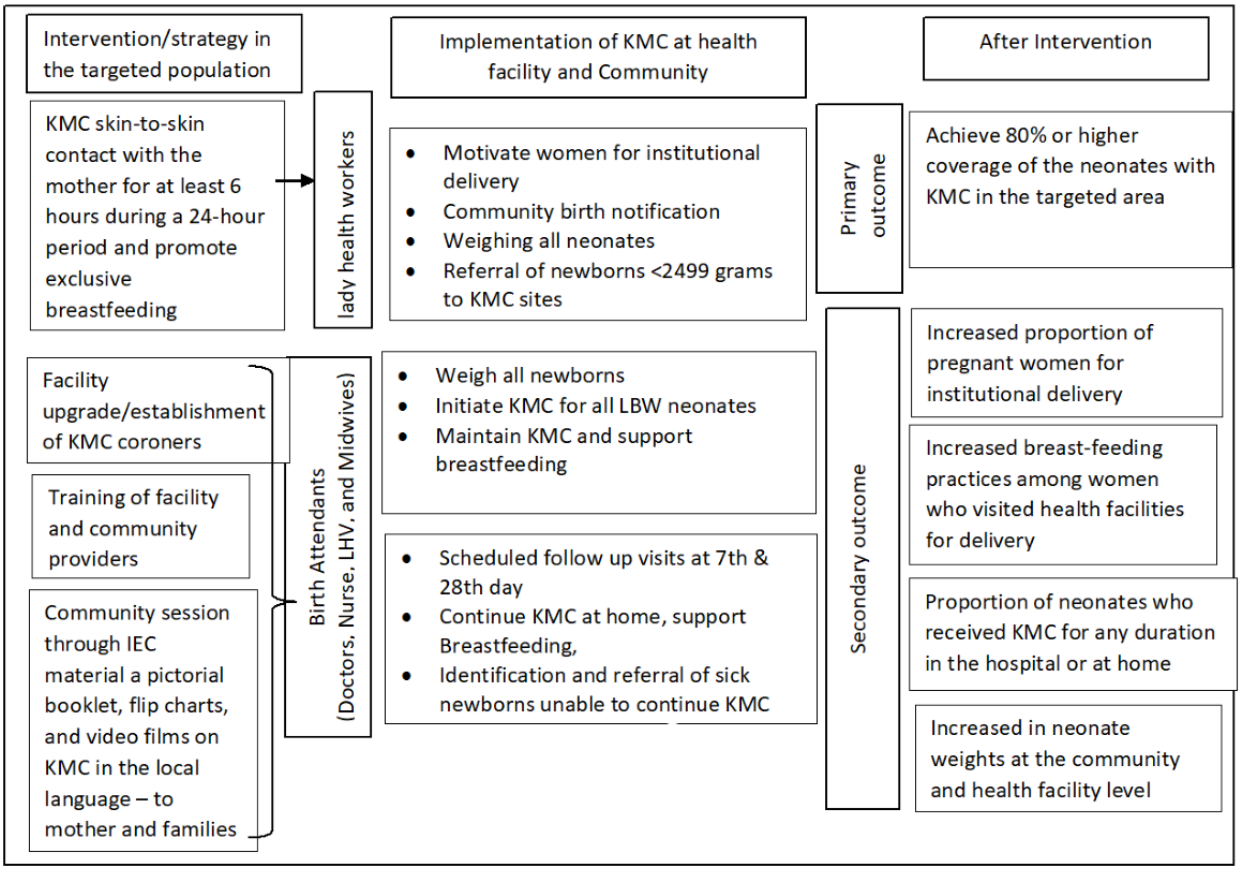
Sample Size

We will include all newborns delivered in the selected facilities according to the inclusion and exclusion criteria over the 18-month implementation period.

Intervention and Study Implementation Strategy

The study will implement the KMC model in District Sanghar which involves skin-to-skin contact between the mother and the infant for a minimum of 6-8 hours within a 24-hour period, along with exclusive breastfeeding. Implementing the KMC delivery model (Figure 1) will take place in 3 stages: prefacility, facility, and postfacility. At each of these stages, various activities will be conducted, which include, enhancing the capacity of both the facility and community health care providers, establishing effective referrals from the community to health care facilities for institutional deliveries and KMC interventions, providing education on KMC to mothers, families, and the community to improve newborn health outcomes, and reinforcing follow-up procedures for both the community and health care facility.

Figure 1. KMC implementation model. IEC: information, education, and communication; KMC: kangaroo mother care; LBW: low birth weight; LHV: lady health visitor.



All stable enrolled newborns (with relevant consent obtained) will be placed with skin-to-skin contact and breastfeeding will be initiated within the first hour of life. Mothers will be given tutorials on administering KMC by a trained physician or nurse or lady health visitor at the facility within 6 hours after delivery. At discharge, mothers and family members will be provided with counseling and encouraged to continue KMC practice at home.

Formative Research Phase

We will use our (Umeed-e-Nau project) [10] project baseline data to assess KMC in the community, to review the current health care system, infrastructure, and resources available in the district. The available information will also help assess the existing newborn care practices, health care staff capacity, and community awareness about KMC. For successful KMC implementation, the study will identify key stakeholders involved in newborn care, including health care providers, administrators, policy makers, community leaders, and parents, and engage them in the planning process, ensuring their perspectives are considered and addressing any potential barriers to successful implementation. As part of our research planning, we will conduct interviews (focused group discussion and in-depth interviews with them to gain insights into the local context and factors influencing newborn care practices). In addition, we will also conduct observations to understand health system barriers, bottlenecks, community beliefs, knowledge, and attitudes toward KMC and further identify any cultural or social barriers that may need to be addressed. For this assessment, we will use the COM-B (Capability, Opportunity, Motivation, and Behavior) [18] to understand better the factors influencing behavior change within the community.

We will adopt a multipronged approach that involves active participation from both mothers and health care staff. This approach will address the various components required for behavior change: capability (knowledge or skill needed to perform a behavior), opportunity (a social environment that enables a behavior), and motivation (effective counseling and follow-ups to encourage and activate behavior change). Based on the findings from the formative phase, we will develop a plan for scaling up KMC across the targeted health facilities within District Sanghar.

Intervention Phase

Prefacility Level

The prefacility-level activities will include training of health care providers, and promoting facility birth by involving lady health workers (LHWs) to refer pregnant women for institutional delivery. This has already been implemented by LHWs, who provide immediate referrals for LBW babies delivered at home or in other facilities through KMC counseling.

Counseling during antenatal care visits by LHWs will help increase institutional deliveries and facilitate intrafacility referrals of LBWs to KMC sites. Each month, LHWs will prepare a list of pregnant women as part of their routine activities, submitting this list with their monthly reports to their

respective lady health supervisors. Data collectors will validate this information during their monthly visits to the LHWs.

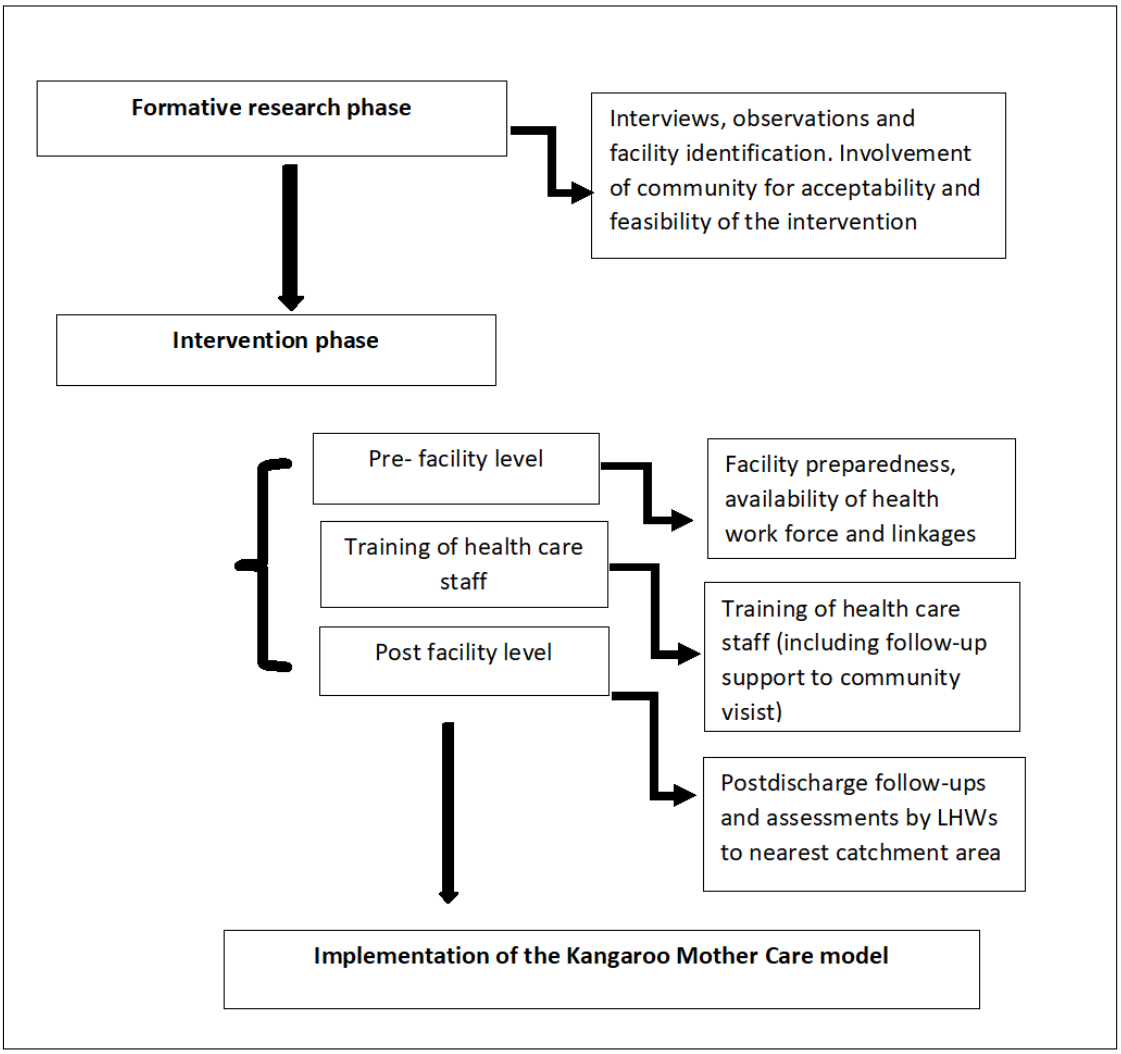
Pregnant women in the community will be encouraged to visit health facilities for antenatal care and institutional delivery through the LHWs, as this is part of their mandate. This antenatal visit and counseling will also include information about KMC. This activity aims to identify the total number of pregnant women who can be referred to the facility for delivery and KMC if their neonates meet the inclusion criteria of weighing >1200 and <2500 g.

All neonates will be screened at birth, and those with a birth weight of >1200 and <2500 g will be referred to the KMC functional site in their respective tehsils or districts. The KMC intervention will be initiated with all LBW babies meeting the inclusion criteria who are delivered within the study catchment area, either at the KMC site or by referral to the KMC sites.

Training of Health Care Staff

KMC experts from Aga Khan University (AKU) will serve as master trainers for the training, based on educational material on KMC in the local language for mothers, families, health facility providers (physicians, nursing staff, and lady health visitor staff), LHWs, and study staff at the district level. The training routine will consist of a 1-day classroom and 2-day real-life field scenario for facility providers. Similarly, the LHWs of the selected facility catchment area will also be trained for institutional delivery referral, KMC case notification, and follow-ups. They will be trained to deliver information, education, and support for the KMC practices at the household level in a 2-day training workshop by respective health facility providers. At discharge, mothers and family members will be counseled so that KMC can be continued at home. Facility staff will notify the data collector of discharges and schedule follow-up visits on the 7th and 28th day (Figure 2).

Figure 2. Flow diagram for study implementation. LHW: lady health worker.



Postfacility Level

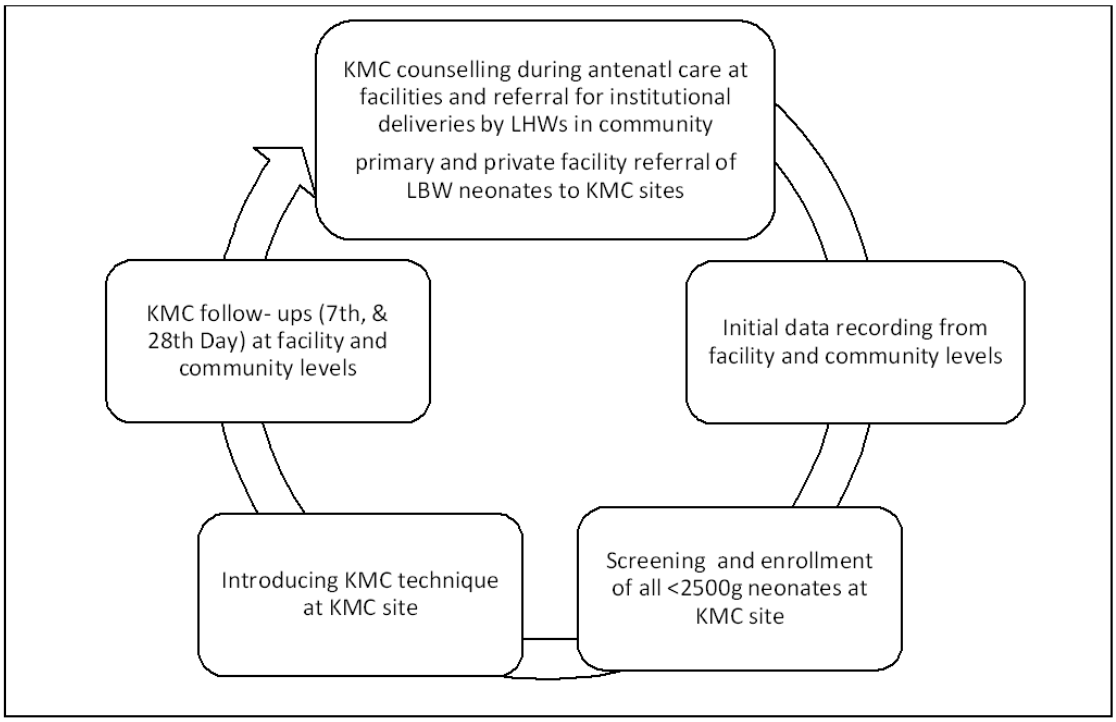
Community-based KMC will be administered at home by LHWs exclusively to enrolled neonates discharged from facilities and those born at home within the catchment population of a designated KMC facility. Postdischarge, follow-up will be conducted by respective LHWs. They will visit the home on the 7th and 28th days to assess the implementation of the postfacility KMC protocol. The follow-up team will continue to monitor the newborn at each visit, using a checklist to assess KMC practices, including skin-to-skin contact duration (hours per day) and breastfeeding status, and recording the newborn's

weight. Additionally, the team will identify and refer sick newborns to the facility and assist with the referral process. This approach, aligned with the health systems strengthening component (continuum of care), aims to create a linkage between facility and community, encouraging the continuation of KMC at home.

Implementation of KMC (The Delivery Model)

The most effective KMC delivery strategy will be determined based on program findings. Data will be gathered from all established KMC sites to assess coverage and adherence to KMC guidelines, including the utilization of communication and training materials and the effectiveness of implementation tools. The results on progress and compliance with process indicators will be shared at the District Health Program Management Team meeting. This meeting will convene key stakeholders, such as health facility managers, LHW program focal persons responsible for managing outreach components, and other individuals involved in the design, implementation, and rollout of the KMC delivery model. Continuous collaboration with these provincial-level stakeholders will enable the integration of best practices and adjustments at the facility level to promote effective KMC and its sustained benefits for vulnerable populations (Figure 3).

Figure 3. Continuous scale-up model of KMC, Umeed-e-Nau, at the facility level. ANC: antenatal care; KMC: kangaroo mother care; LBW: low birth weight; LHW: lady health worker.



Data Collection Teams

The KMC intervention will be carried out by health workers, including facility staff and LHWs, employed by the district or provincial government at both health facility and community levels. The role of the AKU research team in implementation will primarily be supportive, initially focusing on the formulation of the study design and ongoing process assessment for monitoring and evaluating the intervention's outcomes in the target population. The AKU team will also facilitate data collection by conducting interviews with various stakeholders, such as health care providers, administrators, policy makers, community leaders, and parents, to evaluate the feasibility and acceptability of the intervention. Additionally, the team will provide quality assurance and guidance to health facility staff and community-based health care providers to ensure the effective execution of the KMC intervention within a supportive environment.

Data Management

The collected dataset will be linked to participant identification numbers, separate for mothers and newborns. The cleaned dataset will be presented in monthly review meetings with the principal investigator for review and feedback. Data quality assurance methods would include digital real-time checks for missing values and inconsistency, random spot checks, and data validation coupled with independent monthly audits. The collected data will be stored in a password-protected file and only the data manager from the data management unit will be allowed to access the data and will share the analysis elsewhere needed.

Ethical Considerations

The study was approved by the ethical review committee of the AKU, Karachi-Pakistan (2021-6444-19970). Before enrollment into the study, a verbal explanation of the research will be provided, and written consent will be obtained from the mother or an adult family member. In cases where the participant cannot read the informed consent form, a research team member will read it out to them before recruitment. The participants will be

fully informed that they have the right to withdraw from the study at any time, without any negative consequences or compensation, and their decision to withdraw will not impact their access to any services provided by the facility. The study will be scaled up within the existing health system so monetary compensation will be provided. However, all the LBW neonates enrolled in the study will be provided with standardized KMC kit which includes, a shirt for mother and baby suites 3 zero size, diapers, woolen cap, socks, soap bar for neonates.

We will also maintain the participant's confidentiality during our research, all identified information of the study participants will be kept confidential and can only be accessed by the principal investigators or supervisors. The findings will be conveyed to the communities through the health system's channels, as well as district, provincial, and national health authorities will be informed through project dissemination and publication in peer-reviewed journals.

Results

Expected Results

Through the implementation of this research, our results include achieving an 80% improvement in KMC coverage and promoting optimal breastfeeding practices among postpartum mothers. The data collection of our research is completed and so far, 12499 live births have been reported and we enrolled 3046 LBWs for KMC and we successfully followed up all registered neonates. We are currently cleaning and refining our data sets for analysis and the actual results of our research will be available in the original research article. The key indicators to be measured include the proportion of eligible infants enrolled in KMC, the percentage receiving skin-to-skin care within specified timeframes post discharge, and the duration of KMC during the neonatal period. Additionally, the study will assess the proportion of eligible infants exclusively breastfed at various intervals, along with monitoring neonatal weight gain and tracking neonatal deaths within the enrolled cohort. The data management team will evaluate the model's effectiveness in achieving the targeted KMC coverage among the entire study population, as outlined in the outcome measurement section.

Evaluation

Effective KMC coverage is defined as the number of newborns receiving KMC divided by the total number of newborns eligible for KMC (>1200 and <2500 g) at the facility and communities during the evaluation period. To measure the denominator for effective KMC coverage, it is preferred that all facility births be identified during facility visits by reviewing birth registers from all facilities. In addition, the data collector will liaise with LHWs to obtain the number of home births and their birth weights. To calculate the numerator for effective KMC coverage, the data management team will quantify the number of newborns weighing >1200 and <2500 g who received KMC in the study population. All enrolled newborns will be followed by the data collector in the facility or at home to collect data at two points: the 7th and 28th day of initiation of KMC. At each time point, the team will record the data through the KMC checklist. We will disseminate the scaling-up findings of KMC across facilities in Sanghar districts with further dissemination of this scale-up at the provincial and national levels to encourage its implementation within other provinces.

Discussion

Increasing Coverage for Premature and LBW Neonates

This will be the first implementation research project to develop and evaluate scale-up models for achieving high population coverage with KMC in Pakistan. Implementation of a context-specific KMC model in Sanghar within secondary health care facilities and surrounding communities will help to achieve at least 80% KMC coverage for premature and LBW neonates. The model in the targeted facilities and communities will also assess the impact of this low-cost intervention on reducing neonatal morbidity and mortality among premature and LBW newborns within the rural health system of Sindh, Pakistan.

This project is a collaborative initiative between AKU and the provincial government, aiming to evaluate the effectiveness of scaling up KMC coverage. Preliminary data indicates that KMC is currently practiced for <5% of LBW infants in these settings, with no competing interventions promoting KMC at the study sites [6]. There is existing literature on the barriers and facilitators of KMC within health facilities [19-21]. This project presents a timely opportunity to integrate KMC into the existing health care system in partnership with the government. The goal is to identify effective scale-up models for implementation in large, countrywide settings. While the study focuses on KMC coverage as a key outcome, we aim to develop a model that integrates KMC as an essential component of newborn care, rather than projecting it as a standalone vertical program.

The study will exclude community-based follow-ups to evaluate improvements in newborn weight for families that do not provide consent for such follow-ups. Further, the accuracy and reliability of outcome measurements, such as growth parameters and developmental milestones, were not used.

Conclusions

The outcomes of this implementation research will extend beyond the study area to benefit other regions within Pakistan and globally. The findings will inform strategies to enhance essential newborn care provision at health care facilities, seamlessly integrating KMC without the need for a separate vertical program. Insights gained from this research will not only illuminate the challenges associated with scaling up KMC but also offer effective solutions to address them. Furthermore, these experiences hold promise for shaping the design and implementation of future infant and childcare programs, facilitating their swift adoption by both health systems and communities. The findings of this study will provide robust evidence to inform the development of policies and programs aimed at preventing neonatal mortality and improving maternal and child health and growth outcomes in resource-limited settings.

Acknowledgments

This study is funded by the Bill & Melinda Gates Foundation as part of the Umeed o Nau project. We also acknowledge the Directorate General of Health Services, Department of Health, Government of Sindh, along with the District Health Officer's Office in Sanghar, health care facility staff, and the community at large for their invaluable support and collaboration in implementing this project.

Authors' Contributions

ZAB led the funding acquisition of the main kangaroo mother care scaleup intervention project. SM conceptualized the study design with guidance from ZAB. SA, SS, and ZM provided inputs on public sector service delivery platforms. HN, AAS, and SK drafted theoretical framework. SM drafted the first version of the manuscript and HN incorporated feedback from all the coauthors. All authors reviewed subsequent manuscript drafts. All authors have read and approved the final version of the manuscript.

Conflicts of Interest

None declared.

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Abbreviations

AKU: Aga Khan University
COM-B: Capability, Opportunity, Motivation, and Behavior
KMC: kangaroo mother care
LBW: low birth weight
LHW: lady health worker
SBA: skilled birth attendant
WHO: World Health Organization

Edited by A Mavragani; submitted 08.01.24; peer-reviewed by M Stevens-Uninsky, V Liyanage; comments to author 21.03.24; revised version received 23.06.24; accepted 11.09.24; published 29.01.25.

Please cite as:
Muhammad S, Soomro A, Ahmed Khan S, Najmi H, Memon Z, Ariff S, Soofi S, Bhutta ZA
Scaling Up Kangaroo Mother Care Through a Facility Delivery Model in Rural Districts of Pakistan: Protocol for a Mixed Methods Study
JMIR Res Protoc 2025;14:e56142
URL: https://www.researchprotocols.org/2025/1/e56142
doi:10.2196/56142
PMID:

Protocol

Telehomecare Monitoring for Patients Receiving Anticancer Oral Therapy: Protocol for a Mixed Methods Evaluability Study

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Abstract

Background: Telehomecare monitoring (TM) in patients with cancer is a complex intervention. Research shows variations in the benefits and challenges TM brings to equitable access to care, the therapeutic relationship, self-management, and practice transformation. Further investigation into these variations factors will improve implementation processes and produce effective outcomes.

Objective: This study aims to concurrently analyze implementation and evaluate the effectiveness of TM for patients receiving anticancer oral therapy. The objectives are to (1) contextualize how and why TM is implemented according to (a) site characteristics, (b) team characteristics, and (c) characteristics of patients receiving anticancer oral therapy; (2) assess TM effectiveness for recording electronic patient-reported outcome measures (ePROMs) and patient-reported experience measures (ePREMs) according to the site, implementation process, and patient characteristics; (3) describe the acceptability and feasibility of TM from the perspectives of the people directly or indirectly involved and provide evidence-based actionable guidance in anticipation of provincewide implementation.

Methods: This type II hybrid effectiveness-implementation study uses a concurrent mixed methods design. Evaluability assessment is integrated into an emerging practice in 3 participating sites to enable the evaluation of implementation strategies on TM clinical outcomes. Quantitative data for ePROMs and ePREMs will be collected using validated oncology questionnaire. Descriptive statistics and repeated measures using multiple linear mixed models and generalized estimating equations analyses

will be undertaken alongside interpretive descriptive coding of qualitative data. Qualitative data will be gathered from key informants guided by the RE-AIM (reach, efficacy, adoption, implementation, maintenance) framework and its extension, PRISM (practical robust implementation and sustainability model). The concurrent approach allows results at multiple stages of this study to be integrated iteratively. The methodological choice aims to provide real-world data that are rigorous, rapidly usable in practice, and transferable to other settings.

Results: Questionnaires were pretested and the technological platform was codeveloped with members of the cancer care team and patients. Preparatory work was carried out to configure the TM platform and activate coordinating mechanisms between members of the cancer care team, patients, information technology experts, and the research team. A steering committee with 3 working groups was established to oversee the technological, clinical, and evaluation aspects of this study. Recruitment of patients for ePROMs started in February 2024, and data collection is expected to continue until March 2025. Interviews with members of the cancer care team began in November 2024. Full analysis should be completed by September 2025.

Conclusions: This study will clarify how, why, for whom, and under what conditions TM can complement current care models. Our evaluability assessment will help to address implementation complexities and better understand intervention-to-practice operationalization so that implementation might be adapted to contextual factors without potentially harmful or inequitable impacts on patients.

International Registered Report Identifier (IRRID): DERR1-10.2196/63099

(JMIR Res Protoc 2025;14:e63099) doi:10.2196/63099

KEYWORDS

telehealth; virtual care; telehomecare monitoring; anticancer oral therapy; oncology; electronic patient-reported outcomes; electronic patient-reported experience; evaluability study; mixed methods; implementation.

Introduction

Background

Use of anticancer oral therapy, administered alone or in combination, is increasing rapidly in patients with cancer [1,2]. Anticancer oral therapy offers patients the convenience of taking medication at home, which has considerable benefits (eg, reduced hospital visits, time spent in waiting rooms and transport, transportation costs, as well as increased autonomy) [3,4]. However, there are important concerns around nonadherence to treatment [5] and the transfer of responsibility for drug administration, management of side effects, and monitoring of warning signs from the members of the cancer care team to the patients and primary care professionals, who are not always comfortable with these roles. Interdisciplinary cancer care teams (oncologists, nurses, pharmacists, psychologists, social workers, and others) are part of multiteam systems [6] that include primary care professionals (family physicians, nurses, social workers, and community pharmacists), patients, lay caregivers, nonprofit community organization workers, managers, and policy makers. Not everyone is necessarily prepared for the role and practice changes required by telehomecare monitoring (TM) [4,7,8]. Several conditions must be met to assure the safety of patients receiving anticancer oral therapy. For example, patients require capacities for self-management and adherence to treatment, the support of a family member or lay caregiver, and timely access to members of the cancer care team when needed. These team members need to establish regular and proactive monitoring, as well as effective communication and coordination, to ensure prompt response in case of need [3,7,9]. The proposed study aligns with priorities for research on TM [10] by looking specifically at its use among patients receiving anticancer oral therapy. This study focuses on the importance of structuring the increasing use of TM in such a way as to maintain the therapeutic relationship and optimal communication between patients and members of the cancer care team. The proposed structure involves a digital platform that is easy for patients to use and is regularly monitored by members of the cancer care team and alerts them when follow-up is required. This study addresses the integration into clinical processes and the effectiveness of TM on patient-reported outcomes and experience of receiving anticancer oral therapy treatments [11] based on differences in setting, team, and patient characteristics.

There are multiple terms (eg, telecare, virtual care, and eHealth) and definitions of telehealth that frequently overlap [12]. In this study, the term TM is used to describe interactions between patients in their own homes and members of the cancer care team. Telehealth generally refers to a health or social service provided at a distance using synchronous or asynchronous videoconferencing, digital applications, or telephone to improve health [11,13]. Telehealth is not new, but before the COVID-19 pandemic, its use was uncommon in cancer care and limited in most health systems [14]. For example, a 2019 study reported that only 0.6% (3/464) of family physicians in Québec, a province in Canada, had ever used telehealth, compared to 4.2% (108/2569) of the respondents in the rest of Canada [15]. Little data are available on the postpandemic use of telehealth in Canada. A national survey of 1038 participants in the United States found that the proportion of professionals in cancer care teams (oncologists, nurses, and residents) using telehealth increased from 19% to 84% during the COVID-19 pandemic [16].

In the oncology context, a systematic review (2017-2020; where, it should be noted, only 3 of 37 studies were conducted in Canada) concluded that telehealth is appropriate for symptom evaluation in adult patients during active treatment and survivorship [17]. Studies report several telehealth benefits for patients [17-20], namely improved accessibility, satisfaction,

effectiveness, and comfort (especially in people with moderate symptoms or physical limitations); better adherence and treatment persistence; reductions in transportation costs and absences from work for medical follow-up; less decline in quality of life; and fewer emergency department visits. Benefits for members of cancer care teams include the potential to work remotely and thus contribute to maintaining service accessibility [21], real-time monitoring of patients-reported outcomes, and maintenance of communication among the teams involved along the care trajectory [19]. At the health system level, one study finds that telehealth can reduce missed appointments and has the potential to positively impact the efficiency of human resources [22].

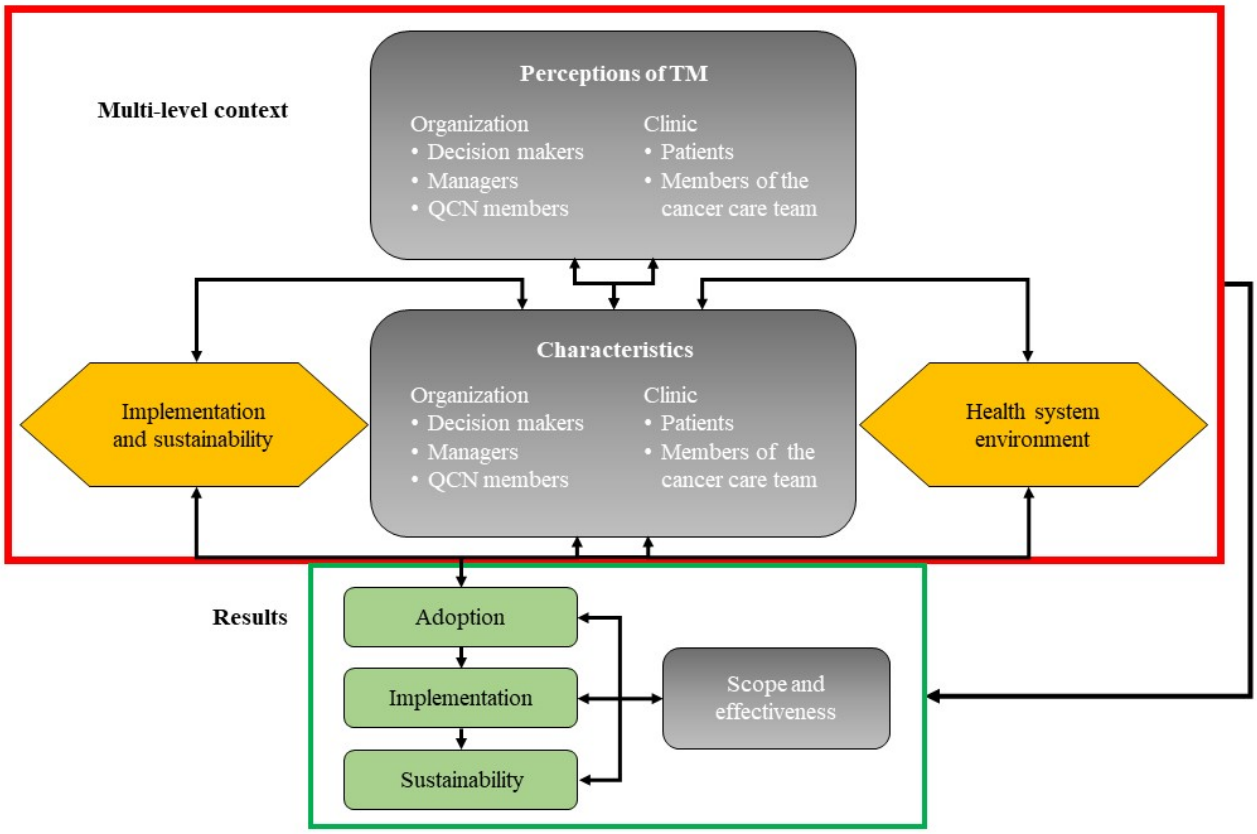
However, the limitations of telehealth must also be recognized. Recent studies find that some patients prefer in-person consultations and do not wish to continue with TM after the pandemic [17], while others prefer a hybrid approach that considers their needs and preferences [21]. Some studies [20,23] warn against a model that replaces in-person visits with telehealth to reduce health care costs or deal with shortages of human resources. Other limitations include poor internet access, the cost of computers and tablets, and difficulties with remote communication, especially for people with low technological or health literacy [24]. It is crucial that recourse to telehealth does not create disparities in access to care, notably for people who may have problems using technology [17,25] and people in situations of vulnerability who require in-person psychosocial support [26]; the risk of disparities is heightened when telehealth is hastily planned, as was the case during the pandemic [24]. For members of the cancer care team, the use of TM depends on new practices, supported by legitimate leaders and dedicated resources, and a context that includes a history of successful transformation [27]. Structures must be in place to identify implementation barriers and find means of overcoming them to prevent undesirable organizational effects (eg, interpersonal conflict, lack of organizational support, burnout, intention to quit, and absenteeism) [28,29] or jeopardize the quality of care (eg, depersonalization of care, diminished partnership in care, and threats to the therapeutic relationship and relational continuity) [30]. The compatibility between TM and established practices, and perception of its usefulness, have a strong impact on TM use and on team members' satisfaction [31]. At an institutional level, major changes require attention to organizational, legal, and ethical challenges (patient records, protection of personal information, professional responsibility, and technological evolution) [32]. To summarize, the scientific literature identifies the benefits and limitations of telehealth in cancer care. However, the diversity of participants and clinical conditions in available studies, the various research methods used, and the plurality of contexts make it difficult to grasp the nature and extent of challenges around TM implementation and effectiveness in a given context [20]. Our study aims to improve understanding of these challenges by producing evidence specific to the local context on predictors of real-world adherence to TM and its potential effects.

TM can be conceptualized as a multifaceted telehealth intervention that involves a network of heterogeneous groups (eg, patients, managers, members of the cancer care team, primary care professionals, decision makers, nonprofit community organization workers, information technology experts, and professional orders or associations), with different and even competing goals and interests and acting at different system levels. The novelty of TM differs between users. Our previous work shows that multifaceted interventions produce anticipated results when the network of people involved rally around a common objective [27], with shared leadership [33], and in partnership with patients [30].

Theoretical and Operational Model

From the perspective of actor-network theory (ANT) [34,35], translating TM into practice occurs through nonlinear processes: common definition of the problem and rationale for TM (problematization), expectations and strategies to engage team and patients (interest generation), role attribution and engagement of the people involved (enrollment), coordination of network action (mobilization), and sustainability (irreversibility). These building blocks, also considered as management tools [36], are consistent with an evaluability assessment [37]. They guide our participatory approach to providing evidence-based and actionable guidance on the use of TM that will benefit patients, their caregivers, and members of the cancer care team. At the operational level, this study is based on the RE-AIM (reach, efficacy, adoption, implementation, and maintenance) framework [38], and its PRISM (practical robust implementation and sustainability model) extension [39]. The RE-AIM/PRISM framework encourages consideration of the characteristics of patients, members of the cancer care team, and their practice setting (Figure 1).

Figure 1. TM study framework adapted from RE-AIM/PRISM. QCN: Québec Cancer Network; PRISM: practical robust implementation and sustainability model; RE-AIM: reach, efficacy, adoption, implementation, maintenance; TM: telehomecare monitoring.



Preparatory Work

The national telehomecare platform is supported by the Québec Ministry of Health and Social Services. The telehealth coordination office, housed in one integrated health and social services center [13], has a mandate to manage the platform's deployment in several hospital centers. TM is based on evidence and adaptation achieved through experimentation in clinical settings. The platform was co-developed with the formal participation of stakeholders (eg, patients, managers, information technology expert collaborators, clinical leaders, and researchers). Preliminary work allowed the TM platform to be configured for use with patients [40]. Locally, its configuration was conceived and undertaken collectively by pharmacists, pivot nurses in oncology, and patients. Various strategies were implemented to support TM use to report symptoms and support self-management (eg, demonstration video, support resources, educational modules, symptom management messages, warning signs or "red flags" with decision supports, and accompaniment by survivors of cancer). Preimplementation indicators were the frequency of evaluations by patients, warning sign thresholds for clinical tools, specific alert management algorithms to guide cancer care team members' interventions, range of monitoring (percentage of potential patients, percentage who accepted, percentage who refused, and percentage of red flags addressed), and teaching and training needs. This preliminary work was financially supported (salaries, equipment, and expertise) and closely accompanied by members of the cancer program of the Québec Ministry of Health and Social Services. The preparatory work revealed challenges in implementation (eg, identifying members of the cancer care team to assign to TM, redistributing work, leadership style, and pace of patient recruitment). Facilitating and impeding factors need to be systematically assessed to achieve expected effectiveness and guide scale-up across the province.

Aim and Objectives

This study aims to concurrently examine the implementation process and evaluate the effectiveness of TM for patients receiving anticancer oral therapy. In line with the conceptual framework, the specific objectives are as follows:

1. To contextualize how and why TM is implemented according to (a) site characteristics (location, mandate, resources, and supports), (b) team characteristics (members of the cancer care team, managers, and coordination with primary care and nonprofit community organizations), and (c) characteristics of the patients receiving anticancer oral therapy.
2. To assess TM effectiveness for digitally recording electronic patient-reported outcome measures (ePROMs) and electronic patient-reported experience measures (ePREMs) according to the site, implementation differences, and patient characteristics.
3. To explore the acceptability and feasibility of TM from the perspective of the people directly or indirectly involved and provide evidence-based actionable guidance in anticipation of provincewide implementation.

Methods

Study Design

This mixed methods evaluability study uses a type II hybrid effectiveness-implementation design. An evaluability assessment is appropriate for all stages of a novel intervention [37,41,42]. It enables (1) formative assessment of clinical, organizational, and technological components through reflection "on and in practice" and rapid feedback on findings; (2) better planning; (3) accelerated integration of research findings through constant interaction between researchers and stakeholders; and (4) identification of new ways of doing things to achieve scale-up objectives [37,41,42]. A type II hybrid effectiveness-implementation design enables in-depth analysis of TM integration in a natural setting (objective 1) and effectiveness for patients receiving anticancer oral therapy (objective 2) [43,44]. Type II refers to the concurrent study of implementation and effectiveness, an approach that is recognized in cancer care interventions [45] and is consistent with the RE-AIM/PRISM framework [43] (objective 3). A mixed concurrent approach, suited to participatory evaluability assessment [37], integrates quantitative and qualitative data [46]. The voluntary participation methodology allows for the inclusion of multiple perspectives, and equity, diversity, and inclusion considerations [47]. Our study adheres to ethical research standards [48] and responsible research conduct [49]. Researchers will endeavor to maintain relationships based on trust and mutual respect by being attentive to issues around the social acceptability of health research, by protecting the identity of participants, and by involving patient partners from the very start of our study [50].

Our study comprises the following interdependent phases:

1. Preparing the ground (objective 1; duration 4 months) includes presentation of the TM study to the actors involved, development of reciprocal engagement between the research team and TM leaders including patient partners and community actors, and an environmental scan [51] to understand local dynamics (potential participants; rate of inclusion in TM; technical, professional, and personal challenges; and workforce or resource challenges). This process of collecting, interpreting, and using information from the internal and external TM environment informs strategic decision-making, guides accompaniment efforts, and ensures the progress of this study by resolving difficulties that may arise.
2. Analysis of implementation and clinical effectiveness based on RE-AIM/PRISM (objectives 1 and 2; duration 12 months) assesses achievement of TM goals and evaluates expected benefits and absence of unexpected negative effects related to its use, ePROMs and ePREMs, and resource use. Markers of TM use will be defined according to patients' perspectives, cancer care team reorganization of work and collaboration with primary care and nonprofit community organization partners, use of human and financial resources in local arrangements, and levers and means used to overcome obstacles to safe implementation while upholding equitable access to care for patients.
3. Integrated planning for sustainability and spread (objective 3; duration 4 months) extracts lessons for eventual changes to be brought to TM to improve sustainability and future scale-up to other groups of patients (eg, intravenous therapy, immunotherapy, postsurgical cancer follow-up, palliative non–end-of-life care, and survivorship follow-up) [4]. This stage will identify the clinical, organizational, and equity challenges of TM as a complex highly context-dependent intervention. The transferability of this real-world study must also be optimized [43], especially where geographic and local dynamics differ.
4. Dissemination of results (duration 4 months) relates to the plan described in the later section of the protocol on integrated knowledge translation, for presenting findings to various groups of end users.

Study Sites

This study will be conducted in 3 cancer centers in the province of Québec, Canada, that have introduced TM over various periods (1 year or 1 month) and dedicated varying levels of human and financial resources. These cancer centers are located in hospitals that are part of the Québec Cancer Network. These centers have distinguishing characteristics (Table 1): geographic location (mega-urban, semiurban, or urban) [52], population served, mandate (academic or community), size of the cancer care team, team caseload (number of visits or number of treatments), primary care centers (number of community service centers or number of family medicine groups), TM work redistribution between members of the cancer care team (designated leadership or shared leadership), and formal partnership with survivors of cancer trained for TM support and research.

Differences between study sites will help understand perceptions of TM in real-world contexts and the influence of various factors on adoption, implementation, effectiveness, and potential sustainability, as illustrated in Figure 1.

Table 1. Characteristics of participating cancer centers[a].

	Site 1	Site 2	Site 3
Organizational			
Geographic location	Mega-urban	Urban	Semiurban
Population, n	229,359	172,713	199,376
Mandate	Community	Academic	Community
Size of the cancer care team	Large	Large	Small
Clinical			
Radiotherapy	Yes	Yes	Yes
Hemato-oncology	Yes	Yes	Yes
Visits to hemato-oncology services, n	63,405	44,245	13,180
Treatments, n	14,758	23,534	5403
Primary care centers			
Community service centers, n	2	5	3
Family medicine groups, n	8	10	8
Implementation			
Patient partners, n	0	1	0
Telehomecare monitoring coordination model[b]	Shared leadership	Designated leadership	Shared leadership

[a]Publicly accessible data (2021-2022).

[b]Coordination model apparent in early implementation.

Participants and Sampling

This study involves key informants knowledgeable of TM. The sampling strategy for patients is nonprobabilistic, based on eligibility criteria preestablished by the cancer care team. Inclusion criteria are receiving anticancer oral therapy, being interested in TM for a minimum duration of 6 months, having internet access and experience using it, being able to report symptoms with existing tools, being open to educational material, and being able to recognize warning signs. For key informants (patients, members of the cancer care team, managers, institutional decision makers, and nonprofit community organization workers), purposive sampling [53] aims to obtain a cross-section of views from people at different decision-making levels around TM (clinical, organizational, or system). These strategies are appropriate given the exploratory nature of an evaluability study.

We estimate from hospital administrative records that between 100 and 200 patients receive anticancer oral therapy each year (N=400 in 3 participating centers). Preparatory work since March 2022 shows that about 160 of these patients would meet our inclusion criteria and about half would continue completion of the ePROMs questionnaires over 6 months (80 patients × 26 weeks × 3 times a week=6240 results) and the ePREMs experience of care questionnaire at 3 months (ePREMs: n=80). A sample of 40 participants is considered sufficient for an exploratory study of a health services intervention [54]. We estimate that about 12 individual interviews per site with patients, members of the cancer care team, and managers (n=36) would allow for theoretical saturation of qualitative data [55]. This will be supplemented by interviews with decision makers (eg, policy level, professional orders, and national organizations; n=9), for a total of 45 interviews of about 60 minutes. Participants will be offered CAD $60 (US $41.90) compensation.

Quantitative Data Collection

Clinical data collection tools for ePROMs are based on those used in the Patient Reported Outcomes to Enhance Cancer Treatment study [56]. Ten questions, with French versions available for Canada [57], are taken from the PRO-CTCAE (Patient-Reported Outcomes Version of the Common Terminology Criteria for Adverse Events) library of the National Cancer Institute (eg, nausea or vomiting, diarrhea, constipation, dyspnea, stomatitis, skin problems, acne, hand-foot syndrome, edema, pyrexia, and more). The items are reported on a 5-point scale. Six questions on symptoms from the Edmonton Symptom Assessment System-revised are included (pain, depression, anxiety, insomnia, and fatigue) [58]. Subquestions on self-management support were created by the interdisciplinary team at the integrated health and social services center overseeing implementation to direct patients to educational modules on the TM platform. The ePROMs responses are collected 1 to 3 times per week according to patients preference. In preparatory work, 90% (144/160) preferred 3 times a week. The ePREMs questionnaire includes dimensions on health system responsiveness adapted for patients [27], satisfaction [56], and health-related quality of life [59], all measured with validated tools. Along with these dependent variables, self-reported clinical data (tumor site, time since diagnosis, treatment type, and comorbidities) and sociodemographic data (sex, gender, age, education, perceived health status, and

economic situation) are collected (control variables) to enable comparison with other studies [56]. The ePREMs questionnaire will be administered 3 months after the start of TM [56]. The time for completing the questionnaire is estimated at 20 minutes, and compensation of CAD $20 (US $13.97) is anticipated. We will monitor the indicators to associate contextual factors with clinical and implementation data and promptly identify unanticipated undesirable effects of TM. These are the dependent variables of this study.

Qualitative Data Collection

Semidirected individual interviews conducted at the mid-point in this study aim to describe enabling and impeding factors for each of the dimensions of the RE-AIM/PRISM framework, which include multilevel aspects (eg, perceptions of TM and characteristics of organizational and clinical stakeholders, the context of implementation and sustainability, and the impact of the wider health system environment) and mechanisms that support adoption, implementation, and sustainability to achieve the scope and effectiveness of TM (Figure 1). For example, questions inspired by other studies [17,56] and adapted to respondent type address the following: ease of understanding and using TM, usefulness and relevance of self-reported items, quality of communication and accessibility, clinical utility, and sense of self-efficacy for patients. Specific questions for members of the cancer care team to focus on the following: effects on their work, time management, ability to adapt their practice, adjustment of follow-up algorithms, and ways that data influence (or not) their discussions with patients. All participants will be questioned about their satisfaction and proposed improvements for scale-up and their perception of added value to the quality and safety of care.

Data Analysis Procedure

Standard descriptive statistics will enable data to be summarized (ePROMs, ePREMs, sociodemographic, symptom severity, and percentage of indicators of the scope of TM). For ePROMs, the number of questionnaires completed will be calculated for each patient, and the number of completed weekly ePROMs questionnaires will be divided by the number of expected questionnaires. Intrasite comparisons between measures will detect differences in exposure to TM and establish key periods on the patients trajectory. Relationships between the ePROMs items and patient characteristics will be described using Spearman correlations and chi-square tests. Multiple linear mixed models and generalized estimating equations for repeated measurements on the ePROMs [60] will be used to assess relationships between patient characteristics, ePROMs items, and ePREMs dimensions. Statistical significance will be $P<.05$. These analyses will identify the most important determinants of health status, relevant indicators, and appropriate moments for measurement.

Recorded and transcribed interviews will be analyzed using a descriptive interpretive approach [61] with 2 coders independently coding meaning units. A first coding cycle will focus on themes of the RE-AIM/PRISM framework, and a second interpretive cycle will identify links between context, implementation, and effects [61]. Finally, a synthesis of this qualitative process integrating quantitative results [62] will be codeveloped with volunteers from patients, people involved in care, and the research team.

The integration (qualitative data+quantitative data) will occur at several stages: (1) methodology, with linking sampling strategies, where participants for interviews are selected from among patients receiving anticancer oral therapy; (2) data collection, by adopting a simultaneous interactive approach [63] in which emerging results will iteratively lead to adjustments to future interview questions; and (3) interpretation, in partnership with spokespersons from the various groups involved (eg, professionals, patients, lay caregivers, nonprofit community organization workers, managers, and policy makers). Attention will be paid to quality criteria for qualitative [61] and mixed methods [62] studies to mitigate study limitations.

Ethical Considerations

This project was approved by the Research Ethics Board of the Research Centre of the Montérégie-Centre Integrated Health and Social Services Centre, which serves as the review board for all sites in this multicenter project (MP-04-2024-825, initial approval: August 29, 2023; renewed approval: June 7, 2024). This study will be conducted according to the Helsinki Declaration, and informed consent will be obtained from all individual participants [48]. Study results will be presented at the group level and will ensure that no individual, whether patients or staff, will be identifiable. Participation is voluntary and participants can withdraw from this study at any time.

Integrated Knowledge Translation

The integrated knowledge translation plan (Textbox 1) includes approaches suited to use during and at the end of the project [64]. The research team considers it important to establish bidirectional exchanges between knowledge producers and users and involves knowledge users at all stages of this study. This approach is chosen strategically for its positive impact on the adoption of new evidence-based practices, as well as for its potential contribution to managing problems that may arise during this study. ANT provides the basis for considering the heterogeneity of people involved in TM. ANT has been widely used in applied research to study the production and use of research evidence [64]. It contributes to a better understanding of why research results do not translate easily and are not integrated rapidly into settings for which the research was produced. This is consistent with the idea that people (professionals, patients, lay caregivers, nonprofit community organization workers, managers, and policy makers) as well as context (technology platform, computers, equipment used, and funding) act on the implementation and effectiveness of TM. The plan is inscribed in a project where sustainability and scale-up are anticipated right from preliminary work. It also aims to amplify the impacts of the research at provincial, national, and international levels. As a result, the activities, format, timing of, and vehicle for dissemination will be adapted to each target audience.

Textbox 1. Integrated knowledge translation plan of audience and activities.

Actors in the field

- Early detection of barriers, facilitators, controversies, and potential solutions
- Accessibility of the research team to actors in the field
- Discussion of interim findings in each setting
- Debriefing meetings to triage adjustments during implementation
- Newsletter published every 4 months on our website, distributed to partner networks of coresearchers and collaborators
- Support for team members for cancer and local managers
- End-of-project presentation of results in each site

Academic and research communities and trainees

- Generation of interest among the next generation of researchers in the renewal of cancer care: graduate students, oncologists, physicians, and health care professionals
- Dissemination of this study and its results in courses offered by research team members in their universities
- Mobilization of the coauthors' networks
- Sharing of tools developed and found useful for consolidating patients-reported outcomes and for team resilience in facing the challenges of telehealth
- Development of evaluative, interventional, and theoretical application of actor-network theory studies and conceptual studies based on the RE-AIM (reach, efficacy, adoption, implementation, maintenance) framework and its extension, PRISM (practical robust implementation and sustainability model)

Institutional stakeholders and knowledge brokers

- Mobilization of partner networks at multiple decision-making levels
- Presentations at collaborator and stakeholder events
- International peer-reviewed scientific conferences
- Websites to reach a wider audience
- Publication in open-access peer-reviewed journals

General public

- Tailored appropriate messages to share knowledge with different interest groups and the general public as part of an open science approach to broad dissemination

Results

An interdisciplinary steering committee including various stakeholders such as researchers, managers, members of the cancer care team, decision makers, and community actors, has been implemented to oversee the TM implementation. Its members are involved in 3 working groups that report to the steering committee; these groups will support the technological, clinical, and evaluation aspects of this study and address and assist in the resolution of controversies. At the onset of the project, our discussions with patients raised awareness that "imposing substitution on everyone could jeopardize the trust that is essential to our relationship with the cancer care team and increase the stress on us and our families; we don't want that."

An expert committee comprising the TM leader, a pharmacist, a pivot nurse, an information technology expert, and the principal investigator supports organizational readiness, ensuring that local needs for implementation are met and that the TM platform is operational at all sites. This committee developed a PowerPoint (Microsoft Corp) presentation aiming to (1) inform members of the cancer care team and managers of the state of science about TM content, structure, and patient-professional communication mechanisms; (2) describe the potential benefits and limitations of TM for patients, members of the cancer care team, and organizations; (3) present the objectives of the evaluability assessment and effectiveness-implementation study design; and (4) describe the ePROMs monitoring platform and ePREMs questionnaire. Between November 2023 and February 2024, a total of 72 members of cancer care teams from the participating settings took part in the 90-minute session and received continuing education credits. Meanwhile, the codebook for ePROMs was developed and questionnaires for ePREMs were pretested in two cycles by a team of patient partners, researchers, and knowledge users.

Access to the TM platform by the research coordinator and principal investigator required institutional authorization and engagement to ensure adherence to strict measures to protect personal data and confidentiality. This authorization process

was initiated in December 2023, with permission granted in March 2024.

Between February and July 2024, a total of 35 patients were enrolled and had completed ePROMs on the TM platform 1 to 3 times a week; 6 interviews of patients had been conducted. As of November 2024, a total of 1831 ePROMs and 41 interviews had been completed. Further, data collection with team members and other people concerned with the implementation had been initiated. The collection of quantitative and qualitative data is expected to be completed by March 2025, and the full analysis is expected to be completed by September 2025.

Preliminary interpretive coding of interviews suggested that the TM platform was easy to use and that members of the cancer care team provided prompt feedback when symptoms persisted despite self-management and educational material. Patients expressed they would like access to the TM platform on small devices that was not yet available and questioned how their oncologist was informed about the ePROMs. Clarification around the roles of nurses and pharmacists was desired to avoid confusion. The most important positive impact was the implication of a patient partner who explained the platform, how to fill in information, and could be reached for further support in using the platform.

Discussion

Expected Findings

This study will produce new data on the deployment of TM to support ambitions to modernize services available to patients [65]. The results will help inform decisions by integrating clinical, organizational, and health system considerations. This multilevel study will contribute to efforts to satisfy the growing appetite for telehealth, as well as its acceptability and feasibility [66]. Expected impacts are (1) a clinical contribution by informing the use of patient-reported outcomes, achievement of self-management objectives, and prompt team response to needs; (2) an organizational contribution by producing information on contextualized best practices, centered on the needs and preferences of patients, that improve access to care and appropriate use of resources and serve as a complement to and not substitution for clinical contact; and (3) a social win-win type contribution by reducing inequalities of access related to geographic or social distance, while providing essential data on opportunities and risks perceived by some groups of patients.

A recent review on telehealth reports that TM is promoted as a promising future direction for the management of anxiety and depression in patients with cancer [67]. Our study will contribute to efforts to identify types of symptoms that can be managed with TM and asynchronous interventions along with others that require in-person encounters. As patients cautioned us during the preimplementation phase, TM should not be a substitute for face-to-face interventions or be used for workforce rationalization. Additionally, our integrated knowledge translation strategy will activate the dissemination of best practices that recommend establishing the patient-professional relationship before integrating telehealth into care [68]. In the context of health human resources, TM promoters should be aware of the temptation to limit the face-to-face component of care, which may be harmful to the quality of care. Although proximity can be established through in-person or online encounters [69], patients participation [30] and collaborative governance [70] appear essential to prevent the expedient use of TM.

This study may also contribute to reducing disparities arising from the uneven use of telehealth technologies. However, other organizational priorities can increase the risk of TM program failure and increase disparities in access according to the capacities of individual patients and the availability of family caregivers to accompany them in using TM.

Strengths and Limitations

The inclusion of 3 settings chosen for their different characteristics increases the originality of this study's contribution. Multisite studies offer a wider perspective and will add to findings from single-institution studies on teleconsultation [17]. Our evaluability assessment will provide new empirical data on models of care that integrate TM services in advancing the quintuple aim of better health, improved care experience, well-being of members of the cancer care team, and health equity throughout the cancer journey. Our focus on how complementarity is achieved between TM and traditional face-to-face encounters aligns with calls for practical evidence in most recent reviews [17,67].

Some limitations are also anticipated in this study. The methodologies have potential biases. These include selection bias arising from convenience sampling and the fairly small sample size of participants, and observation bias due to real-world data collection that may compromise the application of results to wide-scale implementation [71]. These limitations could be compounded by the use of mixed methods [46] and by linking the implementation process to effectiveness in the specific participating sites. However, the production of such evidence provides detailed information that supports knowledge users in their decision-making and helps save time and avoid TM implementation failure.

Conclusions

TM is a complex intervention at the interface of clinical and organizational domains. Telehealth services for patients with cancer emerged as a key theme during the COVID-19 pandemic and will only become more important in the future. Our evaluability assessment will provide new empirical data on how to design TM services that prioritize a patients-centered approach aligned with patient needs, preferences, and realistic expectations. The focus on how complementarity between TM and traditional face-to-face encounters takes shape will answer the call for practical evidence to inform implementation. Our knowledge translation plan will create opportunities to share the successes that emerge and inspire other settings. Findings may also help to improve follow-up care for patients receiving other types of anticancer treatment that require close monitoring and management. In the event of implementation failure in this study, information on contributors to failure will help prevent

TM promotors from falling into some of the potential traps of implementing complex interventions.

Acknowledgments

We are grateful to all members of the cancer care teams and patients who were involved in the preparatory work and will be participating in this study for their time and contributions. We thank the Fonds de recherche du Québec–Santé for their financial support. The funding source has had no role in this study's design and will have no role in the collection, analysis, or interpretation of data, in writing this paper, or in the decision to submit for publication. This study has received funding from the provincial research funder Fonds de recherche du Québec–Santé (Oncopole ACCES-Onco, grant 326483-2023).

Data Availability

The datasets generated or analyzed during this study will not be publicly available due to ethical considerations (ie, conditions of consent received from participants) but will be available from the corresponding author on reasonable request.

Authors' Contributions

DT, TJ-M, AD, MCB, DB, JC, MD, CF, BG, M Larivière, FL, M Lemonde, ÉM, NM, MP, SS, and CW handled the conceptualization, funding acquisition, methodology, and review and editing of the writing of this study. DT, TJ-M, and AD administered the project. DT did the supervision, visualization, and writing of the original draft. DT and DB worked on the validation of this study.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer review report from the Accélération de la recherche et des soins pour le cancer au Québec (ACCES-Onco) (Québec, Canada).
[PDF File (Adobe PDF File), 139 KB - resprot_v14i1e63099_app1.pdf]

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Abbreviations

ANT: actor-network theory
ePREM: electronic patient-reported experience measure
ePROM: electronic patient-reported outcome measure
PRISM: practical robust implementation and sustainability model
PRO-CTCAE: Patient-Reported Outcomes Version of the Common Terminology Criteria for Adverse Events
RE-AIM: reach, efficacy, adoption, implementation, maintenance
TM: telehomecare monitoring

Edited by T Leung; submitted 31.07.24; this is a non–peer-reviewed article;accepted 30.11.24; published 20.01.25.

Please cite as:
Tremblay D, Joly-Mischlich T, Dufour A, Battista MC, Berbiche D, Côté J, Décelles M, Forget C, Guérin B, Larivière M, Lemay F, Lemonde M, Maillet É, Moreau N, Pavic M, Soldera S, Wilhelmy C
Telehomecare Monitoring for Patients Receiving Anticancer Oral Therapy: Protocol for a Mixed Methods Evaluability Study
JMIR Res Protoc 2025;14:e63099
URL: https://www.researchprotocols.org/2025/1/e63099
doi:10.2196/63099
PMID:

Protocol

Preventing Premature Family Maladjustment: Protocol for a Multidisciplinary eHealth Study on Preterm Parents' Well-Being

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Abstract

Background: The consequences of preterm birth extend beyond the clinical conditions of the newborn, profoundly impacting the functioning and well-being of families. Parents of preterm infants often describe the experience of preterm birth and subsequent admission to the neonatal intensive care unit (NICU) as a disruptive event in their lives, triggering feelings of guilt, helplessness, and fear. Although various research examines changes in parents' well-being and perception of self-efficacy during the stay in the NICU, there is a lack of research analyzing what happens in the transition phase at home after the baby's discharge. Recently, scholars have advocated for the use of web-based support programs to monitor and prevent preterm family maladjustment and assist parents.

Objective: This interdisciplinary research will develop a sociopsychological model focused on assessing the well-being of parents of premature infants during and after their stay in a NICU. Specifically, the study aims to (1) monitor the mental health of parents of premature infants both at the time of the child's discharge from the NICU and in the first 6 months after discharge to prevent family maladjustment, (2) deepen our understanding of the role of digital tools in monitoring and supporting preterm parents' well-being, and (3) study the potential impact of the relationship with health care professionals on the overall well-being of parents.

Methods: This project combines mixed methods of social research and psychological support with an eHealth approach. The well-being of parents of premature infants will be assessed using validated scales administered through a questionnaire to parents of preterm infants within 6 NICUs at the time of the child's discharge. Subsequently, a follow-up assessment of parental well-being will be implemented through the administration of the validated scales in a web application. In addition, an ethnographic phase will be conducted in the NICUs involving observation of the interaction between health care professionals and parents as well as narrative interviews with health care staff. Finally, interactions within the digital environment of the web application will be analyzed using a netnographic approach. We expect to shed light on the determinants of well-being among parents of premature infants in relation to varying levels of prematurity severity; sociodemographic characteristics such as gender, age, and socioeconomic status; and parental involvement in NICU care practices. With the follow-up phase via web application, this project also aims to prevent family maladjustment by providing psychological support and using an eHealth tool.

Results: The results are expected by October 2025, the expiration date of the Project of Relevant National Interest.

Conclusions: The eHealth Study on Preterm Parents' Well-Being aims to improve preterm parents' well-being and, indirectly, children's health by reducing social costs. Furthermore, it promotes standardized neonatal care protocols, reducing regional disparities and strengthening collaboration between parents and health care staff.

International Registered Report Identifier (IRRID): PRR1-10.2196/63483

(JMIR Res Protoc 2025;14:e63483) doi:10.2196/63483

KEYWORDS

preterm birth; parental well-being; sociology of health; digital-based monitoring; mixed methods research; eHealth

Introduction

Background

The World Health Organization defines as preterm a birth that occurs before 37 weeks of gestation [1]—in Italy, approximately 6% of newborns are born before term [2]. Preterm birth is a multiproblematic event with 3 main consequences. First, it poses a medical risk to the newborns as many of these infants are in critical condition and can experience a range of substantially and potentially life-threatening medical complications. The second consequence concerns the economic and medical cost of caring for these babies given the advances in perinatal and neonatal care that have contributed to a substantial increase in the survival rate of these infants, particularly for extremely premature ones who, until a few decades ago, had no chance of surviving [3]. The third consequence is that the premature birth of a child and the subsequent admission to the neonatal intensive care unit (NICU) are distressing experiences for parents. Parental stress and parenting difficulties in the first years of the child's life are well-known consequences [4]. Moreover, many longitudinal studies have described how prematurity negatively affects infants' development [5,6], and evidence has been gathered supporting that parent well-being and infants' long-term developmental outcomes are closely related [7]. Parents often describe premature birth and the subsequent hospitalization in a NICU as an emotional roller coaster and a disruptive life event [8]. An unexpected birth can trigger feelings such as guilt for not completing the pregnancy, helplessness, and fear of not being able to protect one's child [6]. Moreover, parent-infant separation once admitted to the NICU represents a major source of stress for both parents and their infants [9]. Prematurity affects not just the child and parents as individuals (eg, by delaying the exploration of the parental role) but also the family triad (and potential siblings) as it hinders the initiation of mutual understanding and the consolidation of affectionate and meaningful relationships. Indeed, the hospital environment limits the parent-child relationship, which primarily develops through the incubator's windows [10]. These restrictions, while serving to protect infants from pathogens, complicate the interaction between parents and newborn, making it even more challenging to activate caregiving modes necessary for the infant's psychological development, a task primarily undertaken by medical staff for clinical reasons [11]. Another important factor to consider, highlighted by Russo et al [12], is that the sociodemographic characteristics of parents act as independent stress predictors, with gender, occupational status, and age particularly playing a role in the levels of stress and depression among parents of hospitalized children. Furthermore, few studies have investigated fathers' experiences in these particular circumstances [6]. In Italy, especially during the COVID-19 pandemic, many NICUs applied restrictions regarding the frequency and time of parents' access, and fathers are usually less involved than mothers in practices such as skin-to-skin contact and kangaroo care, managing to start building a relationship with their babies only after discharge. As researchers have pointed out [13], it is important to consider the characteristics and points of view of both mothers and fathers as both parents are at risk after preterm births. Research suggests how parents' negative feelings can be reduced by giving them value as actors who can make decisions for the newborn [14]. The Family Integrated Care (FICare) model represents an example of a way to address the need for humanization and parent participation in health care for high-risk newborns admitted to the NICUs. Through this approach, parents have the opportunity to become increasingly engaged in their responsibilities, and their active involvement in care is a prerequisite for the consolidation of parenting skills, which are essential to cope with the separation through the NICU [15]. However, a recent study has pointed out that, although most units in different European countries report a neonatal care policy that encourages parents to take part in the care of their infants, parental involvement is still generally limited in Italy [6].

In addition, there is some evidence suggesting that the feasibility of implementing FICare with families of infants who are severely premature or critically ill remains a concern [16]. These cases often involve significant medical complexity, requiring intensive care, which may limit opportunities for parental involvement. Furthermore, the emotional and psychological toll of caring for an infant who is critically ill can hinder parents' ability to participate actively in caregiving activities, highlighting the need for tailored support to address these challenges. Although various research examines changes in parents' well-being and perception of self-efficacy during the stay in the NICU, there is a lack of research analyzing what happens in the delicate transition phase at home after the baby's discharge [17]. Moreover, to the best of our knowledge, no studies have specifically examined how socioeconomic factors such as parental income or geographic distance from the NICU influence participation in FICare. This represents a gap in the literature as these factors may pose challenges for certain families. To fill this gap, the intervention and participatory project aim to give voice to preterm parents and their experiences. An interdisciplinary study to set neonatal practices and enhance families' well-being (the Study on Preterm Parents' Well-Being [ParWelB]) was designed by the Department of Sociology and Social Research of the University of Milano-Bicocca (principal investigator: AD) and funded by the Cariplo Foundation. Starting in May 2021, ParWelB has been promoting constructive communication and collaboration among and between caregivers and parents in the NICU.

Recent studies highlight the importance of fostering the parent-newborn bond, showing that strengthening this interaction benefits both parents—through reduced anxiety and depression—and children, who experience improved neurological outcomes [6]. Longitudinal research further suggests that parental stress and anxiety can impair bonding and family adjustment, with potential consequences for the development of preterm infants [5]. Parental self-efficacy and social support play a crucial role in adapting after an adverse

situation such as preterm birth [18]. Scannel [19] recently suggested how interventions that target the development of parental self-efficacy and social support can strongly impact the sense of competence, satisfaction in the parenting role, and resilience of all members of the family. Furthermore, Ionio et al [20] highlight in their work that having more information on how parents perceive neonatal care and an understanding of their needs also after the discharge of their newborn may allow health care staff to identify parents at risk, plan early interventions to meet their needs, and promote family functioning. Given the importance of building parents' self-efficacy, new neonatal practices (for upcoming preterm infants and parents) should be shaped based not only on the biomedical knowledge perspective but also on preterm parents' values, lived experiences, and perspectives.

The transition from the NICU to the home is a pivotal and challenging period for parents of preterm infants. It involves adjusting from the highly structured and professionally supported NICU environment to taking on full caregiving responsibilities at home. This shift can heighten feelings of uncertainty and stress, particularly as parents face reduced access to health care professionals and must navigate complex medical or developmental needs independently.

Our study is an interdisciplinary research project that, building on the premises of the ParWelB project, strives to assess preterm parents' well-being during and after the hospitalization in the NICU by combining mixed methods (using research strategies such as standardized questionnaires with internationally validated scales and ethnography) and psychological support through an innovative and technology-driven approach. Recently, scholars have championed the use of web- and app-based support programs to both monitor and prevent preterm family maladjustment and assist parents who struggle with transitioning to the home [21,22]. Furthermore, the work of Garfield et al [23] with infants with very low birth weight showed that parents who received an app-based support program improved parental self-efficacy and discharge preparedness compared with the control group. Therefore, the Bicocca research unit decided to team up with the Department of Psychology of the Catholic University of the Sacred Heart of Milan to design an eHealth (information and communications technology use to the advantage of human health) research project that assesses parents' well-being, particularly at the crucial time of discharge and the first 6 months at home, offering support to parents who are more fragile. Parenting self-efficacy has been understood as the way in which parents perceive their ability to care for their child [24] and has been associated with positive parental outcomes [25]. The well-being of parents refers to the fact that, given that preterm birth is a highly stressful event for parents [26], considering the difficulties and uncertainties they experience during this acute phase is of significant importance to prevent family maladjustment [27]. Families' involvement in the care of their high-risk neonates at NICUs represents the main axis of parent-partnered care initiatives. Each preterm parent develops a personal way to evaluate the situation based on the NICU lived experience. Specific characteristics may also influence the response to the hospitalization of one's child. Significant effects have been identified in relation to gender (mothers and fathers seem to differ in responses and relation to certain measures) and to the degree of social support that parents have access to. The latter has been found to impact positively the resiliency factor associated with coping strategies of families who have a child with a chronic illness [28], and there is a great need for studies investigating its impact on preterm parents.

Thus, the main focus of this research project is to develop a sociopsychological model focusing on the assessment of preterm parents' well-being during and after admission to a NICU with the use of eHealth.

Objectives

Stemming from these premises, our research's main aims could be synthesized as follows: (1) to monitor the mental health of parents of premature infants, with a plan for early intervention and a 6-month follow-up to prevent family maladjustment; (2) to stimulate eHealth growth by advancing knowledge on the role of digital-based tools in monitoring and supporting the well-being of parents whose infants have been hospitalized in the NICU for critical health situations (prematurity but also a wide spectrum of disabling or fatal diseases); and (3) to study the potential impact of the relationship with health care staff on the overall well-being of parents. In addition, our research aims to investigate potential differences in psychological well-being between parturients and nonparturients by also studying the impact of certain social characteristics (eg, nationality, educational level, employment status, and cultural enjoyment).

Methods

Ethical Considerations

Participation in the study will be on a strictly voluntary basis. According to the Declaration of Helsinki, respondents will receive written and oral information about the study and provide signed consent. They could withdraw consent at any time with no consequences for the future treatment of themselves or their infants. The eHealth ParWelB (e-ParWelB) project is financed by the Italian Ministry of University and Research with Next Generation EU and was approved in 2022 as a Project of Relevant National Interest (protocol 20225R7XB3). The project was submitted for approval to the ethics committees of the involved universities (University of Milano-Bicocca and Catholic University of the Sacred Heart of Milan) and, subsequently, to the 6 different territorial ethics committees to which the hospitals involved in the study are affiliated. The data are pseudoanonymized, meaning that each questionnaire is linked to a unique alphanumeric code that can be traced back to the user's web application code. Protective measures include compliance with legal and ethical standards; restricted access; and security protocols to prevent unauthorized access, disclosure, modification, or destruction. Finally, the project will not provide specific compensation to participants.

Recruitment

This study will be conducted simultaneously in 6 different Italian NICUs. Focusing on several units simultaneously has several advantages. First, it enables us to build a sample of satisfactory size within a reasonable time frame. Italy has a low birth rate,

and therefore, concentrating on only 1 unit would pose a significant risk of obtaining an inadequate sample for any complex statistical analysis. In addition, the presence of various NICUs introduces a comparative dimension to the study. Previous research on neonatal intensive care [29] has shown that each unit has its own unique identity with different routines, idiosyncrasies, and decision-making processes. This identity is strongly influenced not only by the cultural context in which the unit is embedded but also by the administrative structure of the hospital and the legislative framework foreseen for neonatal care practice. This is particularly relevant in the Italian case, where the management of the public health system happens mainly at the regional level, with relevant differences between regions. Moreover, this study includes 5 NICUs from the public sector and 1 belonging to a private hospital, adding another possible layer of differences in the work culture of the units.

This research focuses mainly on the population of preterm parents—more specifically, parents of children born before 36+6 weeks of gestational age (GA) and hospitalized in intensive or subintensive care units for at least 10 days (critical threshold of hospitalization length). Considering the research objectives, it is crucial to distinguish infants according to the severity of prematurity because of the strong impact that the latter has on the health of the child and the duration of the hospitalization period. Therefore, there will be 3 groups: children born before 28 weeks of GA, infants born between 28+1 and 32 weeks of GA, and children born between 32+1 and 36+6 weeks of GA.

To be included, parents of preterm infants must meet the following criteria: (1) they must speak fluent Italian or English, (2) they must be aged ≥18 years, and (3) their children must not have other genetic pathologies or other pathologies not linked to the preterm birth.

These 3 limitations help us in creating a more consistent sample and, therefore, in obtaining more focused results. Situations such as teenage pregnancies or genetic pathologies further complicate a family's life and, therefore, the task of assessing its well-being. While we acknowledge that they are both worthwhile topics of research, they are beyond the scope of what could reasonably be studied within the framework of our research.

To determine a satisfactory sample size for this research, we calculated using G*Power (Heinrich-Heine-Universität Düsseldorf) that the minimum sample size required, considering a probability of α error of .05, power ($1 - \beta$ error probability) of 0.95, and an effect size of 0.345, will be 175 preterm infants (350 parents).

We want to stress the fact that, due to the very peculiar nature of the studied population, this will not be a probabilistic sample but rather a *convenience* sample. As explained previously, the decline in Italy's birth rate does not allow us to use the yearly average estimation of preterm babies born in each of the partner hospitals as a reliable predictor for constructing our sample.

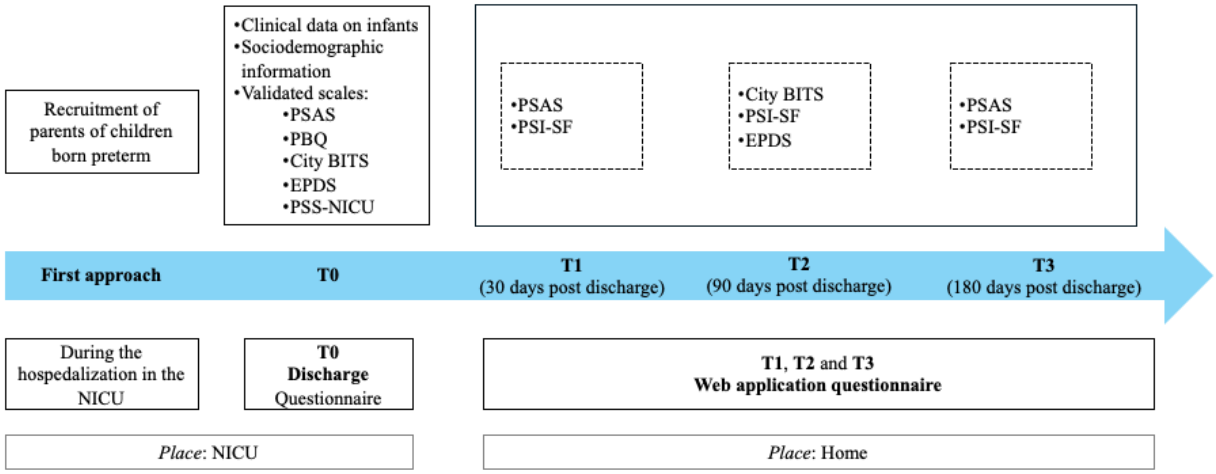
Research Design

To achieve the research objectives, this study will use a mixed methods approach that combines ethnographic observations with standardized questionnaires. The goal of this approach is to enhance the results by complementing the strengths of different methodologies [30]. The quantitative aspect of this research aims to investigate the potential impact of preterm birth on the psychological well-being of parents during the early months of their child's life. Recent literature emphasizes that preterm birth can have a significant impact on parental well-being, exposing them to a high likelihood of developing anxious, depressive, and sometimes even posttraumatic stress symptoms [31]. The questionnaires with validated scales used in this research will be used to create composite statistical indexes that measure, for each responding parent, levels of stress, depression, anxiety, perception of parental self-efficacy, quality of the bond established with their child, and the perception of the social support received. The reasons that prompted us to consider such tools stem from the literature highlighting the necessity of using specific instruments in investigating parental distress in the postpartum period, to adequately capture the specific reasons leading to the experience of such unique feelings [32]. Moreover, questionnaires with validated scales are a valuable tool in psychological research. They allow data to be collected from a large number of participants in an inexpensive and standardized manner. The ease of administration and access to personal information encourage the disclosure of candid data, reducing the social reaction effect as well as allowing people to respond more freely. The qualitative aspect of this research involves the use of the range of methods provided by ethnography, considered particularly suitable for studying the dynamics of critical health practice in action [29,33] as the ethnographic approach allows for an understanding of how medical discourse (eg, protocols, standards, and knowledge) forms within everyday medical practices (eg, informal actions, skills, behaviors, and the physician-patient relationship) that are involved in care trajectories [34]. The e-ParWelB project will use a focused ethnographic research approach with different methods. During the NICU stay, we will combine research strategies, including focused ethnography, which entails observing the relational dynamics between different staff members and between staff and parents; discussing with neonatologists their notes and accounts regarding the neonate's care pathway; observing the habits and procedures of health care staff to reveal how prognostic knowledge is shaped; and, finally, conducting narrative interviews with the staff to capture narratives about family needs and perceptions of care practices.

Parents will be approached and recruited by a psychologist within the NICU or sub-NICU when the medical staff announce their child's discharge. At this stage, the project will be thoroughly explained to them, and they will be requested to provide written informed consent. Parents of premature infants will be invited to participate in this study a few days before the discharge. The timing of recruitment will be individually determined based on the assessment conducted by the neonatologist considering the infant's prognosis. When the health care staff informs the parents that their baby will be discharged, allowing them to envision their return home, an interview will be conducted within the NICU wards (T0). During this session, a structured interview will be administered along with specially designed questionnaires combining internationally validated scales with standardized questions related to

socioeconomic status (Figure 1). The administration of the self-report questionnaires will be carried out via the Qualtrics XM platform (Qualtrics International Inc; managed by the scientific coordinators of the e-ParWelB) accessible through the Qualtrics offline app using tablets.

Figure 1. Study model. BiTS: Birth Trauma Scale; EPDS: Edinburgh Postnatal Depression Scale; NICU: neonatal intensive care unit; NPST: Nurse-Parent Support Tool; PBQ: Postpartum Bonding Questionnaire; PSAS: Postpartum Specific Anxiety Scale; PSI-SF: Parenting Stress Index–Short Form; PSS:NICU: Parental Stressor Scale: Neonatal Intensive Care Unit.



Subsequently, the study includes a follow-up phase to monitor the psychological well-being of parents of premature infants after discharge. The follow-up will be conducted through the use of a specially designed web application accessible only to participants that will allow for the monitoring of parents' adaptation and psychological well-being for up to 6 months after the newborn's discharge from the NICU. Parents will be asked to complete validated scales at 3 specific time points: 30 days (T1), 90 days (T2), and 180 days (T3) after discharge from the NICU (Figure 1). The presentation order of the validated scales will vary during the 3 follow-up time points. This choice will ensure that no mechanisms of response automation based on memory are created. The responses provided by parents to the validated scales used within the web application will trigger automated alerts signaling difficult or potentially risky situations. Parents whose responses have triggered an alert will be contacted by a psychologist to offer them psychological support and possible referral to dedicated services. In addition, during this monitoring period, a series of support forums will be implemented within the e-ParWelB web application—in fact, the web application will incorporate a space for peer discussion where issues related to, for example, daily care practices or family well-being can be discussed; a private messaging channel for psychological support where each user will be able to turn to an experienced psychologist for support in case of need; and, finally, a technical forum where each user can report malfunctions or request technical support regarding the web application's functionality.

A brief overview of the validated scales used in the surveys (in the discharge questionnaire and the follow-up questionnaires) and the topics covered by the standardized questions, which are more sociologically oriented, present in the discharge questionnaire is outlined in the following sections. Finally, a brief description of the netnography and of the focused ethnography that will take place in the NICUs and the related data collection techniques is presented.

Measures and Instruments

Measures at T0 (Discharge Questionnaire)

At the time of the child's discharge from the NICU, the investigation will focus on assessing anxiety, depressive, and posttraumatic symptomatology while also investigating parents' perceptions of their self-efficacy in bonding with their child within the chaotic and stressful environment of the NICU.

For this purpose, several validated scales will be used. Most of the literature on postpartum anxiety [35-37] refers to measures of generalized anxiety, which can often prove problematic from a psychometric perspective [38]. To date, the only available questionnaire specifically measuring postpartum anxiety is the Postpartum Specific Anxiety Scale (PSAS) [39,40]. Furthermore, the instrument has demonstrated excellent psychometric properties (ω ranging from 0.72 to 0.90 across the 4 scales and λ4 ranging from 0.71 to 0.92 across the 4 scales). For these reasons, the research team deemed it the most sensitive and appropriate tool for capturing the construct under investigation in the target population.

Postnatal depression is the most widely measured disorder in the postpartum population, which today, in Italy, is mostly subject to routine screenings for this condition. Following a careful analysis of the most recent literature [41,42], the Edinburgh Postnatal Depression Scale (EPDS) [43,44] emerged as the most widely used self-report questionnaire for measuring postpartum depression due to its ease of administration, cultural adaptability, and excellent psychometric properties. The validated Italian version has demonstrated good validity and reliability (Cronbach α=0.7894), confirming the validity of the EPDS in identifying postnatal depression. For these reasons, the research team deemed it the most sensitive and appropriate tool for capturing the construct under investigation in the target population.

Research on posttraumatic stress disorder (PTSD) during the postpartum period has typically adapted questionnaires developed for other populations, such as war veterans, which often prove poorly suited for capturing the specificities of childbirth trauma. Perinatal research comparing general PTSD measures with specific postpartum PTSD measures has found that, although highly correlated, the agreement between these scales in identifying PTSD diagnoses is low [45]. Therefore, the choice of measurement type is crucial for identifying cases of postpartum PTSD. In addition, the criteria of the American Psychiatric Association for PTSD measurement have significantly changed in the transition from the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition. Therefore, it is essential to adhere to these new measurement criteria. The City Birth Trauma Scale [46] is a tool specifically developed to measure childbirth-related PTSD according to the recent Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, criteria and is, to the authors' knowledge, the only instrument with these specificities. This instrument has previously demonstrated excellent reliability (Cronbach α=0.92). For these reasons, the research team deemed it the most sensitive and appropriate tool for capturing the construct under investigation in the target population.

The Parental Stressor Scale: Neonatal Intensive Care Unit [47,48] aims to capture parents' perception of distress experienced during their children's stay in the NICU. To reconstruct parental distress, the underlying model of the scale considers the interaction between various psychological and physical stress factors, such as stress related to sounds, lights, noises, and other sensory experiences typical of a highly technologized health care setting [47]. The Parental Stressor Scale: Neonatal Intensive Care Unit provides the opportunity to obtain various types of information: levels of stress related to specific situations experienced by parents with preterm infants, overall stress levels, individual stressful elements, and overall tension levels. The translation and validation study in Italian has found good psychometric properties of this tool [48].

Scientific research on the complex experience of preterm birth increasingly emphasizes that such an experience can pose significant challenges for parents, particularly in the development of bonding, which is the early relationship that develops post partum between mother and child [49]. A careful analysis of the literature [50,51] allowed us to select a questionnaire widely used in investigating bonding in the postpartum period: the Postpartum Bonding Questionnaire (PBQ) [52,53], a tool designed to measure the quality of the bond between parents and children and identify whether there are disturbances in the relationship. The Italian adaptation of the PBQ was developed using the back translation procedure [54]. Studies demonstrate that the Italian version of the PBQ has good psychometric properties and can be implemented in the Italian cultural context to assess early mother-child relational difficulties [53].

Moreover, the assessment at discharge will also take into account further aspects in light of the fact that several studies have shown that some minor stress factors such as the distance from one's home to where the child is hospitalized may contribute to a higher level of maternal discomfort [55]. The socioeconomic characteristics of family units, such as educational level, social class, job insecurity, employment status, and migration background, have also been examined as risk factors for preterm birth [56,57]. In addition, the study by Miles et al [58] revealed that the marital status of the mother is also a significant factor in predisposing to or preventing the development of a mood disorder. Specifically, married women who perceived a high level of support from their partners reported lower levels of postpartum depression than unmarried women. Conversely, among women with preterm infants, maternal age or level of education do not appear to be correlated with the onset of mood disorders [59]. Another factor that seems to mitigate the onset of mood disorders in parents of preterm infants is a high level of social support [60]. For these reasons, the discharge questionnaire will gather basic sociodemographic information from parents, such as gender, age, nationality, geographic origin, family composition, and educational level. A series of self-assessment questions will be used to evaluate the perceived social support of parents of premature infants. In particular, we have designed 6 items that inquire about perceived social support from partners, family members, friends, and health care personnel. Furthermore, respondents will be presented with a series of questions regarding the frequency of cultural activities, which will serve as indicators of their level of cultural capital, along with a series of questions aimed at capturing their occupational situation.

Finally, a validated scale will be used to gather information regarding parents' perception of nursing support during the infant's hospitalization, the Nurse-Parent Support Tool (NPST) [61]. Scientific research has highlighted the crucial role of parents' perceptions of the actual support provided by nursing staff in mitigating the stressful effects of the NICU stay [62]. In light of this evidence, Miles et al [61] devised the NPST, a scale specifically addressing the educational and informational aspects of staff support as perceived by parents that is widely used in NICUs today [63]. The NPST is a 5-point Likert-scale questionnaire consisting of 21 items divided into 4 groups: informational support, emotional support, appraisal and parental esteem support, and caregiving support. Each item is rated on a scale from 1 (*Almost never*) to 5 (*Almost always*), with higher scores indicating a higher perceived level of support provided by the nursing staff. The validity and reliability of the Italian version of the NPST were assessed by Montirosso et al [48].

Follow-Up Measures at T1, T2, and T3 (Web Application Questionnaire)

At the time of discharge, the involved parents will be invited to register on the web application specially designed for this research. Through the web application, participants will independently complete 3 short questionnaires at the 3 different times designed for follow-up (T1 at 30 days after discharge of the newborn, T2 at 90 days after discharge of the newborn, and T3 at 180 days after discharge of the newborn) to monitor their mental health status. In the web application, some validated scales already proposed at the time of discharge will be implemented. The scales are presented to participants in different moments to minimize potential bias due to response based on learning or recollection. Specifically, (1) *during T1*, participants

will be invited to independently complete the PSAS and the Parenting Stress Index–Short Form (PSI-SF); (2) *during T2*, participants will be invited to independently complete the City Birth Trauma Scale, the EPDS, and the PSI-SF; and (3) *during T3*, participants will be invited to independently complete the PSAS and the PSI-SF.

The only validated scale for which completion will be required at every follow-up time point is the PSI-SF [64,65]. The existing literature has highlighted the possibility of early identification of stressful parent-child systems to develop interventions aimed at reducing stress that could decrease the frequency and intensity of emotional and behavioral disorders in children in our society [65,66]. The characteristics of the child, those of the parent, the family context, and particularly stressful life events are some of the elements of the parent-child system that have been identified as important [64,67]. The Parenting Stress Index was developed in response to the need for an assessment measure of these characteristics. For the purposes of this scientific research, the PSI-SF was adopted, which is an abbreviated version of the Parenting Stress Index that investigates parental distress, dysfunctional parent-child interactions, and difficult child behaviors. The brevity of the PSI-SF allows primary health care providers to identify families most in need of follow-up services [68]. Furthermore, the PSI-SF represents an extremely interesting, agile, easy-to-administer, and interpretable tool. The Italian version of the PSI-SF has been translated and validated by Guarino et al [69] and investigates stressful systems through 3 subscales: parental distress, dysfunctional parent-child interaction, and difficult child behaviors.

Our intention is to use the PSI-SF as a potential *risk screening tool*, namely, a technique that can identify parent-child systems under excessive stress and, thus, serve as an important component within prevention programs aimed at reducing the frequency and intensity of emotional and behavioral disorders [69]. The responses provided by parents to all validated scales used within the web application, in cases in which they exceed the threshold values established for each scale, will indeed allow for the automated activation of alert signals for situations of difficulty or potential risk. Finally, as mentioned previously, all psychological scales used in this study are internationally validated, ensuring their reliability across diverse populations, including those with preterm infants. The sociodemographic section of the questionnaire was tested in a pilot study involving 104 parents [12], which preceded this project and allowed for refinement of the questions to better suit the target population. While these tools provide a strong foundation for data collection, future research could explore additional validations to further tailor the measures to this specific group.

Netnography

As mentioned previously, the web application will feature three specific communication channels through which users can interact: (1) a public forum for peer discussion only where users will be able to post messages, share opinions and ideas, or ask questions on issues related to the daily childcare at home; (2) a private communication channel through which users can contact the psychologist to ask for support in case of discomfort, uneasiness, or other states of distress; and (3) a forum dedicated to the technological tools available to participants in which it is possible to both report technical malfunctions to IT staff and discuss among parents and researchers the impacts of the eHealth tool on its users and their well-being.

The textual corpora produced by users will be downloaded and will form the empirical basis for data analysis through an approach of digital ethnography.

For many years now, computer-mediated communication has been fully integrated into people's daily lives, blurring the distinction between offline and web-based social worlds as they both coexist and fully overlap [70]. Therefore, it has become increasingly important and relevant for social researchers to study society in and through the internet. Although methodological reflections around digital research have been manifold and have also given rise to different terminologies and definitions, in this contribution, we use the term *netnography*, coined by Kozinets [71], to illustrate our digital ethnography approach that adapts the typical techniques and tools of ethnography to the study of web-based communities, which interact through a computer-mediated communication. The presence of the researchers, as well as the fact that messages written in the forums will be subject to analysis, is clear to the participants from the outset, so our netnography will use an overt observation technique.

In our project, the web-based community is closed, meaning that the web application and its tools can only be accessed through a username and password if one participates in the study and has agreed to take part in the follow-up phase. Some methodological perspectives on web-based research place great importance on the medium [72] and, by consequence, on the specific digital environment and its characteristics that shape the spaces, times, opportunities, and constraints under which web-based interactions take place. In our case, one of the main constraints is that messages in the public forums (*n. 1*, a public forum for peer discussion, and *n. 3*, a forum dedicated to the technological tools) will be published subject to approval by the members of the research team to avoid the use of inappropriate language or extremely off-topic communications. If some messages are rejected, they will also end up in the analysis, but they will obviously not affect the overall interaction as they will not be visible to other users. Time is another important feature that will have consequences for the flow and volume of communications as the web application will see the asynchronous access of participants, who are gradually recruited over time. Although the messages in the public forums will remain fixed and always visible, participants who complete the 180-day follow-up period may have less incentive to access the web application, resulting in no further discussion with other newly recruited participants. On the other hand, the accumulation of messages over time could stimulate other interactions, also providing an incentive for participants to use the web application not only as a tool for filling out periodic questionnaires. From a research point of view, we are particularly interested in the volume, modalities, and content of the digital interactions between participants, aware of the constraints to which such communications are subjected. It will be useful to understand the representations, perceptions, and perspectives of premature parents and the impact of prematurity

and of the care practices in daily life. Moreover, we will pay attention to the adaptation processes carried out to cope with the transition period after discharge from the NICU and how parents deal with their new domestic life. In the analysis, even though the participants are pseudoanonymized through a unique alphanumeric code, we can trace and use as a segmentation variable the one that discriminates between the partner who gave birth and the one who did not, for example, to account for differences in the prevalence and occurrence of the messages and topics reported. Furthermore, the *n. 3* forum has the goal to explore how digital-driven changes affect families. It is dedicated to specifically discussing the tools in the web application through a process of facilitation by a member of the research team stimulating dialogue on dedicated questions. As previously stated, this section of discussion about the web application is intended not only as technical support but also as a space for group reflection on the impact of the digital tools introduced by e-ParWelB to support families' well-being. The material created by users in this section will then be analyzed with the aim to explore whether web-assisted alerts and expert and peer support on the web were beneficial to families' well-being and, eventually, how these tools might be improved in the future. This phase of research will also allow us to reflect upon the implications of introducing a digital medium in the relationship between the health care staff and families [73], as in the tradition of sociology and science and technology studies working together on health care issues [74].

Ethnography

The qualitative part of this research aims to study the NICU environment through the use of focused ethnography [75,76]. This term indicates a research method based on brief and intensive observations with the aim of analyzing well-defined phenomena within a specific context. While the classic form of ethnography is centered on the study of broad topics, such as the holistic observation of social groups or institutions, focused ethnographies narrow down their perspective to the analysis of specific actions, interactions, and social situations. This implies a few changes in the position of the observer compared to the situation of traditional ethnography. First, the researcher cannot face the fieldwork unprepared but must be at least theoretically confident with the context of the actions that are to be studied. Second, traditional ethnography provides a range of observer positions, from participant as observer to observer as participant [77], whereas focused ethnography does not involve the same opportunity for observing as a participant because of the nature of the object of study. It would be both highly inappropriate and technically impossible for the focused ethnographer to participate actively in, for example, a medical examination or an operation. Instead, a more distant observer position is possible. In this way, the focused ethnography researcher may be excluded from contextual factors of importance. While traditional ethnography affords the chance to actually participate in the life of the studied social milieu, focused ethnography does not offer the same opportunities of active participation. This usually happens due to the inherent characteristics of the participants under investigation. Active participation in skill-intensive activities would be both highly unrespectful and unfeasible for the focused ethnographer. Consequently, it is said that, in focused ethnography, researchers are not doing observant participation but that they are participating as observers.

A brief recap of the main traits of focused ethnography and its difference from traditional ethnography is shown in Table 1.

Table 1. Comparison between focused ethnography and traditional ethnography derived from the study by Andreassen et al [78].

Characteristic	Focused ethnography	Traditional ethnography
Subject matter	• Episodes in social fields • Clear research focus • Familiar cultures • Background knowledge before data collection • Applied research	• Entire social fields • Broad research purpose • Foreign cultures • Gaining knowledge from engagement in the field • Basic research
Data collection	• Relatively long planning phase • Intermittent visits with particular time frames • Focused exploration • Video or audio recordings or detailed, focused field notes • Often multi-sited • Time intensity	• Relatively short planning phase • Full-time participant observation over a longer period • Open exploration • Extensive and in-depth written field notes • Often single sited • Time extensity
Researcher role	• Alterity • Observer as participant • Selected informants who hold a specific knowledge serve as key participants	• Strangeness • Participant as observer • Participants are often those with whom the researcher develops close relationships
Data analysis	• Analysis intensity • Collective data analysis sessions	• Experiential intensity • Solitary data analysis

Focused ethnography is a particularly appropriate technique for our research due to the traits of medical practice, which comprise bounded and clearly delineated social occurrences or scripted exchanges. This statement has been proved true by an increasing number of studies using this technique within the hospital setting in recent years [79-82]. This technique affords the means to

investigate particular episodes or interactions within social milieux such as NICUs, facilitating nuanced and comprehensive insights into the influence of sociocultural factors on the interaction between the NICU staff and preterm parents. This specific effort of focused ethnography will be divided into 2 steps, each involving the staff members of NICUs in hospitals collaborating with the project. First, the researcher will observe the routine practices that constitute what is defined as *ward life*, trying to create as little interference as possible with the staff's activities. At this stage, the researcher's focus will not be on individuals but rather on the overall context of neonatal intensive care and the social interactions occurring within it. Second, the researcher will use narrative interviews to gather additional information from the NICU staff. The use of interviews is quite common in focused ethnography, as explained by the relevant literature on the topic: "The focused ethnography researcher may be precluded from contextual factors of importance. Applying method triangulation as a cornerstone in ethnography is a way of overcoming this dilemma. For example, combining short observations with interviews will give opportunities to ask about the context in which the observations take place, as well as to explore how the participants experience being observed" [78]. In these narrative interviews, the researcher will aim to involve staff members with profiles as diverse as possible regarding their roles, length of service, gender, and age. The objective is to achieve what the literature calls a "maximum variation sample" [78], maximizing sample diversity (while acknowledging that this is a nonprobabilistic convenience sample) across certain characteristics to capture the complexity of the studied reality.

Throughout both of the aforementioned steps, this research will try to analyze the meaning and effects of the NICU staff decisions and practices on the parents' well-being. This focus on the analysis of existing procedures in skill-intensive contexts, especially medical-related ones, has been referred to in previous research as *exnovation*. *Exnovation* refers to the attempt to foreground what is already present—though hidden—in specific practices to render explicit what is implicit in them [83]. A focus on exnovation allows us to bring to light implicit matters of actual practice and develop a fresh perspective on the ingenuity of the professionals and the specific structure of their practices. It offers insights into their specific modes of ordering day-to-day practices [84]. Exnovation, in other words, elucidates competencies of coordination and alignment of these modes of ordering of which those involved are not always aware [29]. In other words, this research aims to reflect on existing practices of care aimed at preterm parents and their children and deepen our understanding regarding their effects with the aim of preventing family maladjustment after a traumatic event such as preterm childbirth.

Regarding the organization of the qualitative tools for the research, the access to the field will be negotiated separately in each NICU to take measures to avoid disrupting staff work and minimize impact on organizational routines. To conduct an ethical and respectful data-gathering process, NICU staff will be informed about the research in advance by the department heads, with whom a partnership has been established for the project, thus ensuring that they are aware of the research procedures. Once access is granted, the researcher present in the department will autonomously organize interviews with the staff.

Expected Outcomes

The e-ParWelB central impact will be developing and piloting a model of sociopsychological assessment tailored for parents whose infants have been hospitalized in the NICU for critical health situations connected to prematurity. The model, by increasing preterm parents' perception of self-efficacy and well-being, will allow for the prevention of family maladjustment [5,6] and, therefore, the indirect improvement of preterm child health outcomes [7]. The mixed methods social research that we designed is expected to achieve the following results: (1) to reduce the discomfort and maladjustment caused by prematurity on preterm parents and assess their perceptions of social support (from family, friends, potential employers, and colleagues), perceptions of preparedness, and parental self-efficacy from the time of discharge and for the following 6 months; (2) to analyze the difference between mothers' and partners' responses to preterm birth in terms of stress, negative feelings, and perceptions of parental self-efficacy and social support; (3) to determine which neonatal care practices, forms of communication, and environmental settings of the NICU are more likely to reduce negative feelings and foster the well-being of preterm parents; and (4) to advance the knowledge on the role of a digital-based tool in monitoring and supporting families' well-being during the follow-up.

On the latter point, e-ParWelB intends to engage in the relationships among science, technology, and society by addressing how the hospitalization experience of preterm families may inform technology and science development. At the same time, we aim to identify the effect of the introduction of a digital technology–driven assessment and support model on families' well-being and on care practices in the neonatal intensive care wards. In particular, the e-ParWelB project directly connects with the objectives of (1) developing a public health system enhancing investments in terms of human, digital, structural, instrumental, and technological resources; and (2) improving scientific research in the biomedical and health field.

Indeed, the interdisciplinary approach to promote eHealth in premature families enhances the dialogue between science (health care and medical knowledge) and society (families' perspectives) on the topic of preterm birth through the aid of digital technology. This will be possible with the implementation of the e-ParWelB web application, which will follow processes of responsiveness and adaptation as well as considering criteria of accessibility following responsible research and innovation principles. As the web application constitutes both a tool to periodically monitor parents' well-being and a digital space for sharing and discussion, both with a psychologist and among peers, the project has a multi-side technological and scientific impact.

At the same time, we aim to identify the effect of the introduction of digital technology on families' well-being and on care practices. For instance, through the netnographic exploration of the web-based space of discussion within the e-ParWelB web application, we aim to address the eventual

health care web-based community of practice forming in the forum [85]. Drawing on the idea by Timmermans and Berg [86], an orientation of *technology in practice* allows for a critique by scholars in the social sciences regarding the complicated modalities in which the *social* and the *material* intertwine in technologies for health care, as well as possibly influencing their creation and implementation. Thus, referring to what in science and technology studies literature is known as the *sociotechnical approach*, we are interested in how the social and health care aspects influence the development of the digital technology and, at the same time, in modalities through which the digital medium affects families and the care process, especially after discharge [87,88]. Therefore, we also aim to understand the impact of the web application on families' well-being.

Results

We expect to observe these results by the end of October 2025, the date set as the conclusion of the Project of Relevant National Interest funded by the Ministry of University and Research.

Discussion

Impact

This research project aims to identify the social determinants of preterm parents' well-being. It will monitor their feelings and perceptions of well-being during the baby's hospitalization and after discharge, with the goal of reducing their distress and discomfort. Unlike previous studies, this project places a significant emphasis on both mothers and fathers, analyzing how gender differences and parental roles influence their experiences and affect outcomes related to perceived well-being and social support. Furthermore, using ethnographic methods, this study delves into the everyday life of NICU wards. It examines these environments both as sites of high-skill professional practice and as arenas of social interaction between staff and parents. The aim is to understand the social arrangements and practices that facilitate staff work and parental participation and involvement during the sensitive period of their baby's hospitalization. Finally, the use of technology in this study serves a dual purpose. Instrumentally, it enables the monitoring of parental well-being after discharge, but it also prompts deeper sociological inquiries into its role at the intersection of medical science and society. In addition, technology acts as a medium for mutual aid, fostering specific web-based peer discussions and shaping new forms of social support and community among parents of preterm infants.

The e-ParWelB project not only contributes to scientific and technological development, but its impact on the social and economic dimensions also stems from the premise that, by increasing the well-being of preterm parents it is possible to indirectly improve their infants' health outcomes. As scholars have argued, the abrupt disruption of the establishment and development of parental mental representations, combined with the possibility that both the baby and the mother are in critical condition, can make preterm birth a traumatic event for parents [89]. Therefore, reducing the family's maladjustment enhances future health—including mental health—in premature children [7]. Moreover, parents' mental health is supported, as well as their self-efficiency, preventing a large set of repercussions. For society at large, this also means introducing factors of prevention in terms of social and economic costs that unhealthy individuals and families might incur. Furthermore, the situation of premature birth care in Italy sees scattered NICUs applying different protocols for what concerns the role played by the parents of hospitalized newborns. As the latest report of the Italian Society of Neonatology shows, for instance, just 63% of the NICUs allow free-time access for parents [90]. When looking at the regional location, we observe an unequal distribution of the free-time access wards. Indeed, in the northern regions, 88% of NICUs do grant free-time access, whereas in the south, just 34% percent do [90]. Thus, by developing a piloted model for preterm parents' sociopsychological assessment, e-ParWelB will produce knowledge about the best practices to be implemented in NICUs, enhancing the opportunity for stakeholders and policy makers to make neonatal care protocols less regionally uneven and more efficient when concerning the collaboration between parents and health care staff.

Strengths and Limitations

The e-ParWelB project was preceded by the ParWelB project (principal investigator: AD), and although with a different institutional setup and collaborations with different NICUs, the 2 projects stand in a relationship of continuity, building on the same theoretical and methodological premises. Therefore, practical experiences and careful analyses regarding actual strengths and limitations have already been carried out for the previous project [10].

In general, the greatest strength of the entire research project lies in listening to and empowering the parents of premature children who participate in the study, making them more aware of and helping them deal with the challenging situation of prematurity, advancing deep reflections that do not stop at purely medical practices but also promote a person-centered approach to stimulate new neonatal practices and foster the well-being of families.

In this context, it is essential to reconnect the social dimension with the medical experience, also owing to the support of technology, and this is one of the main objectives of the project.

Indeed, we aim to study a model for monitoring and assessing parental well-being and look at the relationship between the medical-nursing staff and the parents of premature babies from a sociological and psychological perspective with the aim of promoting public awareness and participation, also by involving the medical-nursing staff with respect to the values, personal experiences, and point of view of the parents.

These strengths are accompanied by deep reflection in mapping out the potential limitations of the project and strategies to mitigate them.

Among these, access to the study is worthy of consideration. An actual constraint on access for preterm parents is language—the lack of cultural mediators and translators in the project allows only for participation of people fluent in Italian and English. As Italian and English were also the only languages in the previous ParWelB project, we have already ascertained

that a nonnegligible proportion of parents, often with migration backgrounds, were unable to participate in the study, and we expect this situation to be repeated. This is uncomfortable for mainly 2 reasons. First, it does not allow a specific population of parents, who often are more likely to be in situations of marginality or social isolation, to access the direct and indirect benefits of the project, such as stimulating self-reflections on their parental role and gaining access to psychological support after discharge. Furthermore, from a purely scientific point of view, there is less opportunity to investigate how certain cultural differences and social support (which is often lacking or expressed in different ways among people with a migratory background) impact the well-being of preterm parents and their experiences in the NICU.

One of the main aspects to consider when reflecting upon the pros and cons of this project is the possible bias introduced by the implementation of the web application, which is a digital technology not necessarily available to all social groups. Digital literacy, availability of connection to the internet, and access to digital devices are all necessary conditions to participate in the study, and the lack of one of these aspects may act as an additional exclusion factor, possibly affecting marginalized social groups or groups with specific needs [91,92]. Nonetheless, parents excluded from the digital space are necessarily excluded from tools of expert and peer support.

In addition to access barriers to the study, this project faces other possible limitations regarding engagement and participation during the research activity that can be reversed. In the previous ParWelB project, due to the COVID-19 pandemic, researcher access to the NICU was restricted, so parent recruitment, discharge survey administration, and web application registration were performed entirely by NICU staff, usually by psychologists or neonatologists. Overall, in this way, NICU staff were more involved, but some methodological forms of control by the researchers were lacking regarding modalities of both study presentation and survey administration to parents [93]. In the new e-ParWelB project, while we no longer have the limitations of the pandemic, a blended approach was chosen as we will maintain a deep involvement by NICU staff, especially psychologists, in recruitment, survey administration, and web application enrollment at discharge. Above all, previous experience has shown that the relationship of trust built between the NICU staff and parents is central to engaging the latter in the project. Therefore, it is in the project's interest to maintain these relationships both to provide parents with referents whom they consider reliable and with whom they have already become familiar during their stay in the NICU and to engage the medical-nursing staff further, stimulating an even closer relationship between these 2 social actors beyond purely medical practice. On the other hand, in the previous project, the participation rate dropped by 10% for parents recruited in the second half of the project timeline, an indicator that the motivation and consequent convincing power of the NICU staff toward parents slightly declined over time [93]. Therefore, the presence of a researcher can also be decisive in rekindling motivation and emphasizing the importance of parental participation throughout the recruitment phase. In the e-ParWelB project, in some NICUs, there will be a constant presence of a project researcher, who will take part in recruitment together with the staff and will personally take care of survey administration at discharge and invite participants to register on the web application. In NICUs where the constant presence of the researcher is not expected, it will be arranged if no one in the NICU can recruit parents or the research team notices a decline in the participation rate. Therefore, this flexible choice allows us to maintain and strengthen the bond between the parents and the NICU staff and, at the same time, provide help and support to the participants or NICU staff and ensure the correct conduct of the research from a methodological and ethical point of view.

In conclusion, one of the critical aspects of the ParWelB project was the high dropout rate during the follow-up surveys using the web application. To address this issue, the new project, e-ParWelB, proposes a lighter monitoring approach, with a shorter total period and lower frequency (6 months of monitoring instead of 1 year and 3 surveys instead of 12), thus impacting participants to a lesser extent. A less intrusive follow-up, both in terms of frequency and volume of questionnaire completion, will not affect the capacity of researchers to monitor the well-being of the participants, whereas it will lower the commitment required from users, allowing them to allocate their time and energy to other activities related to the web application, such as forums.

Acknowledgments

This research project would not have been possible without the funding of the Italian Ministry of University and Research as a Project of Relevant National Interest—2022 call for submissions (protocol 20225R7XB3; European Research Council, Social Science and Humanities field; Unique Project Code: H53D23005630006). This project is not sponsored by any entity, organization, or company.

Data Availability

The datasets generated or analyzed during this study are not publicly available due to the inclusion of sensitive information, such as respondents' psychological distress, diagnosis of psychopathology, and clinical data on infants admitted to the neonatal intensive care unit. However, deidentified data may be made available from the corresponding author on reasonable request in accordance with ethical and legal considerations.

Authors' Contributions

AD, FP, GL, MFF, CR, MN, BF, GC, and CI were responsible for conceptualization and investigation. AD, FP, GL, MFF, and CI conducted the methodology and formal analysis. AD and CI managed resources and project administration. The original draft was written by FP, GL, and MFF. AD, FP, GL, MFF, CR, MN, and CI contributed to the review and editing process. Supervision was provided by AD and CI. All authors have read and agreed to the published version of the manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer review report from the Italian Ministry of University and Scientific Research - Project of National Relevance - Bando 2022 / Ministero dell'Università e della Ricerca - Direzione Generale della Ricerca del MUR (Italy).
[PDF File (Adobe PDF File), 65 KB - resprot_v14i1e63483_app1.pdf]

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Abbreviations

e-ParWelB: eHealth Study on Preterm Parents' Well-Being
EPDS: Edinburgh Postnatal Depression Scale
FICare: Family Integrated Care
GA: gestational age
NICU: neonatal intensive care unit
NPST: Nurse-Parent Support Tool
ParWelB: Study on Preterm Parents' Well-Being
PBQ: Postpartum Bonding Questionnaire
PSAS: Postpartum Specific Anxiety Scale
PSI-SF: Parenting Stress Index–Short Form
PTSD: posttraumatic stress disorder

Edited by T Leung; submitted 21.06.24; this is a non–peer-reviewed article;accepted 11.12.24; published 18.03.25.

Please cite as:
Decataldo A, Paleardi F, Lauritano G, Figlino MF, Russo C, Novello M, Fiore B, Ciuffo G, Ionio C
Preventing Premature Family Maladjustment: Protocol for a Multidisciplinary eHealth Study on Preterm Parents' Well-Being
JMIR Res Protoc 2025;14:e63483
URL: https://www.researchprotocols.org/2025/1/e63483
doi:10.2196/63483
PMID:

Protocol

Trajectories of Change, Illness Understanding, and Parental Worries in Children and Adolescents Undergoing Internet-Delivered Cognitive-Behavioral Therapy for Functional Abdominal Pain Disorders: Protocol for a Single-Case Design and Explorative Pilot Study

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Abstract

Background: Functional abdominal pain disorders (FAPDs) are common in young people and are characterized by persistent or recurrent abdominal symptoms without apparent structural or biochemical abnormalities. FAPDs are associated with diminished quality of life, school absence, increased health care use, and comorbid anxiety and depression. Exposure-based internet-delivered cognitive behavioral therapy (ICBT) has demonstrated efficacy in alleviating abdominal symptoms and improving quality of life. However, a deeper understanding of effect mechanisms and identification of possible additional treatment targets could refine treatment.

Objective: This protocol paper aims to describe a study focusing on children and adolescents undergoing ICBT for FAPDs, aiming to further investigate the underlying mechanisms of effect.

Methods: Children (8-12 years), adolescents (13-17 years) with FAPDs, and their respective parents will be included for 10 weeks for ICBT. First, detailed trajectories of effect are examined through a randomized single-case design study involving 6 children and 6 adolescents (substudy 1). Following this, an open-ended explorative pilot study with 30 children and 30 adolescents explores potential illness-related cognitive biases and interoceptive accuracy before and after treatment (substudy 2). Finally, spanning across these 2 substudies, including all parents from substudies 1 and 2, we will assess parental distress and illness worries before and after treatment, and how these factors impact the treatment adherence and outcomes of the child or adolescent (substudy 3).

Results: Recruitment of participants began in June 2022 and is finalized for substudy 1 and ongoing for substudies 2 and 3. Recruitment is expected to be completed by January 2025, with final data collection during April 2025.

Conclusions: The findings have the potential to contribute to the ongoing improvement of specialized psychological treatment for FAPDs in young people.

Trial Registration: ClinicalTrials.gov NCT05237882; https://clinicaltrials.gov/study/NCT05237882; ClinicalTrials.gov NCT05486585; https://clinicaltrials.gov/study/NCT05486585; OSF Registries osf.io/c49k7; https://osf.io/c49k7

International Registered Report Identifier (IRRID): DERR1-10.2196/58563

(JMIR Res Protoc 2025;14:e58563) doi:10.2196/58563

KEYWORDS

functional abdominal pain disorders; abdominal pain; internet-based intervention; cognitive behavioral therapy; interoception; attentional bias; parental distress; single case study; children; adolescents; youth; study protocol; quality of life; treatment; medication; psychological treatment; psychology

Introduction

Functional abdominal pain disorders (FAPDs) affect up to 15% of children and adolescents and are characterized by recurrent or persistent abdominal pain and other debilitating gastrointestinal symptoms such as changes in defecation patterns and nausea [1,2]. The disorders are associated with reduced quality of life, high absence from school, and increased health care use [3]. Psychiatric comorbidities, especially anxiety and depression, are prevalent [4] and up to 40% persist in reporting abdominal symptoms into adulthood [5].

The pathophysiology of FAPDs is not fully understood but recent research suggests a biopsychosocial perspective where the complex interactions of physiological processes such as visceral hypersensitivity, psychological factors like emotional distress and anxiety, and social factors including family dynamics and environmental influences can contribute to the development and maintenance of gastrointestinal symptoms [6]. These factors combined are related to altered processing of sensory stimuli along the brain-gut axis with persistent or recurrent experience of abdominal pain and other gastrointestinal symptoms [7-10]. This altered processing can be understood within the framework of predictive processing, a theory suggesting that the brain consistently evaluates predictions regarding sensory inputs and discrepancies from these predictions [11]. Crucial factors contributing to the development of maladaptive predictive processes encompass cognitive biases marked by symptom-related fear and catastrophizing with an attentional bias toward pain or gastrointestinal stimuli [12-15]. This may be accompanied by the avoidance of situations expected to trigger symptoms [4,16-18] and changes in the interoceptive ability to sense, process, and interpret body signals [19]. Parental behaviors, such as solicitous responses, fearful communication about symptoms, and encouraging avoidance of situations that may provoke symptoms, can further influence the child's perception of bodily stimuli [20-23].

In summary, understanding the pathophysiology of FAPDs involves navigating a complex system of various factors and processes. Consequently, treatment may encompass different targets, including both child-specific and contextual, that is, typically parental-specific factors.

In line with this, cognitive behavioral therapy (CBT) is the treatment supported by the strongest evidence of effect [24-26], with its main focus on restructuring potential child symptom-related maladaptive cognitions, emotions, and behaviors, and often with parental involvement. Swedish studies have documented the efficacy of internet-delivered cognitive behavioral therapy (ICBT) aimed at children and adolescents with FAPDs and their parents [27-29]. The ICBT focuses especially on exposure exercises and parental management of their child or adolescent's symptoms. By enabling the child or adolescent to manage symptoms in previously avoided situations and thereby minimizing the gastrointestinal-specific fear, the treatment reduces the proposed visceral hypersensitivity, which over time leads to fewer abdominal symptoms.

Still, a proportion of the young patients do not improve from ICBT as the number needed to treat has been reported to be around 4, meaning approximately 4 patients must receive the treatment for 1 additional patient to experience adequate symptom relief [27,29]. Therefore, a deeper understanding of the mechanisms of change and the potential influence of additional modifiable factors on the treatment effect is required to improve treatment effects even more.

In the current study, we will evaluate translated versions of the Swedish ICBT for children and adolescents with FAPDs in a Danish context. The treatments target both children (aged 8-12 years) and adolescents (aged 13-17 years) and their parents, which provides a unique possibility to examine both child or adolescent and parental factors before and after treatment. The aims of the study are to (1) investigate the detailed trajectory of the effect of ICBT in children and adolescents with FAPDs, (2) explore potential illness-related cognitive biases and interoceptive accuracy in children and adolescents with FAPDs compared with healthy controls, and if these factors are changed after ICBT, and (3) explore if parental distress, illness worries, and behaviors may impact the child or adolescent's treatment adherence and outcome.

This protocol article is reported following the SPIRIT (Standard Protocol Items Recommendations for Interventional Trials) guidelines [30].

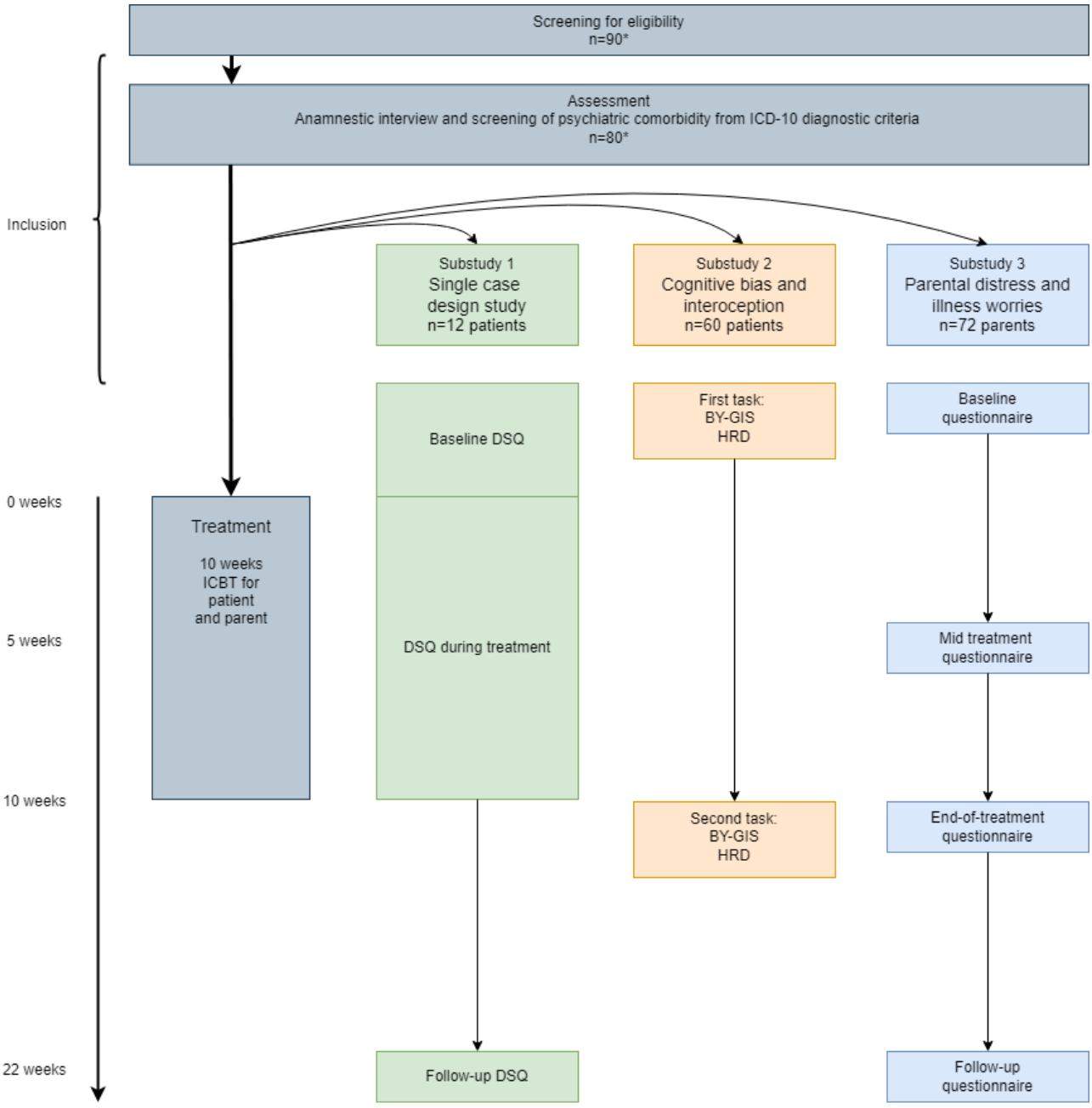
Methods

Study Design

The study includes 2 recruitment phases. The first phase concerns a single case experimental design (SCED) study (substudy 1) with a total of 12 patients (6 children and 6 adolescents, respectively). The second phase concerns an open pilot study on cognitive biases and interoceptive accuracy (substudy 2) with a total of 60 patients (30 children and 30 adolescents, respectively).

Consequently, a total of 72 children and adolescents, along with a corresponding number of parents, will undergo ICBT for FAPDs throughout the entire study. Parental distress and illness worries will be assessed before, during, and after the treatment in all included parents (substudy 3; Figure 1).

Figure 1. Overall study design. BY-GIS: biases in youth toward gastrointestinal-related stimuli; DSQ: daily short questionnaire; HRD: heart rate discrimination; ICBT: internet-delivered cognitive behavioral therapy; ICD-10: International Statistical Classification of Diseases, Tenth Revision.



Study Setting and Recruitment

Children and adolescents diagnosed with FAPD will be referred to the project from pediatric departments located at 4 hospitals (1 university hospital and 3 regional hospitals, respectively) as well as from private pediatric practitioners in the Central Denmark Region. Due to a slow referral rate of adolescents, we have been granted permission from The Central Denmark Region Committees on Health Research Ethics to expand the inclusion area to include additional regions (the North Denmark Region and the Region of Southern Denmark). We will maintain continuous communication with referring pediatricians to ensure sufficient participant enrollment. This will include in-person meetings, emails, and newsletters.

Eligibility Criteria

Eligible participants will be invited for an assessment interview at the Department of Child and Adolescent Psychiatry, Aarhus University Hospital Psychiatry. The assessment will include psychiatric comorbidities, such as neurodevelopmental disorders, mood disorders, and suicidal risk, systematically evaluated according to the *ICD-10* (*International Statistical Classification of Diseases, Tenth Revision*) diagnostic criteria. Assessments

will be performed by medical doctors who are either trainees or specialists in child and adolescent psychiatry.

Inclusion Criteria

First, age 8-17 years. Second, a primary diagnosis according to the ROME-IV criteria of one of the FAPD subtypes—irritable bowel syndrome (IBS) or functional abdominal pain not otherwise specified (FAP-NOS) documented by the child's regular pediatric physician [31]. The somatic evaluation includes recommended routine medical investigations, that is, growth, fecal calprotectin, and blood samples (TSH [thyroid stimulating hormone], total IgA [immunoglobulin A], IgA-tissue transglutaminase, complete blood count, C-reactive protein analysis, and liver enzymes). Third, stable dosage of regular FAPD-related medication such as laxatives, antidiarrheal medicines, or psychopharmacological medication during the past month.

Exclusion Criteria

First, another medical or psychiatric disorder that better explains the symptoms. Second, severe child psychiatric or social problems (eg, high level of suicidal ideation, school absence of more than 40% during the past month, or ongoing substance abuse). Third, ongoing psychological treatment. Fourth, insufficient language or computer skills (patients and parents). Fifth, severe family problems (eg, child maltreatment, parental substance abuse or severe psychiatric illness, and custody fight).

Intervention

Translation Procedure

For this study, the Swedish ICBT programs were translated into Danish. The translation procedure was stepwise; first, a direct translation was performed by native Danish speakers familiar with the Swedish language; second, a mutual discussion of the Danish translation took place within the research group, including a discussion of problematic sentences or wordings; third, remaining issues were discussed with the Swedish authors, and a final consensus on the Danish translation was reached. This translation was reviewed by both a Danish language expert and a clinician with experience with the patient group to make further refinements. Finally, in the last step, the revised translation was reviewed again by the Danish research group for final adjustments.

Design and Content of Treatment

The 4 distinct ICBT programs used in this study are targeted children (8-12 years), adolescents (13-17 years), and the parents of each group, respectively. The treatment lasts for 10 weeks and consists of 10 modules for children, adolescents, and parents of children (with a new module every week) and 5 modules for parents of adolescents (with a new module every other week). An overview of treatment content can be seen in Table 1. The programs include sections with videos, exercises, and quizzes designed to actively engage the child or adolescent in the treatment. Psychoeducation regarding FAPDs, detection of avoidance behavior, a brief mindfulness exercise called "SOL (Stop, observe, let go)" and graded repeated exposure exercises comprise some of the central components covered in the programs for both children and adolescents. The first modules of treatment introduce the above-mentioned concepts whereas later modules focus on repeated exposures. The purpose of "SOL" is Stopping, Observing how the stomach feels, and Letting go of the focus on the stomach and continuing with the activity. The parental programs emphasize supporting their child or adolescent's exposure, decreasing attention to their child or adolescent's abdominal symptoms, and prioritizing shared positive activities. Each module ends with planning of the homework assignments which are evaluated first thing in the next module.

Table 1. Overview of the content of treatment for each module.

Module	Children (8-12 years)	Parents	Adolescents (13-17 years)	Parents
1	• Introduction to the treatment format • Psychoeducation on FAPDs[a] (video) • Mapping "stomach behaviors" (control, avoidance, safety) • Setting treatment goals • Homework: Self-monitoring	• Introduction to the treatment format • Positive attention • Focus shift • Mapping common parental behaviors • Handling personal frustrations • Homework: Focus shift, breaks, involving peers	• Introduction to the treatment format • Psychoeducation on FAPDs (video) • Setting treatment goals • Homework: self-monitoring	• Introduction to the treatment format • Focus on positive attention and shared moments • Mapping common parental behaviors • Homework: Shared positive moments
2	• Psychoeducation on impact of thoughts and "SOL"[b] (video) • Constructing an exposure hierarchy. • Homework: Utilize "SOL" in everyday situations.	• Golden moments • Board game with rewards for exposure exercises. • Homework: Golden moments, focus shift, planning rewards"	• Mapping "stomach behaviors" (control, avoidance, safety) • Behavior analysis • Homework: Behavioral experiment (avoiding "stomach behaviors")	
3	• Behavior analysis • Psychoeducation on exposure exercises (video) • Homework: Exposure exercises.	• Supporting child's exposure exercises • Managing school absences • Homework: board game rewards, golden moments, focus shift	• Psychoeducation on impact of thoughts and "SOL" (video) • Toilet habits (frequent visits, urgency) • Homework: "SOL" and new toilet habits	• Psychoeducation on FAPDs (video) • Acknowledging and shifting focus to reduce symptom focus • Homework: Shared positive moments, letting go of parental behaviors, focusing on alternative adolescent behaviors
4	• Toilet Habits (frequent visits, urgency) • Behavior analysis • Homework: Exposure exercises, new toilet habits, "SOL"	• Parental stress and recreational activities • Homework: recreation, golden moments, board game rewards, focus shift	• Psychoeducation on exposure exercises (video) • Behavior analyses • Construct exposure hierarchy • Homework: "SOL," toilet habits, finish exposure hierarchy	
5	• Repetition • Behavior Analysis • Homework: Exposure exercises, toilet habits, eliminating safety behaviors, "SOL"	• Repetition • Mapping challenges • Homework: recreation, golden moments, board game rewards, focus shift	• Exposure exercises • Anticipatory anxiety • Emotional versus behavioral goals • Homework: Exposure exercises, "SOL," toilet habits.	• Encourage and support the adolescent's exposure • Psychoeducation on exposure exercises (video) • Homework: Shared positive moments, support and encouragement, support adolescent's exposure
6	• Positive analysis of new behaviors • Advancing exposure difficulty • Homework: Advancing exposure exercises, toilet habits, "SOL"	• Problem-solving with child • Homework: recreation, golden moments, board game rewards, focus shift, problem-solving	• Further details on exposure and rewards • Homework: Exposure exercises, "SOL," and toilet habits	

Module	Children (8-12 years)	Parents	Adolescents (13-17 years)	Parents
7	• Positive behavior analyses • Evaluation of Treatment Goals (from Module 1) • Homework: Exposure exercises, toilet habits, "SOL"	• Parental behavior analyses in child interaction • Homework: recreational, golden moments, board game rewards, focus shift	• Level up exposure exercises • Homework: Exposures exercises, "SOL," toilet habits	• Managing personal frustrations • Engaging in recreational activities • Listening effectively • Homework: Shared positive moments, support and encouragement, support adolescent's exposure, active listening, parental recreation
8	• Positive behavior analyses • Advancing exposures to a "Super Hard Day" • Homework: Exposure exercises, the "Super Hard Day," toilet habits, "SOL"	• Review of progress • Reward for efforts • Homework: recreation, golden moments, board game rewards, focus shift, parental reward	• Emphasis on more challenging exposures • Homework: Challenging exposure exercises, "SOL," toilet habits	
9	• Treatment repetition using quizzes • Progress evaluation • Homework: Final exposure exercises, toilet habits, "SOL"	• Progress evaluation • Challenge evaluation • Homework: recreation, golden moments, board game rewards, focus shift.	• Focus on how to further challenge oneself. • Homework: Exposure exercises	• Review of treatment • Parental behavior evaluation (comparison with module 1) • Future training and relapse prevention plan
10	• Treatment goal and exposure hierarchy evaluation • "Stomach behavior" evaluation (comparison with module 1) • Future training and relapse prevention plan	• Parental behavior evaluation (comparison with module 1) • Future training and relapse prevention plan	• Treatment goal and exposure hierarchy evaluation • "Stomach behavior" evaluation (comparison with module 1) • Future training and relapse prevention plan	

[a]FAPDs: Functional abdominal pain disorders.

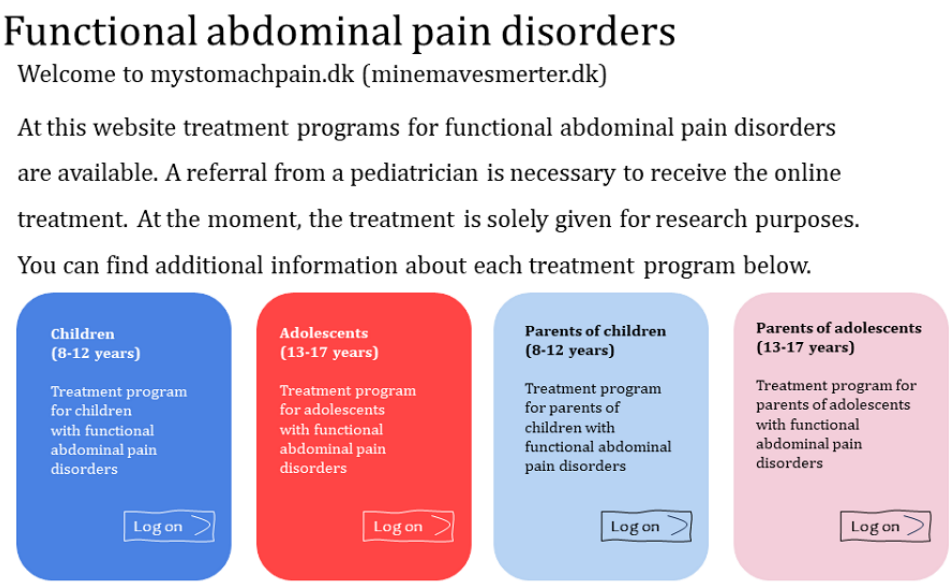
[b]SOL: Stop, observe, let go.

Modifications and Web Page

The Danish versions of the ICBT programs were pretested in 2 children and 2 adolescents with biweekly feedback from the patients and parents on overall experience and content (telephone interviews performed by a research assistant). Minor modifications were performed, mainly in the adolescent program where the IBS treatment was adjusted to include IBS and FAP-NOS. Furthermore, the mindfulness exercise "SOL" was integrated in the adolescent program to further support the process of labeling thoughts and sensations.

All treatment elements are delivered through a web page specifically designed for this study (Figure 2). Each family will choose 1 primary parent to participate in the treatment at the assessment. All 4 treatment programs are supported by a therapist who provides written feedback after each module. The affiliated therapists will be psychologists and medical doctors with knowledge of CBT. They will receive weekly supervision from Danish specialists in CBT and further supervision from the Swedish research team, who developed and tested the original programs.

Figure 2. Screenshot of the start page for the Danish treatment programs (all text is translated from Danish to English).



Measures

Measures in the Single Case Design Study (Substudy 1)

Children and adolescents will answer a daily short questionnaire (DSQ) throughout a pretreatment baseline period, randomized to last between 5 and 15 days, throughout the 10 weeks of treatment, and for a final 7-day follow-up period 3 months after treatment. The DSQ is an 8-item questionnaire, designed in line with the SCRIBE (Single-Case Reporting guideline In BEhavioural interventions) guidelines [32], addressing specific targets of the intervention, with items from different validated questionnaires for children and adolescents [32,33]. The full DSQ questionnaire is shown in Textbox 1. The primary outcome in the SCED study is the level of gastrointestinal symptoms assessed using 2 items from the Pediatric Quality of Life Inventory (PedsQL) Gastrointestinal Symptoms Questionnaire [34]. Secondary outcomes include illness worries, avoidance behavior, and level of pain acceptance as measured by the Visceral Sensitivity Index (VSI), irritable bowel syndrome behavioral response questionnaire (IBS-BRQ), and the Chronic Pain Acceptance Questionnaire – Adolescent Short Form (CPAQ-A8), respectively [35-37]. The items have been modified into questions concerning the last 24 hours and are rated on a 0-10 scale (“not at all” 0, “all the time” 10).

Textbox 1. Daily short questionnaire (DSQ).

During the last 24 hours, on a scale from 0 (not at all) to 10 (all the time)

1) Did your stomach hurt?

2) Did you feel discomfort in your stomach?

3) Did you worry about the problems in your belly?

4) Were you frightened when you felt discomfort in your belly?

5) Did you avoid going out in case you had belly problems?

6) Did you spent more time on the toilet than you ideally would like?

7) Did you do things that are important and things that are fun even though you have problems in your belly?

8) Has the most important thing been to keep your symptoms under control whenever you did something?

Measures on Cognitive Bias and Interoception (Substudy 2)

Cognitive biases will be assessed before and after treatment using a newly developed experimental design with a computerized web-based task: biases in youth toward gastrointestinal-related stimuli (BY-GIS) [38]. The BY-GIS task consists of a combination of a word task, which is a modified version of the Health Norms Sorting Task [39-41] and a picture task inspired by Gehrt et al [42]. The BY-GIS task is adapted to be appropriate for children and adolescents, featuring gastrointestinal-related stimuli (ie, words related to abdominal symptoms and pictures of food, leisure, and school situations). The BY-GIS task has 3 phases—encoding, free recall, and recognition. In the encoding phase, participants are asked to rate words and pictures presented to them. In the free recall phase, participants are instructed to recall as many words and pictures from the encoding phase as possible, and in the recognition phase, they are presented with words and pictures from the encoding phase along with new words and mirror images of the original pictures. They are then asked to mark which items have been presented to them before. The

development, test, and full procedure of the BY-GIS task are described by Bjerre-Nielsen et al [38].

Interoception will be investigated before and after treatment using a psychophysical measure of cardiac interoception, that is, the heart rate discrimination (HRD) task, developed by Legrand et al [43]. During the HRD task, participants have their heart rate monitored using a pulse oximeter while they are presented with auditory and visual stimuli from a computer and answer questions about their sensations of heart rate and subjective confidence in their answers. Thereby, the interoceptive performance (psychometric threshold, slope, and reaction time) and the metacognitive performance (confidence) can be measured. In collaboration with researchers from the Center of Functionally Integrative Neuroscience at Aarhus University, the task was adapted for a younger age group and pretested in 3 children and adolescents. Adaptations consisted of shortening the test by reducing the number of repetitions of trials, as well as replacing written instructions about the conduction of the test with direct oral guidance from a research assistant.

For both studies in substudy 2, we will perform parallel studies on healthy controls. The BY-GIS task was already tested in 96 healthy controls [38], and the interoception test setup will be performed in 60 healthy controls (all aged 8-17 years).

Measures of Parental Factors and Child Treatment Effects (Substudy 3)

To assess how parental distress, illness worry, and behavior impact the child's overall treatment effects in various domains and treatment adherence, all participating parents and children or adolescents in the ICBT programs will answer extensive questionnaires before assessment (T1: baseline), halfway through treatment (T2: mid-treatment), at end of treatment (T3: end of treatment), and 3 months after the end of treatment (T4: follow-up; Figure 1). Furthermore, the number of completed treatment modules will be obtained from the treatment web page after the end of treatment. The specific measures to be used are shown in Table 2 and described subsequently.

Table 2. Overview of questionnaires in substudy 3.

Outcome	Instrument	Time points and respondents[a]			
		T1	T2	T3	T4
Parental factors					
Parental distress	SCL-8[b] [44,45]	P	P	P	P
Parental illness worries	HAPYS[c] [46,47]	P	P	P	P
Parental illness behavior	ARCS[d,e] [48-50]	P	P	P	P
Child treatment effects					
Main measures					
Gastrointestinal symptoms	PedsQL Gastro[f] [34]	C, A, P	C, A, P	C, A, P	C, A, P
Pain intensity	Faces Pain Rating Scale – revised [51,52]	C, A, P	C, A, P	C, A, P	C, A, P
Additional measures					
Quality of life	PedsQL[g] [53]	C, A, P	C, A, P	C, A, P	C, A, P
Overall symptom load	CSSI[h] [54]	C, A, P		C, A, P	C, A, P
Depressive symptoms	MFQS[i] [55,56]	C, A		C, A	C, A
General anxiety	SCAS-S[j] [57,58]	C, A, P		C, A, P	C, A, P
Gastrointestinal anxiety	VSI[k]-short [35,59]	C, A	C, A	C, A	C, A
Avoidance and control behavior	IBS-BRQ-C[l] [36,60]	C, A	C, A	C, A	C, A
Illness perception	B-IPQ[m] [61,62]	C, A, P	C, A, P	C, A, P	C, A, P
Illness worries	CIAS[n,o] [63]	C, A	C, A	C, A	C, A
Pain acceptance	CPAQ-A8[p,q] [37]	C, A	C, A	C, A	C, A
Other measures					
Adverse events	Yes or no, and open question			A, P	
Treatment satisfaction	ESQ[r] [64]			C, A, P	
School absence	Hours past month	A, P	A, P	A, P	A, P
Work absence	Days past month	P	P	P	P

[a]Time points; T1: baseline, T2: mid-treatment, T3: end-of-treatment, T4: follow-up; Respondents: C: child, A: adolescent, P: parent.

[b]SCL-8: Symptom Check List-8.

[c]HAPYS: The Health Anxiety by Proxy Scale.

[d]ARCS: Adult Responses to Children's Symptoms.

[e]The monitor and protect subscales.

[f]PedsQL Gastro: Pediatric Quality of Life Inventory – Gastrointestinal symptoms.

[g]PedsQL: Pediatric Quality of Life Inventory.

[h]CSSI: Children's Somatic Symptom Inventory.

[i]MFQS: Mood and Feelings Questionnaire Short.

[j]SCAS-S: Spence Children Anxiety Scale – Short.

[k]VSI: Visceral Sensitivity Index.

[l]IBS-BRQ-C: irritable bowel syndrome behavioral response questionnaire – Child-adapted short version.

[m]B-IPQ: Brief Illness Perception Questionnaire.

[n]CIAS: Childhood Illness Attitude Scale.

[o]The fear factor subscale.

[p]CPAQ-A8: Chronic Pain Acceptance Questionnaire – Adolescent Short Form.

[q]One question from the pain willingness factor, one from activity engagement.

[r]ESQ: Modified Experience of Service Questionnaire.

Parental Factors

Parental distress will be assessed by the Symptom Checklist-8, an 8-item subscale from the Symptom Checklist Revised-90, screening for emotional symptoms. Items are rated on a 5-point scale from 0 “not at all” to 4 “a whole lot,” with a total range from 0 to 32. Higher scores indicate more emotional distress [44,45].

Parental illness worries will be assessed by the Health Anxiety by Proxy Scale (HAPYS), a newly developed questionnaire assessing parents’ worries about their child’s health [46]. The questionnaire covers 26 items about health anxiety by proxy, rated on a 5-point scale (from 0 “not at all” or “never” to 4 “a whole lot” or “most of the time”), with a sum score range from 0 to 104. In addition, there are 6 items about the impact of the worries rated on a 4-point scale (from 0 “no” to 3 “yes, severely”), with a sum score range from 0 to 18. Higher scores indicate a high level of health anxiety by proxy and the impact of the anxiety, respectively. HAPYS is a valid measure of health anxiety by proxy with good psychometric properties, including high internal reliability and known-groups validity [47].

Parental illness behavior will be measured by the Adult Responses to Children’s Symptoms, which is originally a 29-item questionnaire [48]. In this study, 2 subscales (monitor and protect subscales) comprising 15 items will be used. Items are rated on a 5-point scale from 0 “never” to 4 “always” with a score range from 0 to 60. Higher scores indicate a higher degree of monitoring and protective responses [49,50].

Child or Adolescent Treatment Effects—Main Measures

Gastrointestinal symptoms will be assessed by PedsQL gastrointestinal symptoms [34]. This is a 9-item questionnaire assessing gastrointestinal symptoms related to functional or organic gastrointestinal diseases, during the past month, on a 5-point scale from 0 “never” to 4 “almost always.” Scores are reversed and transformed into a 0-100 scale, with high scores indicating greater quality of life. Pain intensity will be assessed by the Faces Pain Rating Scale – revised (FPS-R) [51]. The FPS-R score includes 6 pictures of faces, each showing an increasing amount of pain and scored on a 2-step scale between “no pain” (0) and “worst pain” (10). The scale is validated in children and adolescents and found to be sensitive to change [52].

Child or Adolescent Treatment Effects—Additional Measures

Quality of life will be measured by the 23-item PedsQL [53], which is a widely used questionnaire to assess quality of life during the past month in children and adolescents. Items are scored on a 5-point scale from 0 “never” to 4 “almost always.” Scores are reversed and transformed into sum scores between 0 and 100, with high scores indicating higher quality of life.

Overall symptom load will be assessed by the Children’s Somatic Symptom Inventory. It measures somatic symptoms during the last 2 weeks using 24 items, rated on a 5-point scale from 0 “not at all” to 4 “a whole lot,” with a range in scores from 0 to 96. High scores indicate a high symptom load. The questionnaire is found to be reliable and psychometrically sound for children and adolescents with abdominal pain disorders [54].

Depressive symptoms will be measured using the Mood and Feelings Questionnaire Short. It comprises 13 items rated on a 3-point scale from 0 “not true” to 2 “true,” with a range from 0 to 26, where higher scores indicate more depressive symptoms. The questionnaire is found reliable for evaluating depressive symptoms in both clinical and community populations of children and adolescents [55,56].

Anxiety levels will be assessed with 2 different questionnaires—the Spence Children Anxiety Scale Short (SCAS-S) [57,58] for general anxiety, and the Visceral Sensitivity Index-Children (VSI-C) [35,59] for gastrointestinal-specific anxiety. SCAS-S contains 19 items which are answered on a 4-point scale from 0 “never” to 3 “always,” with a total range from 0 to 57, where higher scores indicate higher anxiety levels. The questionnaire is designed for use in children and adolescents, and the short version is validated for screening of anxiety levels in children and adolescents [58]. The VSI-C is a shortened child-adapted version of the VSI for adults [35], with 7 items answered on a 6-point scale from 0 “strongly disagree” to 5 “strongly agree,” with a range from 0 to 42, where higher scores indicate more GI-anxiety. It has been found reliable and valid in children and adolescents with FAPDs [60].

Avoidance and control behavior will be assessed by the IBS-BRQ–Child-adapted short version with 11 items, which is an adapted version of the IBS-BRQ for adults [36]. Items are rated on a 7-point scale from 0 “never” to 6 “always,” with scores ranging from 0 to 66, where higher scores indicate more avoidance. It has been validated for children and adolescents with FAPDs [60].

Illness perception will be assessed by the Brief Illness Perception Questionnaire [61,62], which is a 9-item questionnaire where 8 items are answered on an 11-point scale, and 1 item is an open-ended question. The total score range is 0-80, with higher scores indicating more severe illness perception.

Illness worries will be assessed by the Childhood Illness Attitude Scale with 11 items from the fear factor [63]. The questionnaire is developed and validated for children and adolescents. Items are answered on a 3-point scale from 0 “never” to 2 “most of the time,” with a total score range from 0 to 22, and higher scores indicate more illness worries.

Pain acceptance will be assessed by 2 items from the CPAQ-A8 [37]. One regarding pain willingness and one regarding activity engagement. They are both answered on a 5-point scale from 0 “never true” to 4 “always true,” the item on pain willingness is reversed scored, and higher scores then indicate higher pain acceptance.

Other Measures

Parents will provide information about school absence (hours last month) for children (aged 8-12 years) and about their work absence (days past month). Adolescents will provide information about their own school absence (hours last month).

Adverse events will be assessed by adolescents and parents of children using a binary (yes or no) question and an open-ended question to describe the potential event in detail.

Treatment satisfaction will be assessed by the Modified Experience of Service Questionnaire [64], which is a 13-item questionnaire with 10 items scored from "not true" to "certainly true" and 3 free-text items. The total score range is 0-20 with higher scores indicating a better experience with the treatment.

Sample Sizes

According to research design standards [65], a minimum of 3 replications are recommended in a SCED study (substudy 1). However, to achieve sufficient power for randomization tests, a higher number of potential randomizations is recommended [66]. The number of randomizations is influenced by both the number of participants and the number of possible starting points; hence, guided by Levin et al [67], we chose 6 participants in each group.

For substudy 2, we based our power analysis on potential differences in cognitive bias and interoception between cases and healthy controls on a previous similar study on cognitive bias in children and adolescents [40] and studies on interoceptive accuracy in adults with functional disorders [68-69]. Based on these study findings, calculations show that in order to detect a minimum effect size of 0.5 (Cohen *d*), 60 patients and 100 healthy controls are required for the cognitive bias outcome, and a minimum of 51 patients and 51 healthy controls for the interoception outcome to achieve 80% power at an α level of .05. The subsequent analysis of the possible impact of treatment on these 2 factors is more explorative and therefore no a priori power calculation is provided. The same concerns the last study on parental factors (substudy 3) as possible effect moderators. However, here the sample size is the largest possible, comprised of parents from substudies 1 and 2.

Data Collection and Management

The DSQ, the BY-GIS task, and questionnaires are set up in REDCap (Research Electronic data capture; Vanderbilt University) [70], hosted by Aarhus University, and distributed through SMS text message or email. REDCap is a secure, web-based software platform designed to facilitate data capture for research studies.

For the DSQ (substudy 1), a text message reminder will automatically be sent through REDCap 2 hours after the initial SMS text message. If the DSQ is not completed 2 days in a row, a research assistant will contact the family by phone. For the BY-GIS task (substudy 2) and the extensive questionnaire (substudy 3), REDCap will generate automatic email reminders 24, 48, and 72 hours after the initial email if they are not completed. If there is no response after 7 days, a research assistant will contact the family by phone.

The interoception task in substudy 2 will take place at the Center of Functionally Integrative Neuroscience at Aarhus University Hospital in a behavioral testing room, and data will be stored in REDCap.

Data Analyses

In substudy 1, visual inspection analyses will be applied to demonstrate the effect of the intervention on all outcomes [71]. In addition, within-case effect size measurements will be calculated using Tau-U [72] and between-case effect sizes will be determined using hierarchical linear regression models to account for the serial dependency of data [73]. A randomization test will be applied to test differences in means for the baseline versus treatment, and baseline versus follow-up periods, respectively [74].

In substudy 2, participants' descriptions reported in the recall phase of the BY-GIS task will be coded to their corresponding word or picture and category presented in the encoding phase (eg, picture-description "children and cake" coded as the birthday picture within the fun category). Coding for the first 20% of participants will be conducted by 2 independent raters (ESN and EB-N). If the consensus rating exceeds 90%, 1 rater will code the remaining cases independently. A third and experienced rater (TBG) may be consulted to resolve potential disagreements. Baseline data will be analyzed descriptively and compared with (1) data from a healthy control group who performed the same experimental test [38], and (2) end-of-treatment data, exploring potential differences in the outcomes from the encoding, recall, and recognition phases using *t* tests or nonparametric tests, depending on data variability in the samples.

Baseline measures of interoceptive performance and metacognitive measures will be analyzed descriptively and compared with (1) measures from a healthy control group and (2) end-of-treatment measures, using *t* tests or nonparametric tests, depending on data variability in the samples.

In substudy 3, the potential moderation of parental factors on treatment adherence (number of completed modules) and main measure (gastrointestinal symptoms) for children or adolescents will be investigated using negative binomial regression and linear mixed models, respectively, adjusting for baseline parental distress, illness worries, and illness behavior, respectively.

In addition, the potential effect of treatment on these parental factors and all other child or adolescent measures will be analyzed using linear mixed regression models.

An experienced statistician will provide statistical support for all analyses.

Ethical Considerations

The study will be conducted according to the guidelines of the Declaration of Helsinki. The study was approved by The Central Denmark Region Committees on Health Research Ethics (record 1-10-72-277-21, 1-10-72-80-22, and 1-10-72-142-22).

Written informed consent will be obtained from parents and adolescents (≥15 years) whereas children and adolescents (<15 years) will only give oral consent.

Children and adolescents will be compensated with a gift card (value 150 DKK [US $21.13]) for the first time participating in the interoception study. No other compensation will be provided.

Results

Recruitment of participants began in June 2022. Substudy 1 is finalized and expected to be published in 2025. Recruitment for substudies 2 and 3 is ongoing. By November 2024, 45 children and 24 adolescents have been included. Due to a skewed distribution in referrals, with a predominance of referrals on children, we continue to include children and adolescents until we have reached 30 adolescents. Inclusion is expected to be completed by January 2025 and data collection in March 2025.

Discussion

Principal Findings

With this study, we aim to explore previously sparsely investigated areas of ICBT for children and adolescents with FAPDs related to both child or adolescent and parental factors. This includes examining the detailed trajectory of effect, the presence of and potential changes in cognitive biases, and interoceptive inaccuracy after treatment, as well as investigating the potential role of parental distress, illness worries, and behavior as effect moderators.

Previous studies have demonstrated the effectiveness of Swedish ICBT programs in reducing abdominal symptoms and improving the quality of life in children and adolescents with FAPDs. Mediation analyses have shown that positive changes in symptom-specific avoidance behavior and fear mediate the treatment effects [17,18,27,29]. However, the detailed trajectory of treatment effects—specifically when and how possible changes occur during treatment for individual patients—remains unknown, and this will be investigated in substudy 1. This research could provide new insights into the mechanisms of change underlying treatment effects and could be clinically valuable for both therapists and patients.

To the best of our knowledge, this study is one of the first to assess cognitive biases and the ability to sense and interpret signals from the body (ie, interoception) in this patient group in comparison with healthy controls as well as to explore potential changes in these factors after treatment with CBT. Both factors are suggested to play a vital role in the predictive processing model, explaining the pathophysiology of FAPDs [11]. However, so far, they have mainly been studied in adults with various functional disorders [40,68-69,75-78]. By uncovering more knowledge about these factors, the results can potentially be used to further refine already established treatments. For example, this could involve adding biofeedback to train interoceptive accuracy or enhancing exposure exercises addressing specific cognitive biases that lead to fearful responses to gastro-related sensations and avoidance behavior.

Parental worries and anxious behaviors toward the child or adolescent's symptoms can impact the overall well-being of the child or adolescent. These factors are suggested to be part of the complex pathophysiology of FAPDs [9,20,21,48] and are therefore important to investigate further. Parental emotional distress has been found to negatively moderate the effect of ICBT for adolescents with chronic pain [79,80], whereby high levels of parental emotional distress lead to less improvement in disability for the adolescent. However, it is currently unknown how the level of parental distress impacts the effects of the ICBT programs for young patients with FAPDs [29,81]. A specific type of parental emotional distress is health anxiety by proxy, which is a recently described clinical phenomenon characterized by parents' excessive and distressing worries and rumination about their child's health, often involving fears of serious diseases being overlooked by medical professionals [82,83]. This fear may lead to frequent medical visits and investigations of the child [84]. In this study, we will use the newly developed HAPYS questionnaire [46,47] to assess parental health anxiety by proxy. To our knowledge, this is the first systematic examination of this specific type of parental emotional distress in parents of children and adolescents with FAPDs. Such type of parental anxiety may especially lead to symptom-related protective and monitoring behaviors, which are suggested to play a crucial role in the development, maintenance, and even aggravation of the child's FAPD and related health care visits [48-50]. The Swedish ICBT has been shown to effectively reduce such maladaptive parental behavior in both children and adolescents [28,29]. Still, the impact of parental emotional distress, particularly illness worries and related behavioral responses, on the effect of ICBT in children is less well-investigated [85] and no studies have yet been conducted specifically in relation to adolescents. This is why, in this study, we will explore parental distress, illness worries, and behaviors before and after ICBT and examine how these factors impact treatment adherence and treatment effects in both children and adolescents. By uncovering more knowledge about these parental factors, we aim to gain a better understanding of family dynamics and identify potentially important parental characteristics to focus on during treatment, thereby further improving its effectiveness.

The study has some limitations. In substudy 1, the generalizability of SCED study results has traditionally been questioned due to the low number of participants. However, our study adheres to guidelines that include multiple data points across different phases, randomization of the length of the baseline phase, and replication across several participants, thereby optimizing generalizability. Furthermore, participants are expected to answer daily questions for an extended period, which could induce some fatigue in responding and potentially affect reliability. Still, the inclusion of several close data points increases precision in analyses and helps buffer against occasional data loss. In addition, the setup was tested on 4 prestudy patients, who reported that the daily questionnaire was easy and quick to answer.

In substudy 2, we use the BY-GIS task, which is newly developed and has not been previously tested in patients. However, the task is developed based on well-known paradigms and previous tests, and it has already been tested in a sample of 96 healthy age-matched controls with good usability [38]. The interoception HRD measures participants' ability to sense their pulse, which is not directly related to gut sensations but falls within the broader perspective of interoception. However, studies in adults suggest altered interoceptive accuracy across different diagnoses of functional disorders and chronic pain,

which indicates that there may be a general hypersensitivity to inner sensations in this patient group as well [86]. Since this study is one of the first to investigate interoceptive accuracy in children and adolescents with FAPDs, we believe it is still valuable to use this well-known and widely used interoception measure.

Substudy 3 is an open pilot trial without a control group for comparison which means conclusions regarding the clinical effect of the treatment should be interpreted with caution. However, the substudy is explorative and primarily aims to investigate new and additional modifiable treatment targets on a parental level.

Conclusion

In conclusion, this study is expected to provide new and important information about the process of the effect of ICBT, increase our understanding of modifiable treatment targets within the framework of predictive processing in children and adolescents with FAPDs, and shed light on parental factors that are important for the child's treatment adherence and effect. Overall, this research can guide the further development of even more effective psychological treatments for one of the most prevalent chronic pain disorders in children and adolescents.

Acknowledgments

We are thankful to Professor Micah Allen for the development and support on the interoception test method and use of laboratory facilities, statistician Anders Helles Carlsen for statistical support, pediatric departments, and private pediatric practitioners for referral of patients for our study, and Helle Veller Mortensen for language editing.

This project was funded by TrygFonden (grant 153021 and ID 147092), HelseFonden (grant 21-B-0168), Aase og Ejnar Danielsens Fund (grant 19-10-0176), Hartmann brothers Foundation (A34185), Aarhus University (PhD-student grant), and the Department of Child and Adolescents Psychiatry, Research Unit, AUHP.

Authors' Contributions

Conceptualization, methodology, and writing—review and editing were contributed by ESN, KHK, EB-N, TBG, ML, LF, MB, and CUR. Writing—Original Draft Preparation was contributed by ESN. Supervision was handled by KHK, TBG, ML, LF, MB, and CUR. Project administration was managed by ESN, EB-N, KHK, and CUR. Funding acquisition was handled by ESN, LF, and CUR. All authors have read and agreed on the published version of the manuscript.

Conflicts of Interest

None declared.

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Abbreviations

BY-GIS: biases in youth toward gastrointestinal-related stimuli
CBT: cognitive behavioral therapy
CPAQ-A8: Chronic Pain Acceptance Questionnaire – Adolescent Short Form
DSQ: daily short questionnaire
FAP-NOS: functional abdominal pain not otherwise specified
FAPD: Functional abdominal pain disorder
FPS-R: Faces Pain Rating Scale – revised
HAPYS: The Health Anxiety by Proxy Scale
HRD: heart rate discrimination
IBS: irritable bowel syndrome
IBS-BRQ: irritable bowel syndrome behavioral response questionnaire
ICBT: internet-delivered cognitive behavioral therapy
ICD-10: International Statistical Classification of Diseases, Tenth Revision
IgA: Immunoglobulin A
PedsQL: Pediatric Quality of Life Inventory
REDCap: Research Electronic Data Capture
SCAS-S: Spence Children Anxiety Scale – Short
SCED: single case experimental design study
SCRIBE: Single-Case Reporting guideline In BEhavioural interventions
SOL: Stop, observe, let go
SPIRIT: Standard Protocol Items Recommendations for Interventional Trials
TSH: thyroid stimulating hormone
VSI: Visceral Sensitivity Index
VSI-C: Visceral Sensitivity Index-Children

Edited by A Schwartz; submitted 19.03.24; peer-reviewed by U Sinha; comments to author 15.07.24; revised version received 08.08.24; accepted 12.11.24; published 07.01.25.

Please cite as:
Skovslund Nielsen E, Kallesøe K, Bennedsen Gehrt T, Bjerre-Nielsen E, Lalouni M, Frostholm L, Bonnert M, Rask CU
Trajectories of Change, Illness Understanding, and Parental Worries in Children and Adolescents Undergoing Internet-Delivered Cognitive-Behavioral Therapy for Functional Abdominal Pain Disorders: Protocol for a Single-Case Design and Explorative Pilot Study
JMIR Res Protoc 2025;14:e58563
URL: https://www.researchprotocols.org/2025/1/e58563
doi:10.2196/58563
PMID:

Protocol

Co-Designing a Consumer-Focused Digital Reporting Health Platform to Improve Adverse Medicine Event Reporting: Protocol for a Multimethod Research Project (the ReMedi Project)

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Abstract

Background: Adverse medicine events (AMEs) are unintended effects that occur following administration of medicines. Up to 70% of AMEs are not reported to, and hence remain undetected by, health care professionals and only 6% of AMEs are reported to regulators. Increased reporting by consumers, health care professionals, and pharmaceutical companies to medicine regulatory authorities is needed to increase the safety of medicines.

Objective: We describe a project that aims to co-design a digital reporting platform to improve detection and management of AMEs by consumers and health care professionals and improve reporting to regulators.

Methods: The project will be conducted in 3 phases and uses a co-design methodology that prioritizes equity in designing with stakeholders. Our project is guided by the Consolidated Framework for Implementation Research. In phase 1, we will engage with 3 stakeholder groups—consumers, health care professionals, and regulators—to define digital platform development standards. We will conduct a series of individual interviews, focus group discussions, and co-design workshops with the stakeholder groups. In phase 2, we will work with a software developer and user interaction design experts to prototype, test, and develop the digital reporting platform based on findings from phase 1. In phase 3, we will implement and trial the digital reporting platform in South

Australia through general practices and pharmacies. Consumers who have recently started using medicines new to them will be recruited to use the digital reporting platform to report any apparent, suspected, or possible AMEs since starting the new medicine. Process and outcome evaluations will be conducted to assess the implementation process and to determine whether the new platform has increased AME detection and reporting.

Results: This project, initiated in 2023, will run until 2026. Phase 1 will result in persona profiles and user journey maps that define the standards for the user-friendly platform and interactive data visualization tool or dashboard that will be developed and further improved in phase 2. Finally, phase 3 will provide insights of the implemented platform regarding its impact on AME detection, management, and reporting. Findings will be published progressively as we complete the different phases of the project.

Conclusions: This project adopts a co-design methodology to develop a new digital reporting platform for AME detection and reporting, considering the perspectives and lived experience of stakeholders and addressing their requirements throughout the entire process. The overarching goal of the project is to leverage the potential of both consumers and technology to address the existing challenges of underdetection and underreporting of AMEs to health care professionals and regulators. The project potentially will improve individual patient safety and generate new data for regulatory purposes related to medicine safety and effectiveness.

International Registered Report Identifier (IRRID): DERR1-10.2196/60084

(JMIR Res Protoc 2025;14:e60084) doi:10.2196/60084

KEYWORDS

adverse drug events; drug-related side effects and adverse reactions; adverse drug reaction reporting systems; pharmacovigilance; digital health; medication safety; co-design; qualitative research, user-centered design

Introduction

Adverse medicine events (AMEs), also known as adverse drug events, are unintended effects that occur following administration of a medicine and include adverse reactions and harm from medication errors [1]. AMEs are common and result in patient harm. In Australia, an estimated 1.2 million people reportedly experienced an AME within a 6-month period [2]. While AMEs can occur in anyone, people with chronic conditions and older people are particularly vulnerable to and are most affected by AMEs. For example, 1 in 5 hospital admissions of older adults in Australia is due to AME [2-4]. According to a 2022 estimate, medicine-related hospital admissions, including instances of noncompliance, overdose, and AME, incur an estimated annual cost of Aus $1.4 billion (US $870 million) in Australia, with AME being the most prevalent contributing factor [2,5]. Early detection and management of AMEs are crucial to preventing avoidable harms such as medicine-related falls, hospitalizations, and deaths. However, findings from surveys and reviews of consumer medical records conducted internationally suggest that many consumers do not disclose their AMEs unless prompted to do so. Consequently, up to 70% of AMEs are undetected by health care professionals [6,7], emphasizing the need for proactive interventions to identify and resolve AMEs.

AMEs are also underreported to medicine regulatory authorities (“regulators”), making it difficult to understand how medicines affect consumers. Spontaneous reporting of AMEs is the most common mechanism of safety surveillance worldwide after a medicine has been introduced to the market [8]. Spontaneous reporting of AMEs by consumers, health care professionals, and pharmaceutical companies is vital for regulators to identify potential medicine safety signals [9] and—when relevant—mandate necessary changes, such as updating product labels or withdrawing medicines from the market. A major challenge, however, is the very low AME reporting rate; as evidenced by a systematic review of 37 studies from 12 countries, only an estimated 6% of AMEs experienced by patients were reported [10].

Consumers often detect AMEs before their health care professionals notice them [11], and, where patient engagement is implemented, consumer self-report of AMEs alerts regulators to new and previously unknown reactions prior to health professional reports [12,13]. In Australia, however, the number of reports to regulators from consumers is disproportionately low compared with those made by health care professionals and pharmaceutical manufacturers [14], partly because of consumers’ limited awareness of the reporting system and perceived absence of benefits of reporting [15]. The AME reporting system, developed by the medicine regulatory body, the therapeutic goods administration (TGA) [14], has seen limited consumer uptake in Australia. Furthermore, there is currently no Australian-specific AME reporting platform co-designed with consumers. To address this gap, we developed a prototype system in a small pilot project comprising both Android and iOS apps and a public-facing website for consumers to report any AMEs they experienced [16]. The system was shown to be user-friendly. However, the development involved limited stakeholder engagement and participation (3 consumers) due to the inherent nature of a small pilot project.

Building on this pilot project, the current project aims to co-design with stakeholders (consumers, health care professionals, and regulators) a digital reporting platform to improve AME detection, management, and reporting. The ultimate goal of this project is to empower consumers to actively detect, manage, and report AMEs, fostering a collaborative approach with their health care professionals, and at the same time improve AME reporting to the TGA.

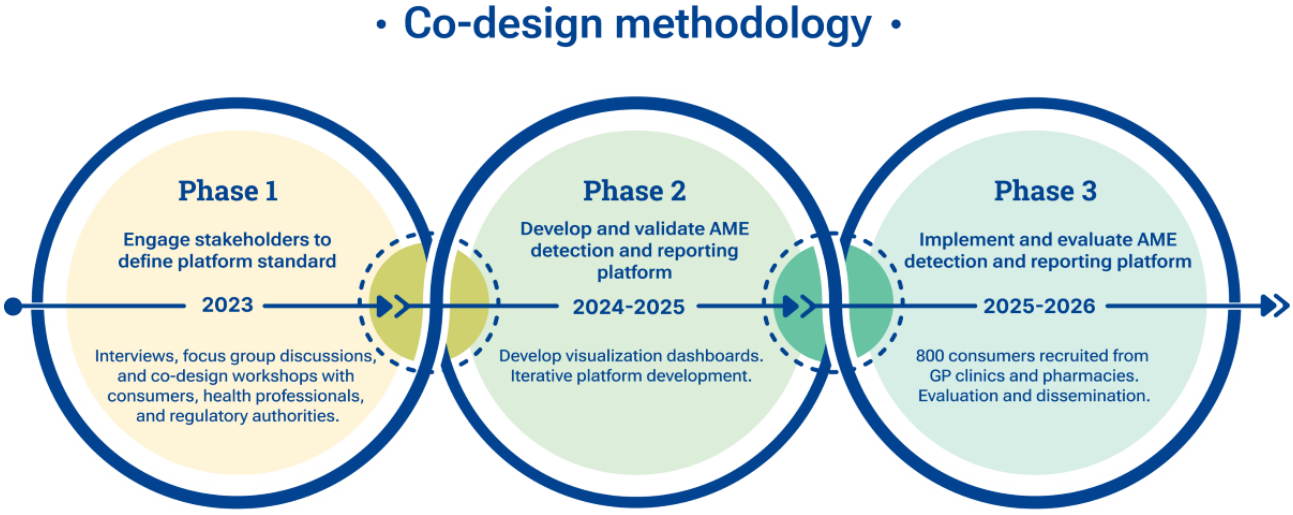
Methods

Study Design

The project is being conducted in 3 phases (Figure 1) from 2023 to 2026 and uses a co-design methodology that prioritizes designing equitably with all stakeholders [17]. Co-design methodology focuses on generating and reflecting on data related to people's lived experiences and engaging participants in action to enhance the quality of their lives. Co-design facilitates collaboration among stakeholders to address challenges within sociotechnical systems and daily services [18,19]. It uses design-based strategies to collect qualitative data around users' experience and the interests of the stakeholders providing services to those users to foster dialogue for mutual insights. Using a range of research methods including stakeholder workshops, focus group discussions, and interviews, co-design aims to describe, categorize, question, and evaluate the needs, experiences, opinions, interests, decisions, and behaviors of stakeholders, ensuring equity through structured reflection. This project builds on the findings of our pilot project [16], using the pilot's prototype as the foundation for developing the co-design activities.

This project builds on the findings of our pilot project [16], engaging stakeholders in phase 1 and advancing to the development and validation of the platform in phase 2. The pilot's prototype serves as a foundation for developing the co-design activities. Our project is guided by the Consolidated Framework for Implementation Research, which considers 5 domains for effective intervention development and implementation: innovation, outer setting, inner setting, individuals, and implementation process [20]. The innovation domain includes the construct's trialability and evidence base, which we addressed in our pilot work [16] and systematic review [21]. We will consider constructs in each domain that influence use of our platform by consumers including innovation, complexity and usability, consumer needs and preferences, feedback, design, and engagement [20,22-24].

Figure 1. Key activities in each phase of the project. AME: adverse medicine event; GP: general practitioner.



Phase 1: Engage With Stakeholders to Define Platform Development Standards

Phase 1 involves interviews, focus groups discussions, and co-design workshops with 3 specific stakeholder groups: consumers, health care professionals, and regulators (Table 1). Consumers eligible for inclusion must be 18 years of age or older, take regular medications or have previously experienced an adverse event from any medication, and own a smartphone or tablet. Health care professionals must be practicing as medical doctors, pharmacists, or nurses in Australia, and regulators will be eligible if they are involved in the postmarketing assessment of safety information for human medicinal products within Australia. Individuals will be excluded if they cannot speak, read, or write in English, or do not provide informed consent.

We will use purposeful sampling to recruit consumers with broad demographic variation to ensure that they represent consumers across different ages and social groups, levels of education and experience, and who have a range of health conditions and use a range of medications to ensure that our platform meets the needs of diverse groups of people. In addition, health care professionals and personnel who work for the medicine regulators will be recruited. All participants will be asked to participate in all 3 activities: semistructured interviews, focus group discussions, and co-design workshops. Attrition is natural in longitudinal projects such as this, and we will mitigate this by recruiting additional participants.

The interviews, focus group discussions, and co-design workshops will be conducted face-to-face where possible and audio- or video-recorded where participants agree. If participants are located interstate from the researchers or prefer to engage remotely for convenience, interviews, focus group discussions, and co-design workshops will be conducted on the web. When preferences differ, separate face-to-face and web-based workshops will be organized to accommodate participants' preferred formats. All recordings will be transcribed verbatim, manually coded inductively, and analyzed thematically in ATLAS.ti software (ATLAS.ti Scientific Software Development GmbH) [25]. Using the Capability, Opportunity, Motivation, Behavior (COM-B) model [26], a well-established model for analyzing and modifying behaviors, the themes identified will inform the recognition of barriers and facilitators to adopting a

digital platform for reporting AMEs. The themes will also be used to highlight key design features essential to meeting the needs and preferences of each of the stakeholder group. Based on these analyses, persona profiles (which will be used to summarize the identified needs, priorities, motivations, goals, and challenges of each user archetype) and user journey maps [27] (which will be used to visualize and document participants' discussions of the likely experience personas might have during the process of reporting or reviewing AMEs as they move through the system) will be developed which will be used to guide subsequent phases of the project.

Table 1. Description of the different activities in phase 1 of the project.

Activity	Number	Aim	Duration	Outcome
Individual semistructured interviews	Ten to fifteen consumers; 10 health care professionals and regulators.	• To understand their experience with, or perspectives toward medicine use and the current AME[a]-reporting process in Australia. • To enable participants to offer their ideas and insights in confidence without the possible influence of bias from other participants.	Approximately 60 minutes per interview.	Findings will be used to develop personas that will then be discussed in focus group discussions to determine their accuracy and thoroughness as exemplar of user groups.
Focus groups discussions	Two focus-group discussions with each of the 3 stakeholder groups.	• To consider and define the respective needs, priorities, and motivations the personas—developed based on the findings from the interviews—might have for reporting an AME and to define the reporting goals for the platform.	Each stakeholder focus group discussion will run for 2 hours.	Outcomes from the discussions will inform the development and delivery of the co-design workshops.
Co-design workshops	Three co-design workshops held for the same stakeholders collectively.	• To employ the co-designed user personas to build a user journey map as a means to evaluate the processes of AME detection, management, and reporting, generate and agree on notional platform content and feature set to guide its subsequent development.	Each co-design workshop will last 3-4 hours and will contain multiple activities, each varying in duration but capped at 60 minutes. Regular breaks will be incorporated between activities to maintain engagement and focus.	The workshops will result in user journey maps which will be used to visualize and document participants' discussions of the likely experience personas might have during the process of reporting or reviewing AMEs as they move through the system.

[a]AME: adverse medicine event.

Phase 2: Develop the Platform and Interactive Data Visualization Tool

The second phase of the project focuses on the development of the platform. First, we will work with a software developer and user interaction designers to develop the underlying relational structure that received data from users might have, how the data function in terms of reporting, and what principle features a front-end user experience might have for gathering them (phase 2a—platform development). At a minimum, the project aims to achieve a fully functioning web-based reporting platform, a mobile app, or both, based on findings from phase 1. It will include a fully refined user interface and database integration and search function to operate with the TGA's Database of Adverse Event Notifications [28]. To ensure equity across stakeholder interests, we will continue to adhere to co-design principles throughout this phase by inviting consumers, health care professionals, and regulators to participate in this process. The platform development will undergo cycles of iteration and review where stakeholders will test, compare, and contribute to decision-making on the content, form, and function of the platform through each iteration. We will perform the iterative cycles with stakeholders until no new issues are identified with the platform. We anticipate that the process will require up to 5 cycles before saturation and a deployable outcome is achieved. Stakeholders recruited in phase 1 will be invited to participate in this process, and additional participants will be invited to compensate for any attrition.

Next, as part of our communication and engagement strategy, we will develop an interactive data visualization tool or dashboard to translate and disseminate the data collected to the public, health care professionals, and regulators (phase 2b—development of interactive data visualization tool). The visualization tool will be implemented with back-end integration in the digital reporting platform and developed collaboratively through 2 co-design workshops with 8 stakeholders. The visualization tool will be configured to allow both consumers and their health care professionals to access the data they provided, obtain information on the medicines they are taking,

and compare their experience with those reported by other consumers taking the same medicines. A separate visualization tool will be developed for use by regulators and will include further levels of configuration necessary for them to examine data relative to their decision-making. All consumer reports will be reviewed by study investigators (clinicians) for causality assessment (ie, likelihood that the medicine caused the observed AME) using the Naranjo probability scale [29]. The causality assessment will be done to determine whether the platform has collected all the information needed for a causality assessment.

Phase 3: Digital Platform Implementation and Evaluation

In the third phase of the project, we will implement the new platform in general practices and pharmacies in South Australia and assess its impact for (1) increasing AME detection, (2) improving AME management, and (3) increasing AME reporting and enhancing existing TGA workflows.

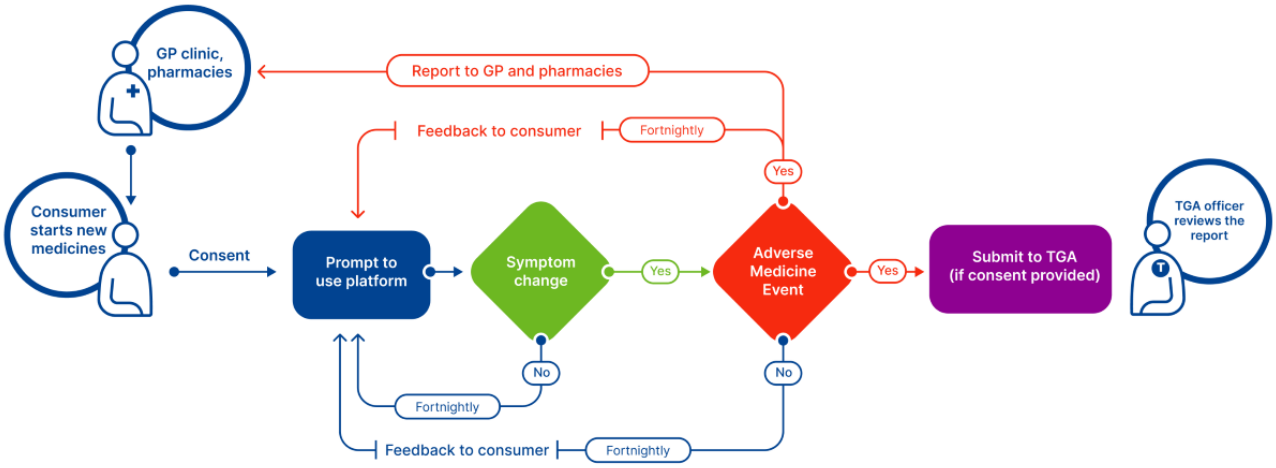
A quasi-experimental study will be conducted to involve consumers who have recently begun taking new medicines. This is because most AMEs tend to occur within 4 weeks of patients commencing new medications [30]. Depending on results from phases 1 and 2, criteria for further inclusion may be specified (eg, consumers initiating medicines with a black triangle warning). Eligible consumers will be identified initially by general practices and pharmacies applying the inclusion or exclusion criteria to their software (eg, Doctors Control Panel software [Doctors Control Panel Software Pty Ltd] [31] and dispensing software used in the pharmacies). Eligible consumers will then be approached by a dedicated research assistant via phone, text message, or email to assess their eligibility, discuss the details of the project, answer any questions, and facilitate the process of obtaining informed consent from interested individuals. We will seek consent to send information reported by consumers to their health care professionals and regulators (ie, the TGA). Consumers will then be prompted to use the platform to report whether they have experienced any suspected or possible AME. Consumers will access the platform either by downloading the mobile app or by visiting the website. Where the consumer has consented, a report will be sent electronically to their general practitioner and pharmacist to enable targeted assessment for managing the AMEs. For those who provided consent, consumer reports will also be submitted to the TGA. Subsequent prompts to use the platform will be sent to the consumers via automated text messages. The frequency of sending the text messages will be determined based on co-design workshops with stakeholder groups. Consumers will be given a summary report of their data and access to the interactive data visualization tool (Figure 2).

Based on interventions to improve AME reporting [32], which report a relative risk of 2.04 (57% in intervention group vs 28% in controls), α value (significance level: rejecting the null hypothesis when it is actually true) of .05, and power of 80%, a total of 80 consumers experiencing and reporting AME is needed. Assuming that 20% of consumers starting medicines experience an AME [33] and half of the consumers will report their AMEs with targeted prompts from the research team [34], we aim to recruit 800 people for phase 3. The sample size was calculated based on Statistical Power Analysis using R [R Foundation for Statistical Computing] [35]. Initial database analysis in one of our participating clinics with 8 full-time equivalent general practitioners indicated that each general practitioner prescribes a medicine that is new to the patient for about 40 people per month (320 per month for the practice), supporting the feasibility of recruitment of 800 participants within 6 months.

To assess whether the platform improved AME detection, interrupted time series analysis will be used to determine the proportion of AME detected before and post platform implementation in the general practices. A random sample of up to 1000 patient records in the participating general practices will be manually reviewed by nurses at the practices to determine the number of AMEs detected up to 3 months prior to platform implementation. Furthermore, we will describe the number of AME reports submitted to the TGA by our study participants post platform implementation.

Finally, we will conduct 2 focus group discussions with the project team and stakeholders to evaluate the implementation process (what works, where, and why) [20], the acceptability of, and satisfaction with the platform. Questions related to the implementation process will be adopted from the Consolidated Framework for Implementation Research interview guide tool [20]. The focus group discussions will be audio-recorded, transcribed, and analyzed using thematic analysis [25].

Figure 2. Flowchart for platform implementation in Australia. GP: general practitioner; TGA: therapeutic goods administration.



Ethical Considerations

Ethics approval for phases 1 and 2 has been received from the University of South Australia human research ethics committee (application ID 204984). Ethics approval will be sought from the same committee prior to starting phase 3. Informed consent will be sought from all participants. All data obtained during the project will be deidentified. Participants in any phase of the project will receive compensation at an hourly rate, provided as either a gift voucher or a direct bank transfer in Australian dollars (Aus $). Compensation rates, approved by the human research ethics committee, are set at Aus $35 (US $21.85) per hour for consumers, Aus $200 (US $124.88) per hour for medical doctors, and Aus $100 (US $62.44) per hour for pharmacists and nurses. Furthermore, participants attending in person will receive a transportation allowance of Aus $30 (US $18.73). No compensation will be provided to regulators, as they are prohibited from accepting it.

Results

This project is initiated in 2023 and will run until 2026. Phase 1 will result in persona profiles and user journey maps that define the standards for the user-friendly web-based communication platform and interactive data visualization tool or dashboard. This platform will be further developed and improved in phase 2. The platform will contain fully refined user interface features, an icon system for nonverbal communication, and integration with TGA's Database of Adverse Event Notifications to support the reporting of AMEs by consumers and health care professionals. The final phase—phase 3—will provide insights of the implemented platform regarding its impact on AME detection, management, and reporting. Altogether, the efforts will result in a platform through which consumers can report AMEs to their general practitioners and pharmacists and TGA. We will publish findings progressively as we complete our analyses. In addition to the traditional research outputs (journal articles and conference papers), the designers on our project team will develop a series of nontraditional research outcomes including the dissemination of visual outcomes in the form of a public exhibition, either on the web or in person. We will organize public displays of the visual works at multiple venues in Australia to increase awareness and discussions about the importance of detecting, managing, and reporting AMEs. We will promote the exhibitions and project findings through our teams' respective institutions' media platforms.

Discussion

Expected Findings and Implications

Medicine safety is complex and requires well-developed systems, strategies, and processes to keep consumers safe. Effective systems and strategies for AME detection, management, and reporting are crucial to ensure that medicines are used safely and effectively. However, AME reporting by consumers remains low [14]. Instead, consumers were generally more likely to report AMEs to doctors or pharmacists [36], potentially stemming from inadequate or lacking systems that enable the proactive detection and management of AMEs. Our project will bring these 2 aspects together to build what we hypothesize to be a single, readily available solution that integrates AME detection and management by consumers in consultation with their general practitioners and pharmacists and which also potentially benefits AME reporting to regulators. As such, our project aims to serve both patient-level clinical needs and population-level regulatory needs on medication safety issues.

The level of end user involvement during the development phase of digital interventions that are implemented in practice is unclear. Despite the development of numerous digital interventions to improve medicine management and safety, the minimal engagement of end users in this process and a failure to meet their needs adequately result in the low adoption of these interventions in practice [37]. For instance, the implementation of GuildCare (GuildLink), an AME surveillance system designed for Australian community pharmacists, was introduced in 2014. While the initial year saw a notable increase in AME reporting rates to the TGA, the subsequent year saw a decline, hinting at challenges in maintaining sustained adoption [38]. Factors influencing the adoption and ongoing use of digital health technologies include cost, simplicity of language, ease of use, design, scientific evidence base, motivation, and perceived value by end users [22-24]. To effectively tackle the challenges related to fulfilling the requirements of stakeholders

and overcoming low adoption rates, our project takes a unique approach by grounding it in a multidisciplinary ideology from its outset. This includes collaborating with experts from various disciplines including medicine safety, co-design, user-experience design, communication design, psychology, engagement, and cybersecurity to address fundamental issues that predict successful implementation of the system in practice. This partnership, grounded in a co-design methodology, also represents one of the first instances where a digital intervention for AMEs is coproduced with consumers, health care professionals, and the regulators. The approach seeks to ensure that the digital intervention directly addresses the needs of the 3 stakeholder groups, thereby increasing the likelihood of adoption in practice and ensuring its long-term sustainability.

AME reporting by consumers has the potential to improve the safety of medicines. In a previous study conducted in Australia, despite acknowledging limited awareness, consumers expressed a positive attitude toward AME reporting [15]. The perceived lack of benefits for the reporting consumer, however, was recognized as a barrier to the reporting process [15]. The significance of our proposed platform lies in its potential to incorporate consumers' voices into their medicine and health care journey, enabling consumers to report AMEs to their health care professionals and to the regulators. If successfully implemented, the proposed platform has the potential to result in an increase in the proportion of consumer AME reports submitted to the TGA, which currently accounts for only 3.4% of the total reports submitted to the TGA [39].

There has been a decline in the percentage of AME reports from doctors in Australia, decreasing from 28% in 2003 to 4% in 2016 [36]. The potential increase in participation by consumers through use of our proposed platform may contribute to increased identification of safety signals. By streamlining the AME reporting process to the TGA, our platform has the potential to contribute to more timely detection and verification of potential medicine safety signals. This initiative addresses a national [40] and global health priority [41] and addresses 2 components of the Australia's National Strategy for Quality Use of Medicines: monitoring outcomes and improving people's ability to solve problems related to medicines, such as negative effects.

The introduction of a visualization tool as part of the platform has the potential to enhance end user interaction and participation in research and may facilitate early and effective communication of safety issues to relevant stakeholders. The development of interactive data visualization tools marks a creative initiative to enhance communication and transparency between consumers and regulators. While visualization tools for conveying important public health issues have become common, especially during the Covid-19 pandemic, they frequently lack transparency in describing the development process, fail to engage end users in design and development, and leave uncertainty about whether they adequately meet the needs of those end users [42]. Our user-centric co-design methodology for this project has the potential to ensure that the visualization tools effectively meet the diverse needs of consumers, health care professionals, and regulators alike.

Limitations

First, the success of our digital reporting platform will ultimately rely on the level of user engagement and participation. Robust stakeholder engagement strategies, including co-design workshops and ongoing collaboration, do not guarantee user uptake and continued use. Factors beyond our control, such as accessibility to devices, individual motivation and preferences, and previous negative experiences with reporting, may influence the level to which consumers actively engage in this new digital platform. The introduction of any new system, service, or technology is frequently considered an additional burden or challenge when implemented in practice. However, our early engagement strategy with stakeholders, from phase 1, is designed to potentially mitigate some of this resistance and to increase the chances of adoption. Second, the reliance on interrupted time series analysis for outcome evaluation introduces potential confounding factors that may not be fully accounted. Third, the small number of consumers recruited in phase 3 means that we will not be able to determine whether the platform had an overall effect on the number of consumer reports to the TGA, or whether the reports from our platform helped generate new or different medicine safety signals. Another potential limitation is that phase 3 will be conducted in South Australia, which may restrict the generalizability of findings to the broader Australian population or internationally. However, this limitation will be mitigated by incorporating insights from participants across multiple states in Australia during phases 1 and 2. Finally, certain processes in our project rely on interim review or support from members of the research team. These workflows and processes will require revision and adaptation when implemented in clinical practice.

Conclusions

This paper describes our co-design project that will actively involve key stakeholders in the development and evaluation of a new digital platform for AME detection, management, and reporting, with a central focus on consumers. The use of a co-design methodology ensures the incorporation of the perspectives and requirements from consumers, health care professionals, and regulators—a crucial element for fostering the adoption and sustainability of the intervention. The project harnesses the potential of both consumers and technology to address the existing challenges in underdetection and reporting of AMEs to health care professionals and regulators. The overarching goal is to enable consumers to actively participate in medication safety-related matters, thus enhancing the quality of their lives, influencing clinical decisions related to their health, and contributing to overall medicine safety.

Acknowledgments

The project is supported by a National Health and Medical Research Council (NHMRC) Ideas Grant (APP2020626) and the NHMRC Centre of Research Excellence in Medicines Intelligence (ID: 1196900). RL is supported by an NHMRC fellowship

(APP1156368). PYC is supported by the Wellcome Trust (220211/Z/20/Z). This research is funded in part by Wellcome Trust (220221/Z/20/Z). For the purpose of Open Access, the authors have applied a CC BY public copyright licence to any Author Accepted Manuscript version arising from this submission.

Authors' Contributions

EAG, CT, MT, STdeV, AQA, LKE, OF, PYC, KKRC, TLL, and RL contributed to the conception and design of the project. EAG and RL drafted the manuscript. All authors revised the manuscript critically for important intellectual content and provided final approval to the manuscript.

Conflicts of Interest

None declared.

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Abbreviations

AME: adverse medicine event
COM-B: Capability, Opportunity, Motivation, Behavior
TGA: therapeutic goods administration

Edited by A Schwartz; submitted 01.05.24; peer-reviewed by L McCann, J Yu; comments to author 22.10.24; revised version received 29.10.24; accepted 12.11.24; published 15.01.25.

Please cite as:
Gebreyohannes EA, Thornton C, Thiessen M, de Vries ST, Q Andrade A, Kalisch Ellett L, Frank O, Cheah PY, Choo KKR, Laba TL, Roughead EE, Hwang I, Moses G, Lim R
Co-Designing a Consumer-Focused Digital Reporting Health Platform to Improve Adverse Medicine Event Reporting: Protocol for a Multimethod Research Project (the ReMedi Project)
JMIR Res Protoc 2025;14:e60084
URL: https://www.researchprotocols.org/2025/1/e60084
doi:10.2196/60084
PMID:

Protocol

A Live Video Resiliency Dyadic Intervention for Persons With Dementia and Their Care-Partners Early After Diagnosis: Protocol for Open Pilot of Resilient Together for Dementia

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Abstract

Background: Alzheimer disease and related dementias (ADRDs) are increasingly common progressive conditions that have a substantial impact on individuals and their primary care partners—together described as a *dyad*. The stressors experienced by dyad members at around the time of ADRD diagnosis commonly produce clinically elevated emotional distress (ie, depression and anxiety symptoms), which can become chronic and negatively impact health, relationships, and the overall quality of life. Dyads commonly report unmet needs for early support to address these challenges early after diagnosis.

Objective: This study is part of a larger study that has the primary objective to develop, adapt, and establish the feasibility of Resilient Together for Dementia (RT-ADRD), a novel dyadic skills-based intervention aimed at preventing chronic emotional distress early after diagnosis. The present study protocol describes an open pilot of the RT-ADRD intervention. This study will allow the study team to gather feedback on intervention components, administration of study measures, issues within general protocol, and perceptions about live video interventions prior to a larger feasibility trial.

Methods: All study procedures will be conducted on the web (via phone and health care system–supported videoconferencing) to optimize accessibility, inclusion, and representativeness. Eligible dyads will include couples (up to N=10) referred from Mount Sinai Hospital (MSH) clinics within 3 months of an ADRD diagnosis. Dyads will be referred by their diagnosing clinicians (eg, neurologists, geriatricians, and neuropsychologists) and screened for eligibility. Eligible dyads will have at least one member who exhibits clinically elevated emotional distress and will demonstrate capacity to consent to research participation on a standardized assessment. Consenting dyads will complete baseline assessments of emotional distress, quality of life, relationship

functioning, and resiliency skills. Dyads will then participate in 6 weekly RT-ADRD sessions together (30-60 minutes each). After the conclusion of the intervention, dyad members will complete posttest assessments with similar measures as the pretest. Finally, dyads will participate together in a single 60-minute exit interview to gather information on intervention content and procedures to refine the intervention before a pilot feasibility trial.

Results: This study has been approved by the MSH institutional review board and is registered on ClinicalTrials.gov (NCT06421545). We anticipate that the study will be completed by late 2024.

Conclusions: We will use these results to administer changes and develop procedures for a pilot feasibility trial of RT-ADRD relative to a minimally enhanced control condition. Our study will allow us to gather comprehensive information on proposed RT-ADRD procedures and content and the best ways of delivering prevention-focused interventions to reduce the potential for chronic emotional distress stemming from ADRDs.

International Registered Report Identifier (IRRID): DERR1-10.2196/60382

(JMIR Res Protoc 2025;14:e60382) doi:10.2196/60382

KEYWORDS

dementia; dyad; emotional distress; intervention; diagnosis; telehealth; resilient; dyadic intervention; care-partner; Alzheimer's disease; ADRD; psychosocial; depression

Introduction

Background

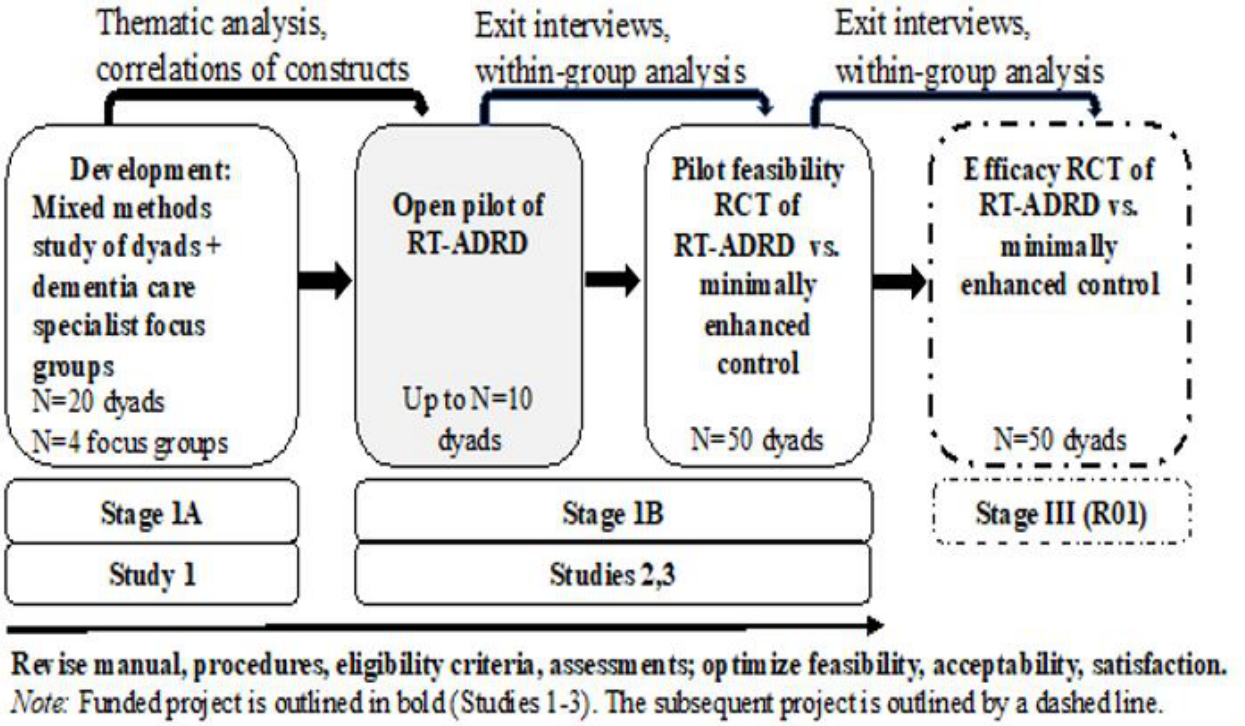
Alzheimer disease and Alzheimer disease-related dementias (ADRDs) are conditions characterized by progressive declines in memory, language, behavior, and personality and produce early symptoms that include increased forgetfulness, communication challenges, and loss of recognition of places, time, and routines [1-3]. These early symptoms tend to worsen over time and undermine the independence, health, and well-being of persons living with ADRDs and their family care partners, many of whom are romantic or spousal partners [4-6]. Because both individuals and their partners (often referred to as "the second patient") experience life disruptions stemming from ADRD symptoms that amplify stress, role changes, and relationship strain [6,7], both individuals and their romantic partners require early support [8]. This need is ever more pressing; by 2030, it is expected that 75 million individuals will be living with ADRD worldwide [5].

In the time following the onset of ADRD symptoms and particularly after receiving a formal diagnosis, many individuals (23%-53%) and their care partners (35%-50%) experience clinically elevated emotional distress (ie, depression and anxiety symptoms) [9-13]. These elevated rates are not surprising given the poor prognosis and lack of disease-modifying interventions for ADRDs, limited resources to assist with early challenges, difficulties engaging in social support, and changes to established roles and responsibilities (eg, caretaking) [14-16]. Early emotional distress is an important intervention target in dyads facing ADRDs for several reasons. First, distress is *interdependent* (ie, correlated and bidirectionally influenced) within dyads. Second, untreated distress is likely to become chronic, and chronic emotional distress is difficult to treat and linked to the deterioration of dyads' physical and mental health, relationship quality, and quality of life [9,14,17,18]. Third, distress interferes with dyads' ability to effectively communicate and cope with early challenges linked to ADRDs, which can impact long-term adjustment [9,14].

Early psychosocial interventions may help individuals with ADRDs and their care partners adjust to challenges and plan collaboratively for the future, which can alleviate distress and maintain overall relationship quality and well-being [8]. Existing interventions for early or moderate-stage ADRDs primarily target family care partners, and several interventions demonstrate lasting improvements in depression symptoms and quality of life [5]. Dyads commonly express strong preferences to participate in interventions together, and dyadic interventions in the first few years of ADRD diagnosis demonstrate promise in reducing dyads' emotional distress as well as neuropsychiatric symptoms expressed by the person living with ADRD [19]. Interventions have historically ignored the "window of opportunity" to meaningfully include persons with ADRDs in interventions shortly after diagnosis, limiting their potential to assist in collaborative treatment and planning before symptoms progress [20-22]. Currently, there are no dyadic psychosocial interventions that prioritize delivery in the first weeks and months after diagnosis to promote dyadic adjustment to ADRDs [20,23-25].

Dyadic interventions may be a more effective, efficient, and economical avenue for promoting positive adjustment to ADRDs for individuals and their care partners earlier in the course of the illness [24,26]. Our team has developed successful dyadic interventions to prevent distress following medical adversity, including Recovering Together, a 6-session dyadic resiliency intervention that addresses emotional distress in patients and informal care partners shortly after neurointensive care unit admission for acute neurological conditions [27,28]. Recovering Together program uses interpersonal theories of adjustment aimed toward preventing chronic stress and transdiagnostic resiliency skills that we expect could also serve as mechanistic treatment targets for other neurological conditions such as ADRDs [29-37]. We then leveraged the NIH (National Institutes of Health) Stage Model for intervention development and in-depth interviews with ADRD clinician experts and dyads (Figure 1) to inform the development of a similar intervention to address early challenges linked to ADRDs [38,39].

Figure 1. Iterative Development of RT-ADRD (Resilient Together for Dementia).



This Study

This study protocol is part of a larger 5-year study that aims to use the prior research, methodology, program content, and procedures of the Recovering Together program as a basis for developing the novel Resilient Together for Dementia (RT-ADRD). Our primary objective is to describe the protocol for the open pilot study of RT-ADRD that will inform a subsequent pilot feasibility trial of the program relative to a control condition (NIH Stage Model Stage 1a). In this study, we aim to gather comprehensive information from dyads regarding the feasibility of assessment, feedback on the intervention components, applicability of study measures, and to identify potential issues prior to the feasibility trial.

Methods

Ethical Considerations

This open pilot study was approved by the Icahn School of Medicine at Mount Sinai Independent Review Board (23-01360) and is registered on ClinicalTrials.gov (NCT06421545). Participants will provide electronic consent to participate via the REDCap (Research Electronic Data Capture; Vanderbilt University) HIPAA (Health Insurance Portability and Accountability Act)-compliant web-based application using a hospital-approved e-consent feature. Prospective participants will be given ample time to review the contents of the consent form as well as speak with the study coordinator who will provide detailed information about the study and answer any questions. The participants will also be reminded that they may decline to participate and can discontinue participation at any time. Participants will be given a copy of the consent form and will be invited to ask questions about their participation at any point over the course of the study. The identity of the participants will not be revealed in the presentation or publication of any results from this project. To protect confidentiality, all data will be deidentified and only identifiable by subject codes. Participants will be individually compensated US $80 for completion of the pre- and posttest assessments, for a total of US $160 per dyad at the end of the program.

Study Design

We will conduct an open pilot of RT-ADRD dyadic intervention involving dyads comprising (1) individuals with a recent ADRD diagnosis and (2) their spousal or romantic care partners, with a target recruitment of up to N=10 dyads, or 20 total participants. This study is designed to gather data that can be used to revise the intervention before a larger pilot feasibility trial.

Inclusion and Exclusion Criteria

Eligible participants will be adult dyads who are partners that currently live together and are willing to participate in the RT-ADRD intervention that are (1) English speaking, (2) patient with newly diagnosed (within 3 months) with an ADRD diagnosis after age 65 years (determined by medical chart review and provider referral), (3) patient with cognitive assessment scores and symptoms consistent with early-stage ADRD, as determined by Clinical Dementia Rating scale scores of 0.5 (very mild) or 1.0 (mild dementia) and Montreal Cognitive Assessment (MoCA) scores of 17-25, obtained via a review of medical records (if patients do not have cognitive assessment scores available, we will administer the MoCA to confirm eligibility), (4) either partner demonstrates clinically elevated emotional distress, as determined by Hospital Anxiety and Depression Scale [40], subscale scores >8 or Geriatric Depression Scale [41], scores > 5, and (5) both partners demonstrate the ability to understand study and research protocol, as determined by the University of California Brief Assessment of Capacity to Consent [42], >12. Individuals will

not be eligible for the study if (1) either partner has a co-occurring terminal illness, and (2) patient was diagnosed with forms of dementia with clinical profiles that would preclude participation (eg, highly symptomatic Frontotemporal Dementia–behavioral variant), as determined by the treatment team.

Study Procedures

Dyads will be recruited from the Mount Sinai Departments of Neurology, Geriatrics and Palliative Medicine, and the hospital system's broader dementia clinical care infrastructure. We will circulate information via flyers, presentations, and word-of-mouth referrals, and dyads can be self-referred or be referred by their treating dementia care providers. The study team will present the aims to all staff at the clinics to explain the purpose of the study, potential benefits to participants, and discuss best ways to facilitate referrals. The study team obtained a waiver of informed consent for the purpose of eligibility screening and will also review electronic medical records of patients treated in relevant clinics to inform providers of potential eligibility prior to diagnostic disclosure visits. All recruitment, screening, and consent procedures will be performed remotely via telephone, electronic survey through REDCap, email, and over a live video using health care system–supported videoconferencing.

Treating providers will obtain permission from the dyad to be contacted by the study team. If self-referred, interested dyads will also have the option to respond to a brief survey via QR code or URL to a secure REDCap platform listed on the distributed study flyers. The study team will contact interested participants via telephone to schedule a telephone or live video call with the study research assistant, who will describe the study to potential participants and conduct screening for eligibility (including capacity to consent). If either dyad member is deemed ineligible based on screening criteria, the study team will provide dyad with a comprehensive list of resources containing local and national resources and document ineligibility in REDCap. If eligible and interested in participating, individuals will complete consent procedures by indicating verbal consent and documenting electronic consent a secure password-protected REDCap platform.

After enrollment, participants will be sent a baseline survey via a secure REDCap link to assess demographics, emotional distress, resiliency factors, and relationship functioning. Participants can also complete assessments via health care system–supported videoconferencing with the help of a trained research assistant. Once the dyad has completed the baseline survey, a member of the research team will schedule the first of 6 RT-ADRD treatment sessions together led by a PhD-level clinical psychologist with expertise in conducting dyadic interventions (SB). In advance of the treatment session, the dyad will be sent copy of the treatment manual to review the skills that will be taught during the 6-week treatment program. Each session will be audio recorded for the purpose of manual refinement. After completing treatment, dyad members will complete a similar set of surveys at posttest. Finally, they will participate in a single 60-minute exit interview together to gather comprehensive feedback on the material to further refine the intervention. Each dyad member will be compensated US $80 for completion of the pre- and posttest assessments, for a total of US $160 per dyad at the end of the program.

RT-ADRD Intervention Content

The RT-ADRD intervention will have 6 weekly live video treatment sessions lasting 30-60 minutes each delivered over health care system–supported videoconferencing; in-person and hybrid session options will be available as well, according to dyad preference. The content and procedures were developed by adapting the Recovering Together dyadic resiliency intervention for neurointensive care unit admitted dyads [27], and then revised using feedback from interviews with dementia care specialists [38], and from dyads interviewed after ADRD diagnosis [39]. Sessions for RT-ADRD contain content and training in resiliency skills that are particularly relevant after ADRD diagnosis for patients and their care partners. RT-ADRD was designed to include individual and interpersonal coping skills that are *transdiagnostic* (ie, relevant across mental and physical health conditions) and drawn from prominent evidence-based therapy approaches (eg, mindfulness, Dialectical Behavior Therapy, and Cognitive Behavioral Therapy). The sessions emphasize ways of using skills to cope with the common challenges experienced early after dementia diagnosis and focus on navigating challenges as a dyadic unit Dyads will also receive links with downloadable recordings of exercises for home practice of skills. The sessions are modular in nature, and dyads will choose 6 modules from a selection of 8 possible modules. The 8 modules are presented in Table 1.

Table 1. Sessions' outlines for the Resilient Together for Dementia (RT-ADRD) program.

Sessions	RT-ADRD topics	Content and skills (all sessions include home-practice of skills)
1	Being in the Here and Now	Deep breathing, mindfulness, and 24-hour block
2	Complex and Conflicting Experiences	Dialectics, mindfulness meditation, and open stress communication
3	Current and Future Challenges	Distress spiral, hands as worries, and acceptance and change
4	Planning and Coping Ahead	Cope ahead, cultivating routines, and coping as a team
5	Difficult Topics	Clarifying goals, effective communication, and relationship repair
6	Relationship Changes	Navigating support and defining roles
7	The Uncertain Future	Goal setting and coping plan
8	Accepting Changes and Making Meaning	Reflection for meaning making

Assessments

After consent, both dyad members will independently complete a pretest survey via a secure REDCap link (~30 minutes each) sent by a research coordinator. If needed, participants will also have the option of completing surveys with the assistance of a trained research coordinator via the videoconferencing "Share Screen" tool. The survey will include validated measures to gather information on hypothesized mechanisms of intervention, intervention targets, and treatment moderators, consistent with the overall conceptual model (Figure 2). The primary intervention targets (Table 2, secondary outcomes) are individuals' emotional distress, relationship quality, and quality of life, which were selected based on their interdependence within dyads and the link of emotional distress to long-term mental and physical health outcomes and relationship functioning [9,14,17,18]. The hypothesized intervention mechanisms (Table 2; described further below) are transdiagnostic resiliency skills that demonstrated links to the same intervention targets in studies of prior dyadic interventions [27]. Following completion of the treatment sessions, dyads will complete a similar posttest survey in REDCap. Responses will be used to compare scores to population norms, examine interrelations among constructs, and inform procedures and the tailoring of RT-ADRD. The primary outcomes for this trial are feasibility and acceptability. In addition, we will use the 6-item Credibility and Expectancy Questionnaire [43] to assess treatment credibility at baseline. We will also use the 3-item Client Satisfaction Questionnaire [44] to assess satisfaction with RT-ADRD at posttest. We will gather comprehensive qualitative feedback on these benchmarks and report detailed information on study screening, enrollment, and intervention deliveries via health care system–supported videoconferencing or in person, to refine feasibility and acceptability benchmarks prior to further testing. A description of study measures is provided below (Table 2).

Figure 2. RT-ADRD Conceptual Model.

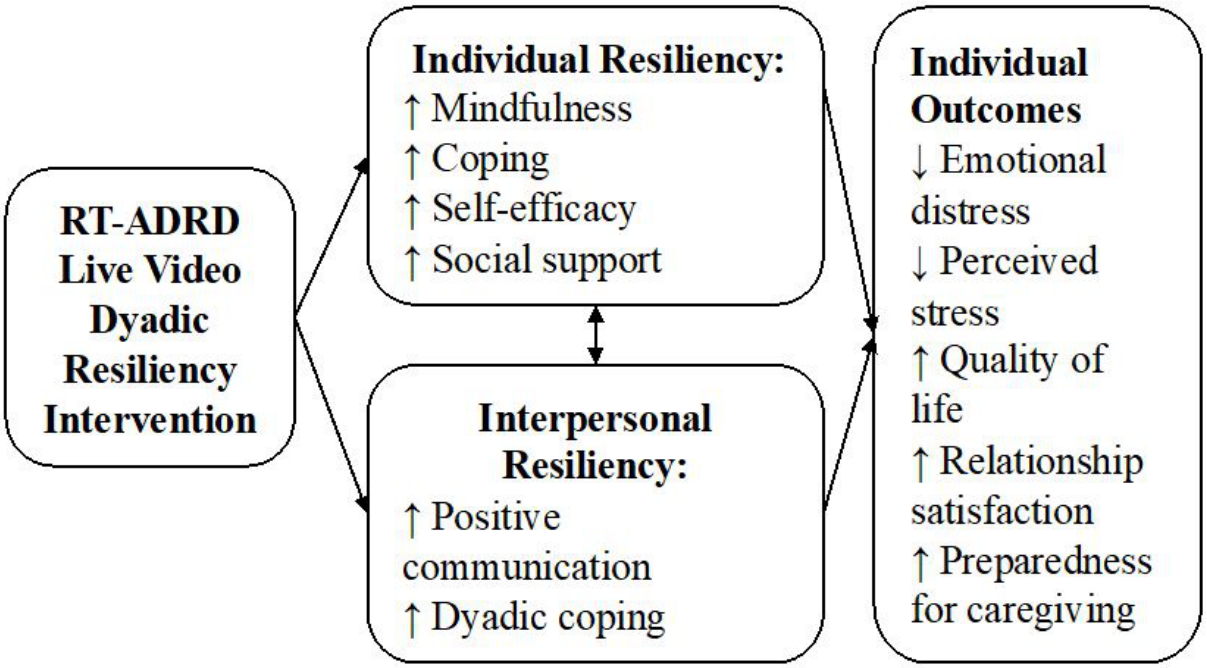


Table 2. Assessment measures.

Construct	Description	Base	Post
Primary outcomes			
Feasibility	• Procedures: suitability and practicality of RT-ADRD[a] and procedures; qualitative feedback from exit interviews	X	X
	• Screening: proportion of dyads who screen eligible of those who undergo screening		X
	• Recruitment and Consent: proportion of dyads who are approached and agree to participate in the intervention		X
	• Engagement: proportion of dyads who are enrolled and complete 4 out of 6 sessions		X
	• Assessment: proportion of individuals who are enrolled and complete baseline and post-test assessments		
Acceptability	• Credibility and Expectancy Questionnaire (6 items)—assess how credible dyads perceive RT-ADRD	*X*	*X*
	• Client Satisfaction Questionnaire (3 items)—a measure of satisfaction with RT-ADRD		*X*
	• Qualitative feedback from exit interviews		
Covariates			
Demographics	• Review of medical records and participant self-report: age, sex and gender, race and ethnicity, education, and income		
Clinical Characteristics	• Review of medical records and participant self-report: type of ADRDb diagnosis, time since diagnosis, and cognitive tests	X	
Secondary Outcomes			
Emotional Distress	• Hospital Depression and Anxiety Scale (14 items)—a measure of emotional distress (anxiety and depression subscales) Geriatric Depression Scale (15 items)—a measure of depression symptoms	X	X
		X	X
Perceived Stress	• Perceived Stress Scale (4 items)—a measure of perceived stress	X	X
Quality of Life	• WHO Quality of Life-Short Form (26 items)—a measure of quality of life	X	X
Relationship Satisfaction	• Couples Satisfaction Inventory (16 items)—a measure of couple relationship satisfaction	X	X
Preparedness for Caregiving (Care partners only)	• Preparedness for Caregiving Scale (8 items)- readiness for caregiving in relation to spouse	X	X
Intervention Mechanisms			
Mindfulness	• Cognitive and Affective Mindfulness-Scale (12 items)—a measure of mindfulness skills	X	X
Coping	• Brief COPE (28 items)—a measure of adaptive and maladaptive coping strategies	X	X
Self-efficacy	• General Self-Efficacy scale-6 (6 items)—a measure of self-efficacy	X	X
Social Support	• Social Support Questionnaire, Short Form—Revised (12 items)—a measure of satisfaction with social support	X	X
Interpersonal Communication and Coping	• Dyadic Relationship Scale (10 items—patients, 11 items—caregivers)—a measure of positive and negative dyadic interactions	X	X
	• Dyadic Coping Inventory (9 items)—a measure of dyadic stress management	X	X

Covariates

We will collect demographic information on participants' gender, age, race, ethnicity, marital status, relationship length, education level (number of years in school), employment (status, occupation, and income), and mental health history. We will also collect ADRD clinical characteristics via electronic medical records, including the type of diagnosis, age at diagnosis, and date of diagnosis.

Secondary Outcomes

Overview

We will use the 14-item Hospital Anxiety and Depression Scale (HADS) [40] total score to assess emotional distress once at

baseline, and again at the completion of the program. We will examine the 7-item depression and anxiety subscales of the HADS separately (HADS-D and HADS-A, respectively). Scores range from 0 to 21, where a score >7 indicates significant depression or anxiety. We will also use the 15-item Geriatric Depression Scale–Short Form [41], to assess depression symptoms over the past week. Scores range from 0 to 15, with scores ≥5 suggesting the presence of clinically elevated depression symptoms. We will assess perceived stress over the past month using the Perceived Stress Scale [45]. Scores range from 0 to 16, with higher scores indicating greater perceived stress. To assess perceived quality of life, we will use the 26-item brief World Health Organization Quality of Life assessment [46], which captures quality of life across 4 subscales (physical health, psychological, social relationships, and environment). The first 2 items provide a global assessment of quality of life, and the subscale scores are calculated by summing items and transforming scores to a 0 to 100-point interval, with higher scores indicating a greater perceived quality of life. To assess relationship satisfaction, we will use the 16-item Couple Satisfaction Index [47]. Total scores range from 0 to 81, with higher scores indicating greater relationship satisfaction. Finally, for spousal care partners we will use the 8-item Preparedness for Caregiving Scale (9) to evaluate readiness for caregiving in relation to their spouse. Total scores range from 0 to 32, with higher scores indicating greater preparedness for caregiving.

Treatment Mechanisms

We selected treatment mechanisms assessing individual and dyadic coping and relationship functioning based on our hypothesized mechanisms underlying changes in proposed outcomes (ie, emotional distress, quality of life). We will use the 12-item Cognitive and Affective Mindfulness Scale, Revised [48], to assess mindfulness. Total scores range from 12 to 48, with higher scores indicating greater engagement in mindfulness practices. We will use the 28-item Brief Coping Orientation to Problems Experienced (Brief COPE) [49], to measure ways of individually coping with stressful events. The Brief COPE includes three subscales that assess coping styles: (1) problem-focused (8 items), (2) emotional-focused (12 items), and (3) avoidant coping (8 items). Scores for each subscale are calculated by taking the mean of all items, with higher scores indicating greater use of that coping style. We will assess perceived self-efficacy with the 10-item General Self-Efficacy Scale [50]. Total scores range from 10 to 40, with higher scores indicating greater perceived self-efficacy. We will use the 12-item brief Social Support Questionnaire (SSQR) [51] to assess social support availability and satisfaction. The SSQR consists of 2 subscales: support network availability (SSQR-N) and overall satisfaction (SSQR-S). Each item assesses support availability and satisfaction in separate parts; participants will be asked to indicate (1) how many people they can count on for various types of support and (2) how satisfied they are with the support. The SSQR-N subscale composite is calculated by taking the mean of all items. For the SSQR-S subscale, total scores are calculated by adding subscale items and range from 6 to 36, with higher scores indicating greater social support satisfaction.

To assess the perceptions of dyadic stress management, we will use the items from the Dyadic Coping Inventory [52,53] subscales: common dyadic coping and negative dyadic coping. The common dyadic coping subscale includes 5 items that assess dyads' ability to cope with problems together and search for solutions. Scores range from 5 to 25, with higher scores indicating greater perceptions of the dyad's use of common coping. Negative dyadic coping will also be assessed using the Dyadic Coping Inventory (4 items). Scores range from 4 to 20, with higher scores indicating greater perceptions of the dyads using negative dyadic coping. In addition, we will assess dyadic relationship strain in the context of caregiving using the dyadic strain subscale of the Dyadic Relationship Scale (DRS) [54], which has a 10-item-Patient version and an 11-item Caregiver version. Subscale scores range from 1 to 10 and 1 to 11 for the DRS-Patient and DRS-Caregiver, respectively, with higher scores indicating greater relationship strain.

Exit Interviews

At the conclusion of the intervention sessions, dyads will participate together in a single 60-minute exit interview over health care system–supported videoconferencing to gather information on session content and procedures to refine intervention methods prior to the feasibility trial. Topics will include: what was most and least helpful about the intervention, topics or skills that were not included that might be helpful, whether additional sessions would be preferred, perceptions of skills, comfort with participating in sessions together, and barriers and facilitators of engagement in RT-ADRD procedures and the intervention. A trained research assistant will complete the interviews using an interview guide (see Supplemental Materials). As part of the interview, the research assistant will also capture observations within session domains, important quotes, and other important notes using a rapid data analysis template.

Data Analysis

Feasibility-related measures will be assessed and compared to our prior dyadic intervention studies [27] using proportions at the individual-level on feasibility markers outlined in Table 2, as well as qualitative feedback from exit interviews. Acceptability will be evaluated with the percentage of individuals with scores above the midpoint on self-report questionnaires (Table 2), as well as feedback from exit interviews. Given our primary goal of establishing feasibility and acceptability, this open pilot was not powered to statistically evaluate signal of improvement in quantitative outcomes. However, we will examine preliminary effectiveness of the secondary outcomes using estimated treatment effects for each measure. We will also assess the relationship among treatment mechanisms and secondary outcomes using bivariate correlations, focusing on whether the direction of the association is consistent with our conceptual model. Qualitative data obtained from exit interview transcripts will be analyzed using a rapid data analysis approach to thematic analysis [55]. We will use overarching themes surrounding feasibility markers and participant suggestions to further refine the intervention.

Results

This study was supported by a grant from the National Institute on Aging (1K23AG075188-02) to SB. It was approved by the institutional review board of the Mount Sinai Hospital in April 2024. Recruitment began in April 2024 and will continue through August 2024. Data collection and analysis is anticipated to be complete by August 2024.

Discussion

Anticipated Findings

ADRDs are conditions that are increasingly common among the aging population and have considerable negative impacts on individuals living with ADRD and their spousal care partners [5]. Currently, these dyads have few resources to assist them in navigating early challenges together and adjusting positively to the diagnosis and symptoms [24,25]. Dyads describe an interest in participating in interventions together early after ADRD diagnosis to assist in navigating support and adjusting to symptoms [8]; however, no such interventions exist. Adapting existing interventions has the potential to be effective and efficient in addressing dyads' challenges to promote dyadic adjustment [27,28], and aid in preventing chronic individual and interpersonal stress. Thus, the RT-ADRD program is a timely potential solution to unmet needs reported by dyads at the time of ADRD diagnosis. The present study aims to refine RT-ADRD, a novel dyadic resiliency intervention for dyads at risk of chronic emotional distress early after ADRD diagnoses that includes individual and interpersonal resiliency training for both dyad members simultaneously to promote adjustment to ADRD.

The larger plan to develop and revise RT-ADRD is guided by the NIH Stage Model for behavioral intervention development [56]. This protocol provides the framework of our open pilot trial of RT-ADRD, stage 1B of the development of RT-ADRD. The intervention is novel and flexible, providing live video delivery of treatment sessions to maximize feasibility and adherence, while also providing the option of in-person sessions upon request. We will use the open pilot results to refine the program and inform the subsequent stage—a larger feasibility trial of RT-ADRD relative to an educational control condition (target N=60 dyads).

Limitations

Currently, we are only conducting the intervention in English and with couple dyads. This results in important limitations for non–English speakers and for other caregiving dyads commonly facing ADRDs (eg, parent-child dyads). We plan to address these limitations with parallel studies and in subsequent trials by creating a version of the program in Spanish using established guidelines for linguistic adaptation. We also plan to conduct additional qualitative studies to identify adaptations needed to address a range of caregiving dyads.

Conclusions

The results from this open pilot trial will be used to inform the development of Resilient Together for Dementia, a dyadic resiliency program for those living with ADRDs and their romantic or spousal care partners. Our study will provide quantitative and qualitative data that we will use to refine the current iteration of the program. We will then test the refined intervention in a larger feasibility trial relative to an educational control condition.

Acknowledgments

We would like to thank the members of the Center for Health Outcomes and Interdisciplinary Research at Massachusetts General Hospital (MGH CHOIR) laboratory members and the MGH CHOIR Recovering Together Working Group for their feedback on proposed open pilot procedures and the first version of the RT-ADRD manual. This study was funded by grants from the National Institute on Aging (1K23AG075188-01A1) to SB, and grants from the National Institute of Nursing Research (R01NR019982-01) and National Center for Complementary and Integrative Health (1K24AT011760-01) to AV. We would also like to acknowledge Dr. Jonathan Jackson for his contributions to the larger study design and proposed procedures that informed the current study protocol.

Data Availability

Data collection and analysis instruments are available in the Multimedia Appendices. The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Conflicts of Interest

BD is a Consultant for Acadia, Alector, Arkuda, Biogen, Cervomed, Eisai, Genentech, Ilios, Lilly, Merck, and Quanterix. BD receives royalties from Cambridge University Press, Elsevier, and Oxford University Press.

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Abbreviations

ADRD: Alzheimer disease and related dementia
Brief COPE: Brief Coping Orientation to Problems Experienced
DRS: Dyadic Relationship Scale
HADS: Hospital Anxiety and Depression Scale
HIPAA: Health Insurance Portability and Accountability Act
MoCA: Montreal Cognitive Assessment
NIH: National Institutes of Health
REDCap: Research Electronic Data Capture
RT-ADRD: Resilient Together for Dementia
SSQR: Social Support Questionnaire
SSQR-N: Social Support Questionnaire-network availability
SSQR-S: Social Support Questionnaire-overall satisfaction

Edited by T de Azevedo Cardoso; submitted 17.05.24; peer-reviewed by U Sinha; comments to author 04.07.24; revised version received 16.07.24; accepted 22.07.24; published 15.01.25.

Please cite as:
McCage S, Walker K, Cornelius T, Parker RA, Dams-O'Connor K, Dickerson B, Ritchie C, Vranceanu AM, Bannon S
A Live Video Resiliency Dyadic Intervention for Persons With Dementia and Their Care-Partners Early After Diagnosis: Protocol for Open Pilot of Resilient Together for Dementia
JMIR Res Protoc 2025;14:e60382
URL: https://www.researchprotocols.org/2025/1/e60382
doi:10.2196/60382
PMID:

Protocol

Evaluation of the Feasibility of Transfusing Leukocyte Depletion Filter–Processed Intraoperative Cell Salvage Blood in Metastatic Spine Tumor Surgery: Protocol for a Non–Randomized Study

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Abstract

Background: Metastatic spine tumor surgery (MSTS) is often complex and extensive leading to significant blood loss. Allogeneic blood transfusion (ABT) is the mainstay of blood replenishment but with immune-mediated postoperative complications. Alternative blood management techniques (salvaged blood transfusion [SBT]) allow us to overcome such complications. Despite widespread use of intraoperative cell salvage (IOCS) in oncological and nononcological surgical procedures, surgeons remain reluctant to use IOCS in MSTS.

Objective: This study aims to analyze safety of IOCS-leukocyte depletion filter (LDF)–processed blood transfusion for patients undergoing MSTS by assessing clinical outcomes—disease progression: tumor progression and overall survival. This study evaluates whether reinfusion of IOCS-LDF–processed blood reduces ABT rates in patients undergoing MSTS by sorting patients undergoing MSTS who require ABT into patients who consent to receive or not receive SBT.

Methods: We aim to recruit a minimum of 90 patients—30 patients for SBT, 30 patients for ABT, and 30 patients with no blood transfusion. SBT and ABT form the 2 experimental arms, whereas no blood transfusion forms the control cohort. Available patient data will be reviewed to determine tumor burden secondary to metastasis and postoperative survival and disease progression, improvement in pain, and neurological and ambulatory status. Data collected will be studied postoperatively at 3, 6, 12, 24, 36, and 48 months or until demise, whichever occurs first. Outcomes of the experimental groups will be compared with those of the control group. Outcomes will be analyzed using 1-way ANOVA and Fisher exact test. The Kaplan-Meier curve and a log-rank test will be used to study overall survival. A multivariate and competing risk analysis will be used to study the association between blood transfusion type and tumor progression. All statistical analyses will be done using Stata Special Edition 14.0 (StataCorp LP).

Results: This is the largest clinical study on use of IOCS in MSTS from various primary malignancies to date. It will provide significant clinical evidence regarding the safety and applicability of IOCS in MSTS. It will help reduce use of ABT, improving overall blood management of patients undergoing MSTS. A limitation of this study is that not all patients undergoing MSTS will survive for the follow-up period (4 years), theoretically leading to underreporting of disease progression. Study commenced in 2016 and patient recruitment continued till 2019. As of September 2019, we have collected operative data on 140 patients. However, the 2-year outcomes of about 40.0% (56/140) of patients are in the process of collection. The study is aimed to be published in the years 2023-2024.

Conclusions: Results will be disseminated via peer-reviewed publications, paving the way for future studies.

International Registered Report Identifier (IRRID): DERR1-10.2196/54609

(JMIR Res Protoc 2025;14:e54609) doi:10.2196/54609

KEYWORDS

blood transfusion; autologous blood transfusion; operative blood salvage; leukocyte reduction filtration; intraoperative blood cell salvage; extramedullary spinal cord compression; metastases; tumors; leukocytes

Introduction

Background

The skeletal system is the third most common site of metastases, and cadaveric studies show that spinal metastases can be found in 30% to 90% of patients who die of cancer [1,2]. Surgery for metastatic spine disease (MSD) is complex, often requiring wide resection and extensive reconstruction leading to significant blood loss [1,2]. Emergency surgical treatment is often indicated for spinal cord compression with actual or impending paralysis or for spinal instability with severe pain that reduces the quality of life and mobility [3].

Typical blood loss in a patient undergoing tumor decompression and instrumentation in the thoracic and lumbar spine is about 1500 mL, and this requires an average of 3 units of packed red blood cells [4,5]. This blood loss is currently replenished by allogeneic blood transfusion (ABT) across the world, placing a significant burden on the already limited blood bank resources [6,7]. On the contrary, there is increasing evidence of the deleterious effects of ABT. Many studies have shown an increased incidence of postoperative infections [8] and promotion of tumor growth [8,9], which is thought to occur secondary to immunosuppression and other transfusion reactions.

Despite evidence describing multiple postoperative complications related to ABT [10,11], it remains to be the mainstay of blood replenishment in patients with heavy intraoperative blood loss [12]. These are immune-mediated complications and commonly affect the lungs (eg, transfusion-related acute lung injury) [13,14], wound healing [15-17], and survival duration [11,16]. This has prompted efforts to decrease reliance on ABT and to increase the utilization of alternatives, such as autologous predonation or intraoperative cell salvage (IOCS). Autologous predonation may not always be possible in metastatic spine tumor surgery (MSTS) because of suboptimal patient status, medical comorbidities, and in cases where emergency surgery is indicated.

Patient blood management is an evidence-based, patient-tailored approach aimed at reducing the need for ABT and its associated risks [18]. Patient blood management has both preoperative and perioperative components. Preoperative techniques include patient optimization via cessation of antiplatelet and anticoagulant medications [19,20] and anemia management [18]. Perioperative management comprises achieving surgical hemostasis, reinfusion of intraoperatively salvaged blood, the use of erythropoietic agents, and hemostatic drugs such as tranexamic acid. Randomized [21,22] and nonrandomized [23] studies on the use of IOCS in nononcological surgical procedures indicate that salvaged blood transfusion (SBT) significantly reduces the need for ABT [21-23]. Despite extensive use of SBT in orthopedic, trauma, and cardiac surgical procedures [24], the concern of reinfusion of tumor cells leading to disease progression persists [25-27]. The initial lack of literary evidence on the safety of SBT in oncological surgical procedures has made oncological surgeons reluctant to use SBT in MSTS [25-27].

This reluctance dates to an American Medical Council report from 1986, which stated that SBT was not suitable for use in tumor surgery [28]. This was in turn based on a case report from 1975 where tumor cells were found in salvaged blood [29]. There were concerns that tumor manipulation and resection would result in the spillage of tumor cells into the surgical field [30], which would lead to further metastasis if reinfused via SBT. Recent evidence indicates that circulating tumor cells (CTCs), which are shed by the primary tumor [31], are the most likely cause of tumor metastasis in oncological patients. CTCs have been shown to be eliminated by the reticular endothelial system [32], once they fail to metastasize (unable to complete the process of metastasis). Other CTCs may undergo cellular apoptosis after being retained in the capillary bed or the bone marrow [32]. These host defense mechanisms can prevent metastasis by reducing the metastatic ability of the vast majority of CTCs [33]. Consequently, one can ask, “Can SBT with a limited load of damaged malignant tumor cells cause tumor metastasis and disease progression?”

Investigation on the use of salvaged blood in MSTS started with a systematic review that we published [34]. It was envisaged that there is a place for salvaged blood in MSTS, provided the safety of IOCS in MSTS is established by the following steps. Our first step was to establish *basic cellular evidence* that there are no viable tumor cells in the salvaged blood. Second, we aimed to *quantify the number of tumor cells in the salvaged blood*, if any, and to demonstrate that the CTCs in the patient’s own blood are far more than those present in the salvaged blood. Our proposed *final phase* of study was to provide *clinical evidence* that SBT is safe for use in oncological surgical procedures, without increasing the risk of disease progression or tumor recurrence or resulting in poorer prognosis [32].

Our working hypothesis for the preclinical phase of this study was that the blood salvaged from patients undergoing MSTS does not contain viable tumor cells, and even if it did, viable tumor cells in the salvaged blood would be significantly lower than the number of CTCs present in the patient’s own blood at any given point in time. Therefore, there should be no increase in the risk of disease progression, in terms of further tumor dissemination, decreased survival, or increased tumor recurrence.

To test this hypothesis, we first conducted a study that analyzed the morphology and structural integrity of the tumor cells present in the patient’s circulation, operative field, and pre- and postfiltration samples of the salvaged blood [24,35]. Using the cell block technique, salvaged blood in the pre- and postfiltration samples was shown to mostly comprise cytoplasmic debris with no viable nuclei [24,25], thereby establishing the safety of IOCS in oncological surgery [36]. This is also supported by evidence from other studies [37] stating that upon passing through the

IOCS system, 62% of tumor cells were destroyed, whereas the remaining 38% were morphologically altered.

Using flow cytometric studies, we then compared the number of CTCs present in the patient's own blood with that in salvaged blood [38]. We found that salvaged blood contained a significantly lower number of CTCs than those present in the patient's circulation [38]. Furthermore, we provided corroborative evidence that tumor cells passing through IOCS become nonviable and therefore cannot form new metastatic lesions [36]. We were able to demonstrate that CTCs lost the ability to develop into new metastatic lesions after passing through the IOCS apparatus, even without the use of leukocyte depletion filters (LDFs) [36]. LDFs are used to prevent leukocyte-mediated adverse reactions and have applications in both transplant surgery and treatment of hematological conditions [39]. LDFs are used for filtrating blood and have been proven to have the capability to remove tumor cells from the filtrate [38].

Currently, there is ample evidence in the literature for the clinical safety of salvaged blood used in oncological surgical procedures, including gastrointestinal [40], gynecological [41-43], hepatobiliary [40,44-46], and urological [47-54] surgical procedures (Multimedia Appendix 1 [55-64]). Although patients who received SBT required significantly lower amounts of allogeneic blood, their survival rates [44,49,51,52] and disease progression remained comparable with those who did not receive SBT [42,46,54,65]. Patients who received SBT had lower or similar rates of recurrence compared with the control cohort [47,49,51,53].

Despite the validity of the abovementioned literature, there still is hesitation to use IOCS in MSTS [34]. This can be addressed only by using a clinical study. Hence, we have designed this study to analyze the clinical use of IOCS in patients undergoing MSTS.

Objectives

Primary Objectives

This study aims to investigate the following clinical outcomes: disease progression, in terms of tumor progression (increase in size of existing metastatic lesions with or without the appearance of new metastasis), and the overall survival (OS) in patients who receive *IOCS in combination with LDF* (IOCS-LDF)–processed blood during MSTS. Therefore, this study aims to refute the prevailing conception that cell salvage should be avoided in MSTS owing to concerns of tumor dissemination.

Secondary Objectives

The secondary objectives of the study are to investigate whether reinfusion of IOCS-LDF–processed blood can reduce ABT rates in patients undergoing MSTS. We will also compare the length of stay and overall complication rate of patients who receive salvaged blood and those who receive ABT or no blood transfusion (NBT).

Hypothesis

The working hypotheses of this study are as follows:

1. Reinfusion of IOCS-LDF–processed blood of patients undergoing MSTS does not increase the risk of disease progression, in terms of tumor progression (increase in size of existing metastatic lesions with or without the appearance of new metastasis) and OS.
2. Patients receiving IOCS-LDF blood transfusion require less ABT.
3. Patients receiving IOCS-LDF blood transfusion will experience fewer overall complications and shorter length of stay than patients receiving ABT.

Methods

Recruitment

This study aims to recruit a minimum of 90 patients of whom 30 will receive SBT (with or with no allogeneic blood), 30 will undergo ABT, and the remaining 30 will have NBT. From our experience of treating patients with tumor, there are likely to be very few patients who receive only SBT. The majority of patients receiving SBT are likely to receive both SBT and ABT in various proportions. SBT and ABT form the 2 experimental arms, whereas patients with NBT form the control cohort. We will compare the number of patients receiving only SBT with those receiving ABT, if the sample sizes are sufficient.

Patients will be selected from specialist outpatient spine clinics or inpatient wards. These patients may be referred from an inpatient medical oncology team for management, especially in the setting of MSD with cord compression resulting in symptoms such as pain or neurology. A thorough examination of clinical history, physical examination, and review of imaging will be done, and appropriate patient management options will be discussed by the attending orthopedic surgeon. During the enrollment period, whenever a spine surgeon has obtained surgical consent for MSTS in patients with MSD, the principal investigator (NK) will be informed either by a telephone call or by text messaging.

The *research assistant* who is on-site at the National University Hospital during office hours or any member of the research team who is available will interview the patient. During this interview, the interviewer will confirm whether the inclusion criteria are fully met. The study will be explained to suitable subjects, including the advantages as well as possible intra- and postoperative risks of the reinfusion of salvaged blood. A copy of the *patient information sheet and consent form* will be provided to the patient, detailing the recruitment procedures, our objectives, hypotheses, and background information, and any queries will be addressed. Subsequently, written informed consent will be obtained from the patient.

Blood transfusion details will be collected from anesthetists immediately after the operation. Depending on the type of blood transfusion done during the surgery, that is, ABT only or SBT with or with no ABT or NBT, the patient will be categorized into the appropriate study cohort. All patients undergoing MSTS will receive tranexamic acid as an intravenous bolus before induction of anesthesia as per the department protocol, with subsequent top-up dosages every 4 hours during MSTS. If excessive blood loss is expected during surgery, such as in a

separation surgery, continuous infusion of tranexamic acid is given to the patient.

Postoperatively, all subjects will be followed up individually by their operating surgeons, as per the standard of care at the National University Hospital. No additional patient follow-up sessions by the research team will be required. Clinical data and patient outcomes will be accessed via the computerized patient support system and EPIC system at monthly intervals. All available radiological data and clinical notes from the patients' follow-up by their treating surgeons or physicians will be reviewed by the research team. This is to determine the postoperative outcomes such as survival and disease progression. The collected data will be analyzed postoperatively at 3, 6, 12, 24, 36, and 48 months. The data collection and follow-up of available records will continue over a period of 4 years postoperatively or until the patient's demise, whichever occurs first. The collected outcomes of the 2 experimental groups (patients who received SBT with or without ABT) will be compared with those of the control group (patients who received NBT) as well as with the available historical data from the literature.

Statistical Analysis

We have defined *disease progression* as the increase in the size of an existing metastatic lesion or the appearance of a new lesion in the lung, liver, or the spinal column, which can be visualized by using radiological imaging.

Demographic and clinical characteristics of patients will be summarized using mean (SD) values for continuous variables with approximately normal distribution, median (IQR) values for continuous variables with skewed distribution, and frequency (percentage) for categorical variables. A 1-way ANOVA will be used to compare the mean of a normally distributed variable across the 3 blood transfusion groups, whereas a Kruskal-Wallis rank test will be used for the comparison of medians. A Fisher exact test will be implemented for categorical variables accounting for potential small frequencies.

The association between individual characteristics and OS will be studied by using the Kaplan-Meier curve and a log-rank test. The crude hazard ratio and its 95% CI will be used to measure the association between individual characteristics and OS and will be calculated based on their original definitions. Multivariate Cox proportional hazard regression will then be used to adjust for statistically significant confounders for the relationship between the type of blood transfusion and OS. The proportional hazards assumption will be tested after the final model is obtained.

The association between the type of blood transfusion and tumor progression will be investigated by the competing risks analysis, taking death without tumor progression as the competing event. First, cumulative incidence curves of the 3 blood transfusion groups will be plotted nonparametrically, and then we will model the relation via a subdistribution hazard regression model. The measure of association will be quantified by the crude subdistribution hazard ratio; its 95% CI and *P* value will be analyzed in a univariate analysis. Subsequently, a multivariate analysis will be used to adjust for potential confounders. All statistical analyses will be done using Stata Special Edition 14.0 (StataCorp LP). The statistical tests will be assumed to be 2-sided, with the conventional 5% significance level.

Analysis of Primary Outcome Measures

We intend to compare the proportion of patients with MSTS requiring blood transfusion and the amount of ABT required. The primary analysis will be based on the intention-to-treat principle. A Fisher exact test will be used to compare the 2 arms. The exact 95% CI will also be calculated for the difference in the ABT rate between the 2 arms.

Analysis of Secondary Outcome Measures

The progression of disease will be assessed using the internationally accepted Response Evaluation Criteria in Solid Tumors (version 1.1) [66,67]. Disease progression is defined as at least a 20% increase in the sum of the diameters of measurable target lesions (eg, lymph nodes and bone metastases with soft tissue components), unequivocal progression of nontarget lesions (eg, malignant ascites or pleural effusions), or the appearance of 1 or more new metastatic lesions.

Computed tomography of chest or abdomen and pelvis will be used to assess metastases in the lymph nodes, lung, liver, or any abdominal organ, all of which can be visualized adequately. Magnetic resonance imaging of whole spine and nuclear medicine bone will also be performed because of their increased sensitivity in detecting early new spinal or skeletal metastases [68]. A lesion identified in a follow-up study in an anatomical location that is not present at baseline is considered a new lesion and will indicate disease progression.

The OS rate will be defined as the proportion of patients who survive until the end of the study period. Median survival times and 95% CI will be estimated using Kaplan-Meier curves for experimental and control groups. The median OS times will be compared using a log-rank test. The survival rate at 6 months after surgery will also be estimated using Kaplan-Meier curves.

Ethical Considerations

The domain-specific review board of the National Healthcare Group, Singapore (reference numbers: 2014/00065 and 2022/00866), has granted ethical approval for this study. Written informed consent regarding participation in this research study and receiving SBT will be obtained from each patient before the patient is recruited for the study. Data have been anonymized and deidentified. No compensation was provided to patients for this study.

Results

This study has been funded by the National Medical Research Council of Singapore in November 2016 and approved by domain-specific review board of the National Health Group in April 2016.

Data were collected from November 2016 to present (as of submission date of manuscript). Numbers recruited into study, as of submission of the manuscript, were 140. The status of data analysis and expected results are expected to be published in the years 2023-2024, when the information is available.

Discussion

Study Findings

This is the largest prospective clinical study on the use of IOCS in MSTS from a variety of primary malignancies. It will provide significant clinical evidence regarding the safety and applicability of IOCS in MSTS. The clinical safety of the use of IOCS has been established in oncological surgical procedures involving gastrointestinal [40], gynecological [41-43], hepatobiliary [40,44-46,55-57], and urological [47-54,58-62] specialties (Multimedia Appendix 1). However, the use of IOCS has neither been studied nor practiced regularly in metastatic musculoskeletal tumor surgeries (MMTSs). This may be because of the skepticism among surgeons about the safety of SBT in MMTSs, despite the presence of substantial supporting evidence in other surgical specialties in the field of oncology [40-54,63,64]. Amidst all the apprehension regarding IOCS, a retrospective comparative review has shown that SBT indeed reduces the need for postoperative ABT [69]. More recently, the use of SBT has been studied prospectively, demonstrating its safety for IOCS in MSTS [70]. Nonetheless, these studies did not have a comparative arm and had a small sample size.

This prospective clinical study is founded on substantiating evidence that salvaged blood is free from viable tumor cells, proven in our earlier methodical basic sciences approach [32,38]. We aim to study the OS, as well as tumor progression in MSTS patients through analysis of their various outcome measures. The results from this approach will help debunk the prevailing myth that IOCS contributes to disease progression either in the form of new metastasis or in the form of an increase in the size of the index lesion.

Limitations

The limitation of this study is that not all patients undergoing MSTS will survive for the total follow-up period of 4 years, thereby theoretically leading to potential underreporting of disease progression. The sheer number of possible primary tumors in MSD also inevitably leads to heterogeneity, which can be overcome through propensity score–matching analysis.

Broader Implications

Through the reporting of our analysis, this study will help reduce the use of ABT, reduce the burden on blood banks, and improve the overall blood management of patients with MSTS. This improvement in blood management will prevail even with the improvement of surgical techniques in the management of MSTS, that is, introduction of minimally invasive surgery techniques and the regular use of navigation. This is because the 2 techniques mentioned earlier will reduce blood loss during the steps of spinal instrumentation but are unlikely to have any effect on blood loss while performing decompression. Decompression and separation surgery presently still form a major component of MSTS and will continue to do so, resulting in significant bleeding that requires replenishment potentially in the form of SBT.

In this protocol, we have proposed a prospective observational nonrandomized study design as the ethical appropriateness of blinding or randomizing these patients is a key concern in our region and country. Blinding or randomization of patients with MSD could be deemed unethical, especially among patients who may not agree to receive SBT or ABT as this will limit the blood transfusion type applicable for them. This could be attributed to the current lack of clinical evidence that SBT does not lead to disease progression or shortened survival among patients undergoing MSTS who receive SBT. With this research proposal, we aim to highlight the safety profile of SBT, together with a design protocol applicable for use in patients with MSD. Future research, such as propensity-matched studies, can be done to further validate the outcomes from our current protocol.

Conclusions

We surmise that the results of our proposed study design will pave the way for future randomized studies on the use of IOCS in MSTS and MMTSs, given that the granting bodies and their reviewers would be more open to considering funding for such studies.

Acknowledgments

The authors would like to thank the following from National University Health System: Karthigesh Palanichami for his contribution to the preparation and proofreading of the manuscript; Aye Sander Zaw for her contribution in the preparation of this study protocol; and James Hallinan for his contribution in the radiological evaluation of disease progression

Data Availability

All data generated or analyzed during this study will be included in published manuscripts and their supplementary information files.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Key papers evaluating the use of intraoperative cell salvage in various cancer surgeries.
[DOCX File , 39 KB - resprot_v14i1e54609_app1.docx]

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Abbreviations

ABT: allogeneic blood transfusion
CTC: circulating tumor cell
IOCS: intraoperative cell salvage
LDF: leukocyte depletion filter
MMTS: metastatic musculoskeletal tumor surgery
MSD: metastatic spine disease
MSTS: metastatic spine tumor surgery
NBT: no blood transfusion
OS: overall survival
SBT: salvaged blood transfusion

Edited by A Mavragani; submitted 16.11.23; peer-reviewed by R Agrawal, K Chen; comments to author 14.03.24; revised version received 16.03.24; accepted 15.07.24; published 17.01.25.

Please cite as:
Kumar N, Hui SJ, Lee R, Athia S, Tan JYH, Tan JJH
Evaluation of the Feasibility of Transfusing Leukocyte Depletion Filter–Processed Intraoperative Cell Salvage Blood in Metastatic Spine Tumor Surgery: Protocol for a Non–Randomized Study
JMIR Res Protoc 2025;14:e54609
URL: https://www.researchprotocols.org/2025/1/e54609
doi:10.2196/54609
PMID:

Protocol

Clinical Characteristics of Virologically Confirmed Respiratory Syncytial Virus in English Primary Care: Protocol for an Observational Study of Acute Respiratory Infection

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Abstract

Background: There are gaps in our understanding of the clinical characteristics and disease burden of the respiratory syncytial virus (RSV) among community-dwelling adults. This is in part due to a lack of routine testing at the point of care. More data would enhance our assessment of the need for an RSV vaccination program for adults in the United Kingdom.

Objective: This study aimed to implement point-of-care-testing (POCT) in primary care to describe the incidence, clinical presentation, risk factors, and economic burden of RSV among adults presenting with acute respiratory infection.

Methods: We are recruiting up to 3600 patients from at least 21 practices across England to participate in the Royal College of General Practitioners Research Surveillance Centre. Practices are selected if they undertake reference virology sampling for the Royal College of General Practitioners Research Surveillance Centre and had previous experience with respiratory illness studies. Any adult, ≥40 years old, presenting with acute respiratory infection with onset ≤10 days, but without RSV within the past 28 days, will be eligible to participate. We will estimate the incidence proportion of RSV, describe the clinical features, and risk factors of patients with RSV infection, and measure the economic burden of RSV infection.

Results: A total of 25 practices across different English health administrative regions expressed interest and were recruited to participate. We have created and tested an educational program to deploy POCT for RSV in primary care. In addition to using the POCT device, we provide suggestions about how to integrate POCT into primary care workflow and templates for high-quality data recording of diagnosis, symptoms, and signs. In the 2023-2024 winter RSV detection in the sentinel network grew between

October and late November. According to data from the UK Health Security Agency, the peak RSV swab positivity was in International Standards Organization week 48, 2023. Data collection remains ongoing, and results from the subset of practices participating in this study are not yet available.

Conclusions: This study will provide data on the RSV incidence in the community as well as rapid information to inform sentinel surveillance and vaccination programs. This information could potentially improve clinical decision-making.

International Registered Report Identifier (IRRID): DERR1-10.2196/60669

(JMIR Res Protoc 2025;14:e60669) doi:10.2196/60669

KEYWORDS

infectious diseases; primary care; sentinel surveillance; point-of-care system; virologically; respiratory syncytial virus; acute respiratory infection; clinical characteristics; community dwelling; adult; vaccination; programme; united kingdom; incidence; elderly

Introduction

Background

Respiratory syncytial virus (RSV) infection in adults is reported to be a substantial burden to health care systems globally [1]. A recent systematic review of the disease burden of RSV in older adults in the United Kingdom reported an average of 175,070 primary care physician episodes and 7915 deaths per season attributed to RSV, equivalent to 1946 primary care physician episodes per 100,000 population and 88 deaths per 100,000 population older than 65 years of age [2,3]. Another meta-analysis reported that RSV caused 4.66% (95% CI 3.34-6.48) of symptomatic respiratory infections in annual studies and 7.80% (95% CI 5.77-10.45) in seasonal studies among adults older than 60 years [4].

However, RSV is not widely recognized as a cause of respiratory infections in adults as its clinical manifestations are often nonspecific [5-10]. Among those with predisposing factors, such as older age, weakened immune systems, or underlying cardiopulmonary conditions, RSV can increase the risk of developing serious acute lower respiratory tract infection (LRTI), cardiovascular sequela, and exacerbation of underlying conditions, all of which are associated with a significant risk of hospitalization and mortality [5,6,11].

Current guidelines do not recommend rapid diagnostic testing for respiratory viruses in primary care in England [12,13] and a recent scoping review showed the paucity of literature on studies of RSV tests in specific populations and settings [14] despite the difficulty of clinical diagnosis and the availability of a number of highly accurate point-of-care tests (POCT) platforms for RSV in the National Health Service (NHS) [9,15]. Recent studies have estimated that limited routine clinical testing can result in more than 100-fold underestimation of RSV incidence in laboratory surveillance studies [16]. RSV disease burden is of considerable interest because of the development of new vaccines and monoclonal therapies [17-19]. The UK's Joint Committee on Vaccination and Immunization advised that an immunization program for RSV be established for older adults aged 75 years and older [17]. More precise contemporary data to estimate the incidence of RSV in the community and understand the clinical and economic burden of RSV infection in adults would assist in planning any new RSV vaccination program.

Deployed at scale, POCT for RSV has the potential to address the gaps in our knowledge about incidence, clinical presentation, and disease burden.

Aim and Objectives

The aim of the Observational Study of Acute Respiratory Infection (ObservatARI) study is to deploy POCT in primary care clinics to provide data about the incidence, clinical presentation, risk factors, and economic burden of virologically confirmed RSV among older adults presenting with acute respiratory infection (ARI).

Our primary objective is to calculate the incidence proportion of virologically confirmed RSV among adults aged ≥40 years, in a primary care-based sentinel surveillance cohort overall and by age, sex, and subgroups of interest.

Secondary objectives include (1) examining the population-level incidence of RSV, (2) the incidence of RSV-LRTI, (3) use of secondary care, (4) clinical profile, and (5) comparison of clinical and economic burden in cases with and without RSV. Prespecified subgroups (sample size permitting) include age and sex.

Methods

Coordinating Center

The coordinating center for this study was the Nuffield Department of Primary Care Health Sciences, University of Oxford, Oxford, United Kingdom.

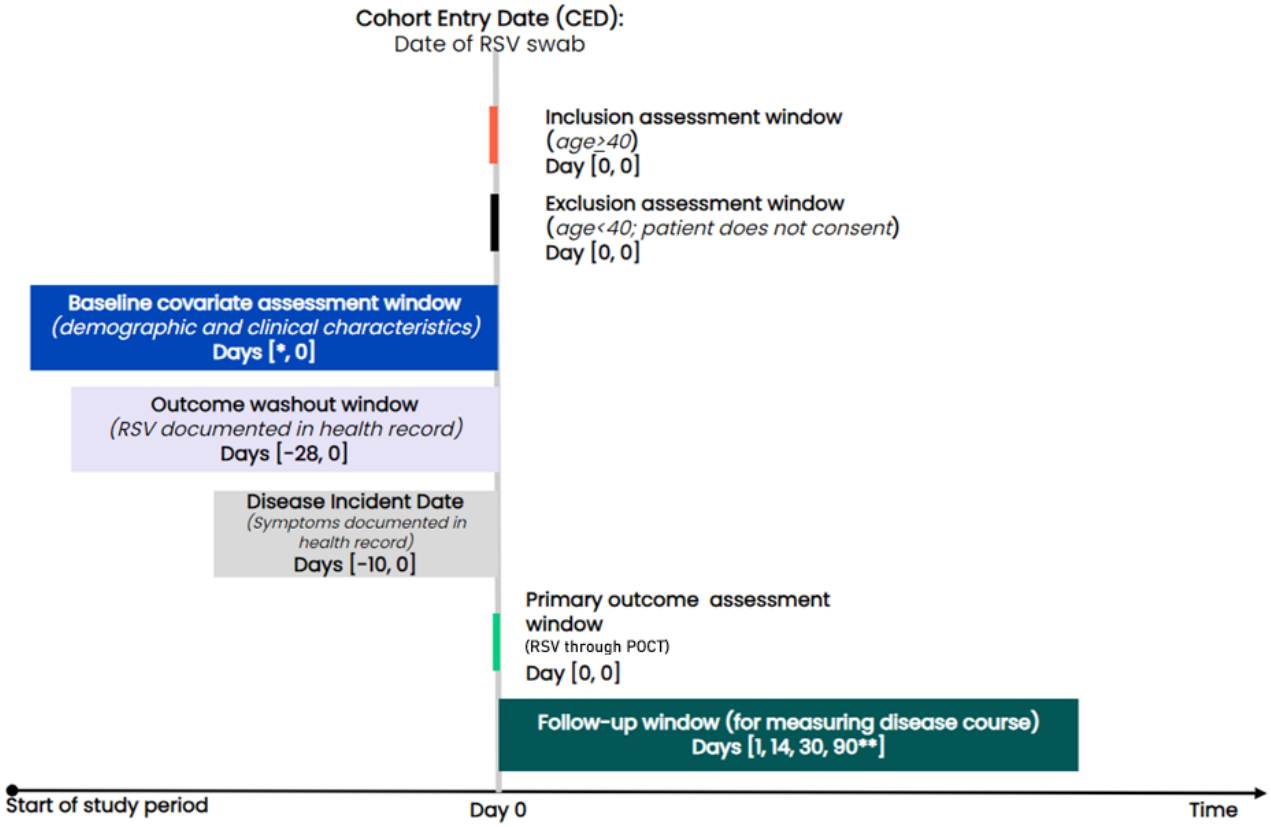
Study Design

The ObservatARI study is ongoing, taking place between November 2023 and November 2024. It is nested within the English national sentinel network, the Oxford-Royal College of General Practitioners (RCGP) Research and Surveillance Centre (RSC), at the Nuffield Department of Primary Care, University of Oxford. This network of over 2000 primary care providers in England, referred to as general practices, is the primary care infectious disease surveillance network for England recruited to be representative of the English population [20]. It has been providing weekly data for over 57 years and is used to monitor trends in infectious disease and investigate real-world vaccine and treatment effectiveness [21].

All practices that contribute data to the RSC are eligible to participate in the ObservatARI study. We will prioritize those practices that currently undertake reference virology sampling for the sentinel network and have previous experience with undertaking respiratory illness studies, including POCT studies. In order to ensure geographic representation, up to 3 practices in each English health region (East of England, London, Midlands, North East, Yorkshire, North West, and South East and South West) have been selected to participate in the study [22]. These sites will receive training on the appropriate use of the POCT device from the manufacturer, which will be documented on a training log. Provision of the POCT device to these sentinel surveillance sites will allow for the collection of data on RSV, which is not routinely tested as part of usual care.

Figure 1 shows the cohort entry date of recruited patients is the date the POCT swab is taken and will serve as the study index date. Baseline covariates are assessed in the period of up to 5 years before cohort entry, and the precise lookback period will vary depending on the variable of interest.

Figure 1. ObservatARI study design. ARI: acute respiratory infection; RSV: Research Surveillance Centre, POCT: point-of-care-testing. The study time period was from November 2023 to November 2024. *Lookback for baseline covariates will vary by variable using windows established by existing sentinel surveillance efforts. **Patients censored due to death or disenrollment from the clinic.



We will follow-up enrolled patients for up to 14 days, 30 days, and 90 days for secondary outcomes of interest, such as clinical outcomes and health service usage. This information will be presented according to the test result from POCT (ie, RSV-positive and RSV-negative).

Case Definition of Eligible Patients

Fully registered primary care patients, of study practices, who present with ARI, with its onset in the last 10 days (including index date), where illness is not due to another plausible diagnosis, are eligible for enrollment in the ObservatARI study. These are the same criteria currently used by the UK Health Security Agency (UKHSA) sentinel surveillance system [23].

Sampling and Data Collection

We are undertaking opportunistic virology sampling [24], with potential participants being identified from fully registered patients and temporarily registered patients who present to the participating study practices with respiratory symptoms described in the case definition.

ObservatARI practices are advised to take 2 swabs, and 1 nasopharyngeal swab for testing using the Cepheid POCT analyzer. Nasopharyngeal swab samples have been studied and validated for the detection and quantification of respiratory viruses and are considered more accurate for RSV than nasal swabs [15,25,26]. The second one is a nasal swab for testing using the UKHSA National Virology Reference Laboratory as per Oxford-RCGP RSC's standard practice [23].

Eligible patients are approached by their practice receive an explanation about the study and are asked for consent to take part when they present for a face-to-face consultation at the practice. Patients are informed that they are free to withdraw from the study at any time without giving any reason and without their legal rights being affected. Study participants will not receive compensation for taking part in this study.

After obtaining consent using a form with a prepopulated study number, the primary care physician or research nurse will take the virology swabs [25,26]. The nasopharyngeal swab is inoculated in a test kit and tested using the POCT analyzer as soon as possible after being taken. Only the patient study number is entered into the POCT machine.

We are using the Cepheid GeneXpert Xpress CoV-2, Flu, RSV plus POCT analyzer for this study. This multiplex polymerase chain reaction system tests for SARS CoV-2, influenza A, influenza B, and RSV. It has demonstrated excellent performance comparable to gold-standard laboratory assays with a sensitivity for RSV of 0.979 (95% CI 0.889-0.996) and specificity of 1.000 (95% CI 0.981-1.000) [27]. It has Conformité Européenne marking in the European Union. In the United States, it is approved by the US Food and Drug Administration and it is also waived for use by the Clinical Laboratory Improvement Amendments for rapid RSV testing. This study will not assess the accuracy of the POCT analyzer but will use the machine for its approved purpose.

The clinician is also asked to enter the following date of onset of four symptoms in the patient's computerized medical record (CMR): (1) the presence or absence of fever because of infection, (2) cough (and if coughing is productive), (3) sore throat, and (4) shortness of breath or wheezing. In addition, the following four signs will be recorded in the CMR: (1) measured temperature (ear or tympanic preferred) ≥38 °C for fever, (2) peripheral oxygen saturation, (3) pulse rate >90 beats per minute for tachycardia, and (4) respiratory rate >20 breaths per minute for tachypnoea (Textbox 1). After the POCT analyzer has finished, the clinician is asked to code the result into the patient's CMR.

To facilitate the standardized collection of symptoms, signs, and POCT or laboratory results for the study, we have developed data entry templates for study practices using either the Egton Medical Information Systems or The Phoenix Partnership computerized medical systems available to participating practices (Figure 2). This allows clinicians in study practices to record respiratory symptoms and signs, and study consent, through dropdown menus and tick boxes. The results of POCT testing and reference laboratory testing will also be entered using these templates. The information from the templates is automatically entered into the patient's CMR as a relevant Systemized Nomenclature of Medicine Clinical Terms, which will be extracted for data analysis as part of this study.

Textbox 1. Key data on symptoms and signs of acute respiratory infection.

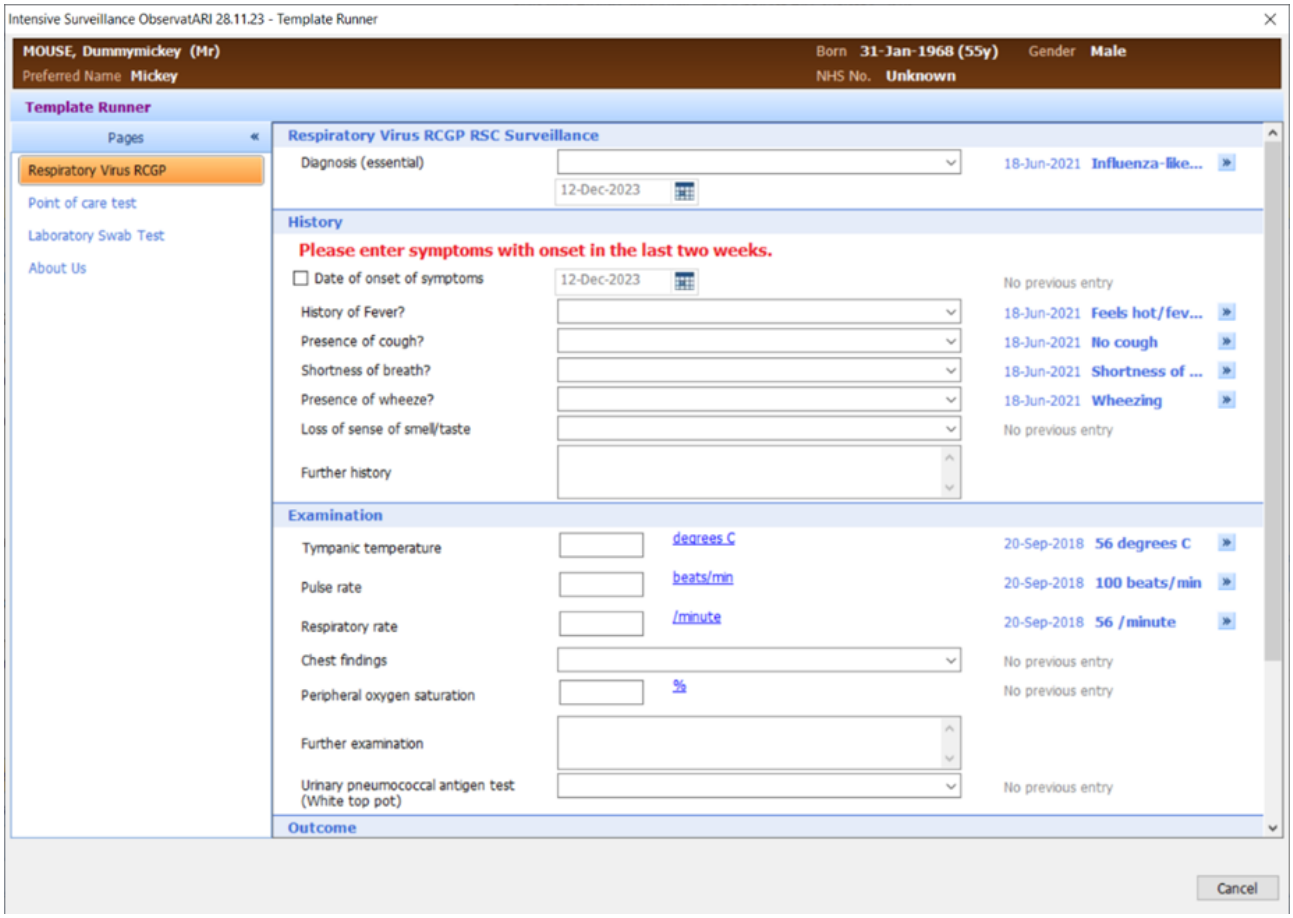
Symptoms data

- Presence or absence of fever because of infection
- Cough (and if coughing is productive)
- Sore throat
- Shortness of breath or wheezing

Signs data

- Measured temperature (ear or tympanic preferred) ≥38 °C for fever
- Peripheral oxygen saturation
- Pulse rate >90 beats per minute for tachycardia
- Respiratory rate >20 breaths per minute for tachypnea

Figure 2. Sample ObservatARI data collection form. ARI: acute respiratory infection; RCGP: Royal College of General Practitioners; RSC: Research Surveillance Centre.



Data Sources

The Oxford-RCGP Clinical Informatics Digital Hub (ORCHID) trusted research environment will house the data required for this study.

We will use a pseudonymized NHS number to allow the linkage of ObservatARI data to national datasets. With appropriate approval, these data assets are held within the ORCHID trusted research environment. Data assets used for this study are as follows.

The primary virology diagnosis will be from POCT data collected from participating ObservatARI practices.

Supplemental data on test positivity will be available approximately a week later from the UKHSA reference laboratory data. In the event of a discrepancy between the POCT and UKHSA reference laboratory data, the POCT test will be selected as the main result with the proportion of discrepant results reported.

In addition, virology data from UKHSA virology sampling during the study period will be accessed to augment data obtained from POCT.

Pseudonymized patient data are also linked to UKHSA National Virology Reference Laboratory data results. NHS England national data collection provides access to hospitalization, intensive care unit admission, mortality, and other national datasets.

Hospital Episode Statistics (HES) is the transformed data, initially part of the Commissioning Data Set, covering patients attending accident and emergency units, admitted for treatment, or attending outpatient clinics at NHS hospitals in England, including details about length of stay and Health Care Resource Groups (HRGs) to enable health economic analysis. HRG consists of patient events that have been judged to consume a similar level of resource, which can be linked to an appropriate NHS tariff. Statistical controls have been applied to HES products. Data on cost will be extracted from HES using HRG. Health care resource use data during hospital admissions are not granularly available and, therefore, HRG codes will need to be used as a proxy for costing.

Emergency Care Data Set collects data from accident and emergency departments.

Civil Registrations include information including date, place, and certificated cause of death from the Office for National Statistics.

Data derived from primary and secondary care encounters are recorded using the Systemized Nomenclature of Medicine-Clinical Terms and *ICD-10* (*International Statistical Classification of Diseases, Tenth Revision*) codes, respectively [28]. The clinical concepts captured include diagnoses, therapy, test results, and other data [29]. Patient medical records in UK general practice have been computerized since the late 1990s, with pay-for-performance incentives introduced in 2004 for chronic disease management [30].

Sample Size Calculation

Up to 3600 POCT swabs will be taken from consented, volunteer patients registered with the 21 ObservatARI general practices. Based upon the annual disease prevalence of 6% and reported sensitivity of 0.979 (95% CI 0.889-0.996) and specificity of 1.000 (95% CI 0.981-1.000) [27], we estimated the number of participants with and without RSV that would test positive and negative with the POCT if we sampled 3600 with ARI (Table 1).

Table 1. Expected counts (±95% CIs) for respiratory syncytial virus (RSV).

	RSV, expected count (95% CI)	No RSV, expected count (95% CI)	Total, n
Positive POCT[a]	211 (192-215)	0 (0-64)	211
Negative POCT	5 (1-24)	3384 (3320-3384)	3389
Total	216	3384	3600

[a]POCT: point-of-care-testing.

Given our estimates of prevalence, sensitivity, specificity, and the total available number of swabs in 21 practices in one season, we would expect to observe approximately 211 POCT true-positive RSV cases, which is sufficient to meet our primary objective of estimating the incidence proportion of POCT confirmed RSV.

We performed additional sensitivity analyses, keeping constant the number of swabs and prevalence of RSV, but assuming lower values of POCT sensitivity (90% and 80%) and estimated that 194 and 173 true-positive RSV cases would be detected, respectively. With smaller RSV case counts, SE of the incidence proportion (primary objective) would remain very similar and precise enough to generate meaningful inferences.

We have previously found that RCGP RSC practices using a POCT to diagnose respiratory viruses collect on average 6 swabs per practice per week over the winter season [31]. Thus, for our study in 21 practices over 12 months, we estimate that the target of 3600 swabs would be achievable.

Covariate Ascertainment

Tables 2 and 3 show the covariates we will use for this study which are known to be associated with the incidence and severity of respiratory syncytial virus [32].

Table 2. Covariates associated with the incidence and severity of the respiratory syncytial virus.

Covariate	Categories
Age	• As whole years • 5-year increments (broader 10-year age bands may be considered)
Sex	• Male or female
Ethnicity	• White, Asian, Black, other, or mixed
Region	• Divided into areas served by an integrated care system
Urban or rural designation	• Urban or rural
Household composition	• Divided into categories 1, 2, 3, 4-5, 6-10, 11, or more
Socioeconomic status will be measured using the index of multiple deprivation [32]	• Quintiles from 1 (most deprived), 2, 3, 4, and 5 (least deprived)
BMI	• Obese or not obese (BMI ≥ or <30), • Also stratified as <18.5, 18.5-24.9, 25.0-29.9, 30.0-39.9, 40.0, or more)
Smoking status	• Current smoker, previous smoker, or nonsmoker
Cambridge Multi-Morbidity Score	• Quartiles • No comorbidities, 1, 2, 3, 4, or more comorbidities
Comorbidities known to relate to increased risk of severe respiratory illness, or suboptimal vaccine response, or vaccine contraindication	• Chronic respiratory disease • Chronic obstructive pulmonary disease • Chronic heart failure • Chronic heart disease and vascular disease • Chronic kidney disease • Chronic liver disease • Chronic neurological disease • Diabetes mellitus • Severe mental illness • Morbid obesity • Asplenia, or dysfunction of the spleen, immunosuppression due to disease, or treatment
Vaccination status within the season	• Influenza vaccination • COVID-19 vaccination • Pneumococcal vaccination

Table 3. Covariates and categories.

Covariates	Categories
Age	• As whole years • 5-year increments (broader 10-year age bands may be considered)
Sex	• Male or female
Ethnicity	• White, Asian, Black, other, or mixed
Region	• Divided into areas served by an integrated care system
Urban/rural designation	• Urban or rural
Household composition	• Divided into categories 1, 2, 3, 4-5, 6-10, 11, or more
Socioeconomic status will be measured using the index of multiple deprivation [32]	• Quintiles from 1 (most deprived), 2, 3, 4, 5 (least deprived)
BMI	• Obese or not obese (BMI ≥ or <30) • Also stratified as <18.5, 18.5-24.9, 25-29.9, 30-39.9, 40, or more)
Smoking status	• Current smoker, previous smoker, or nonsmoker
Cambridge Multi-Morbidity Score	• Quartiles • No comorbidities, 1, 2, 3, 4, or more comorbidities
Comorbidities known to relate to increased risk of severe respiratory illness or suboptimal vaccine response or vaccine contraindication	• Chronic respiratory disease • Chronic obstructive pulmonary disease • Chronic heart failure • Chronic heart disease and vascular disease • Chronic kidney disease • Chronic liver disease • Chronic neurological disease • Diabetes mellitus • Severe mental illness • Morbid obesity • Asplenia or dysfunction of the spleen, immunosuppression due to disease, or treatment
Vaccination status within the season	• Influenza vaccination • COVID-19 vaccination • Pneumococcal vaccination

Statistical Analyses

For the primary objective, the incidence proportion of virologically confirmed RSV will be calculated as the number of swabs testing positive for RSV in the POCT, divided by the number of people fully registered at all 21 sites each month. Exact 95% CIs will be estimated using the Wilson method [33]. We will also calculate percent positivity as the number of positive cases divided by the number swabbed. Estimates will be presented overall and by key demographic and patient characteristics as defined above. Incidence proportions will be calculated by time (eg, moving average and monthly) depending on the sample size.

To approximate the response rate, and investigate potential selection bias, and external validity, we will compare the characteristics of patients for whom a swab was taken, with those who are ≥40 years presenting with an ARI code in the participating practices, and in the whole RSC network, respectively. This analysis will be restricted to the same study period.

For secondary objective 1, the incidence proportions (and 95% CI) estimated from the primary objective will be standardized (using the direct method) to the UK general population based on age or sex distribution [34].

For secondary objective 2, incidence proportions (and 95% CI) of RSV-LRTI will be calculated by dividing the number of cases meeting each of the three case definitions by the number of people at risk, for example, in a subgroup of interest.

For secondary objective 3, descriptive statistics (mean [SD], median [IQR], range [minimum and maximum], frequency [percentage]) will be used to describe the patient's clinical features at presentation, for all patients and RSV-positive patients (eg, signs and symptoms; Textbox 1). For reference, the same information will be presented for patients with ARI who test negative for RSV. We will adjust for variables that are hypothesized to lead to the development of symptoms as well

as RSV positivity. Crude and adjusted odds ratios and 95% CIs indicating the association between these variables and testing positive for RSV (vs testing negative) will be presented.

For secondary objective 4, descriptive statistics will be used to describe the patient covariates listed in Table 2. These covariate characteristics will be examined among all patients, with the information presented according to POCT status (ie, RSV-positive and RSV-negative). As in secondary objective 3, logistic regression will be used to estimate crude and adjusted odds ratios.

For secondary objective 5, the clinical and economic burden of RSV will be assessed by comparing the number of health care visits (eg, visits to the general practitioner, hospitalization, and intensive care unit visits), medication use (eg, antiviral and antimicrobial therapy), receipt of ventilation and supplemental oxygen use up to 6 months after the swab. Additional outcomes of interest will include primary care costs, prescription costs, medical test costs, and secondary care costs.

Our approach to the analysis will depend on the type of outcome variable. For instance, cumulative health care resource costs covering primary and secondary health care services for the cohorts will be calculated for each patient by attaching unit costs to each service encounter. This will enable us to present initial estimates of the costs associated with health care usage across each group in terms of means, SD, median, IQR, minimum, and maximum. We will examine the distribution of the health care costs to identify outliers. This information will be presented according to POCT status (ie, RSV-positive and RSV-negative) and further, by the subgroup of interest. These steps will ensure that we fully comprehend the nature of the cost data [35].

Ethical Considerations

Data for the study are held on dedicated secure servers within the ORCHID TRE. The Research Group's secure network is sited behind a firewall within the University's network. Only staff members or associated members of the Research Group who have been appropriately trained and approved by the Head of Department can access the data from secure workstations or secure laptops with encrypted drives. All staff members of the Research Group working within the team base work from secure workstations or secure laptops with encrypted drives within the Research Group's secure network. The staff of the study sponsor will be provided with aggregate-level study data only. A risk assessment of the physical security of the Research Group's offices and server room has been conducted by the Building and Facilities Manager, the Faculty IT Service Manager, and the Research Group's Information Governance Lead. The University is compliant with the Data Protection Act and UK General Data Protection Regulation and has systems for technical and organizational controls for information security, including a University-level Information Security and Governance Group, chaired by the University Senior Information Risk Owner. The Research Group's private network has its own system-level security policy and is tested for vulnerabilities annually.

Study practices are given a stipend to cover the costs of training staff members and hosting the study. A small remuneration is also provided to practices for each POCT swab and reference laboratory virology sample taken to cover the additional time taken during each consultation to undertake swabbing for this study. Patients are not remunerated for taking part in this study.

The study received ethical approval for England and Wales from the Health Research Authority and Health and Care Research Wales on September 14, 2023 (Integrated Research Application System project ID: 329790, south central Oxford A Research Ethics Committee reference number 23/SC/0320).

The study and data extract were approved by the ORCHID Caldicott Guardian, the Primary Care Hosted Research Data sets Independent Scientific Committee of the Nuffield Department of Primary Care Sciences at the University of Oxford on November 7, 2023 (application reference PD-0030-2023).

Protocol Amendments

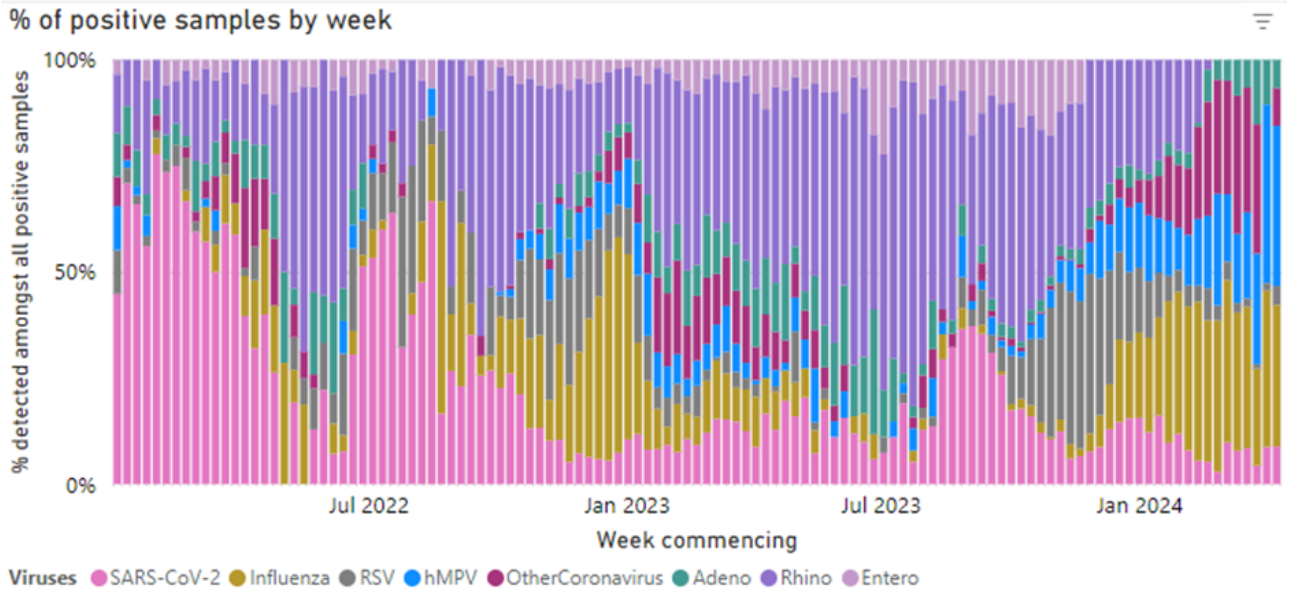
Important protocol amendments will be referred to the English National Research Ethics Committees for ethical approval. Once approved, it will be communicated directly with the recruiting study practices. The amended protocol will be shared with all relevant parties, for example, investigators and clinical research networks in a timely manner.

Results

We have received expressions of interest from 25 practices and have purposively recruited 21 practices from across the English health administrative regions.

In the 2023-2024 winter season, RSV detection in the sentinel network grew between October and late November. According to data from the UKHSA, the peak RSV swab positivity was in International Organization for Standardization week 48, 2023 (Figure 3 [36]). Data collection remains ongoing, and results from the subset of practices participating in this study are not yet available.

Figure 3. The UK Health Security Agency virology swabbing positivity in 2023-2024 [36].



Discussion

Anticipated Findings

This study will generate contemporary data about the clinical presentation and disease burden of RSV among middle-aged and older adults in the community. Our primary outcome is the incidence of virologically confirmed, symptomatic, RSV infection presenting to primary care providers in England.

This study has a number of limitations. First, even with a sampling of 3600 eligible patients with ARI, it is expected that this study will only yield approximately 200 positive cases of RSV with the POCT. While this would be enough to estimate the incidence of RSV cases presenting to primary care with sufficient precision, the low number of cases could impact the number of covariates that we can adjust for in secondary objectives, as well as the estimation of ORs for categories with low frequencies (eg, underweight BMI category) and our ability to conduct subgroup analysis.

Second, there is inherent variation in clinical assessment and, thus, the decision to swab an eligible participant and exclude anyone with an illness due to another plausible diagnosis may potentially introduce bias. To minimize this variation, we will have robust site training available at the start of the study and throughout for new members of staff. We will also quantify any individual selection bias by comparing the characteristics of eligible swabbed and unsampled patients in POCT practices.

Third, a limitation of our opportunistic sampling strategy is that we will sample both fully registered and temporarily registered patients from study practices with eligible symptoms. Temporarily registered patients may include people at increased risk of infection or severe consequences of infection as well as people with less available information in their medical records such as refugee populations. We will quantify the effect this may have by comparing the characteristics of fully registered and temporarily registered patients in POCT practices.

Fourth, the study practices are not randomly selected so the results from the POCT surveillance cohort will not generalize beyond the selected clinics. To quantify any practice selection bias, we will compare the characteristics of patients for whom a swab was taken, with those presenting with an ARI code in the 21 participating practices, and in the whole RCGP RSC network, respectively.

Finally, the use of nasopharyngeal sampling is invasive and uncomfortable for the patient and it requires a trained provider to perform the collection. This may negatively impact the sensitivity of POCT in this older adult population, potentially biasing incidence estimates downwards. However, nasopharyngeal swabs have been validated for the detection and quantification of respiratory viruses [25,26]. They are considered the most accurate method for sampling RSV and practices in the Oxford-RCGP RSC sentinel network have many years of experience with undertaking nasopharyngeal swabs as part of national virological respiratory disease surveillance, which should reduce this risk [21,25,26]. In addition, where the virus has progressed lower in the respiratory tract, a nasopharyngeal swab may not detect these cases and a sputum sample may be required.

The limitations of the study must be considered in the context of its strengths. First, the study is nested within the English sentinel network, which includes participating practices that have developed expertise in identifying respiratory infections for the past 5 decades [21] and have a robust reporting infrastructure that supports rapid, accurate respiratory disease surveillance.

Second, the study uses a robust reverse transcription-polymerase chain reaction multiplex POCT platform that is rapid, accurate, cost-effective, simple to use, and reliable, and will provide viral positivity results for RSV, influenza, and SARS-CoV-2.

Third, the study leverages the NHS data system and a broader network of virology testing within the sentinel surveillance network to expand the breadth of the dataset (eg, clinical, economic, and humanistic variables) and ensure broader

applicability of findings. Thus, we will have the opportunity to leverage the broader dataset of laboratory results and other data from patients from outside the 21 clinical sites in the analysis as needed.

Conclusion

We have started to deploy POCT for RSV in primary care and believe that if done at scale, POCT may provide data on the RSV incidence in the community as well as rapid information to inform sentinel surveillance. This information may also provide data to inform decisions about the benefits of a UK-wide RSV vaccination program for the adult population.

Acknowledgments

We would like to thank participating practices for sharing data and patients and their carers for volunteering to participate in this study. Magentus and Egton Medical Information Systems for their collaboration with pseudonymized data extraction.

Moderna funded and sponsored this study, and reviewed and proposed edits to the study protocol and study documents before submission for ethics approval and peer review publication.

Data Availability

The datasets generated during and/or analyzed during this study are available from the corresponding author on reasonable request and with permission of RCGP RSC [37].

Conflicts of Interest

SdL is the director of the Oxford RCGP Research and Surveillance Centre. Through his university he has received funding for vaccine-related research from AstraZeneca, GlaxoSmithKline (GSK), Sanofi, Seqirus, and Takeda; he has been a member of advisory boards for AstraZeneca, Sanofi, and Seqirus. UH has undertaken continuing professional development podcasts funded by Seqirus and has been a member of advisory boards for Jansen. JR, ABA, CAP, OB, MD, AE, TL, and DM are employees and/or potential owners of Moderna stock.

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Abbreviations

ARI: acute respiratory infections
CMR: computerized medical record
HES: hospital episode statistics
HRG: health care resource groups
ICD-10: International Statistical Classification of Diseases, Tenth Revision
LRTI: lower respiratory tract infection
NHS: National Health Service
ORCHID: Oxford-RCGP Clinical Informatics Digital Hub
POCT: point-of-care test
RCGP: Oxford-Royal College of General Practitioners
RSC: Research and Surveillance Centre
RSV: respiratory syncytial virus
UKHSA: UK Health Security Agency

Edited by A Schwartz; submitted 17.05.24; peer-reviewed by O Olasunkanmi; comments to author 05.11.24; revised version received 15.11.24; accepted 28.11.24; published 22.01.25.

Please cite as:
Hoang U, Agrawal U, Ordóñez-Mena JM, Marcum Z, Radin J, Araujo A, Panozzo CA, Balogh O, Desai M, Eltayeb A, Lu T, Nicodemo C, Gu X, Goudie R, Fan X, Button E, Smylie J, Joy M, Jamie G, Elson W, Byford R, Madia J, Anand S, Ferreira F, Petrou S, Martin D, de Lusignan S
Clinical Characteristics of Virologically Confirmed Respiratory Syncytial Virus in English Primary Care: Protocol for an Observational Study of Acute Respiratory Infection
JMIR Res Protoc 2025;14:e60669
URL: https://www.researchprotocols.org/2025/1/e60669
doi:10.2196/60669
PMID:39841515

Protocol

Use of Machine Learning to Predict Individual Postprandial Glycemic Responses to Food Among Individuals With Type 2 Diabetes in India: Protocol for a Prospective Cohort Study

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Abstract

Background: Type 2 diabetes (T2D) is a leading cause of premature morbidity and mortality globally and affects more than 100 million people in the world's most populous country, India. Nutrition is a critical and evidence-based component of effective blood glucose control and most dietary advice emphasizes carbohydrate and calorie reduction. Emerging global evidence demonstrates marked interindividual differences in postprandial glucose response (PPGR) although no such data exists in India and previous studies have primarily evaluated PPGR variation in individuals without diabetes.

Objective: This prospective cohort study seeks to characterize the PPGR variability among individuals with diabetes living in India and to identify factors associated with these differences.

Methods: Adults with T2D and a hemoglobin A_{1c} of ≥7 are being enrolled from 14 sites around India. Participants wear a continuous glucose monitor, eat a series of standardized meals, and record all free-living foods, activities, and medication use for a 14-day period. The study's primary outcome is PPGR, calculated as the incremental area under the curve 2 hours after each logged meal.

Results: Data collection commenced in May 2022, and the results will be ready for publication by September 2025. Results from our study will generate data to facilitate the creation of machine learning models to predict individual PPGR responses and to facilitate the prescription of personalized diets for individuals with T2D.

Conclusions: This study will provide the first large scale examination variability in blood glucose responses to food in India and will be among the first to estimate PPGR variability for individuals with T2D in any jurisdiction.

Trial Registration: Clinical Trials Registry-India CTRI/2022/02/040619; https://tinyurl.com/mrywf6bf

International Registered Report Identifier (IRRID): DERR1-10.2196/59308

(JMIR Res Protoc 2025;14:e59308) doi:10.2196/59308

KEYWORDS

diabetes; T2DM; diabetes management; food responsiveness; postprandial glucose response; food intake; diet logs; dietary intake; machine learning

Introduction

Type 2 diabetes mellitus (T2D) is the leading cause of chronic kidney disease, end-stage renal disease, blindness, and nontraumatic amputation; it also substantially increases the risk of myocardial infarction, stroke, and heart failure [1]. Its prevalence is particularly high in India, which is now the most populous country in the world. As of 2023, more than 100 million people living in India have diabetes, representing more than 11% of the population and an additional 136 million have

prediabetes [2]. These numbers are anticipated to continue to grow rapidly. The lifetime risk of T2D among 20-year-olds who are obese and living in India is estimated to be more than 86% [3]. The rising prevalence of this condition in India is believed to be the result of changing diets, increasingly sedentary occupations, lower levels of physical activity in the context of urbanization, and rapidly increasing rates of obesity [4].

These trends are particularly concerning because of important differences between the presentation and consequences in T2D among individuals of South Asian origin compared with other racial and ethnic groups. These differences, which often referred to as the "Indian Phenotype" or "South Asian Phenotype" [5-7], are characterized by the onset of T2D at a younger age and substantially lower BMI than people of other races and ethnicities [8-10]. Individuals of Indian origin have higher levels of insulin resistance (and for longer periods of time) and premature beta-cell failure [7]. They are more likely to develop the fatal complications of T2D, most notably heart disease [7]. These features are thought to result from a mix of lifestyle, epigenetics, and fetal programming factors [7,11,12].

The fundamental goal of diabetes management is to maintain near-normal glucose levels. A variety of self-management behaviors, in particular adherence to diet and regular exercise, are central to this goal. An extensive body of evidence demonstrates that aiding patients with T2D with self-management behaviors is associated with improvements in a wide range of outcomes including knowledge, self-care behaviors, weight, quality of life, hemoglobin A_{1c} (HbA_{1c}), all-cause mortality, and health care costs [13,14].

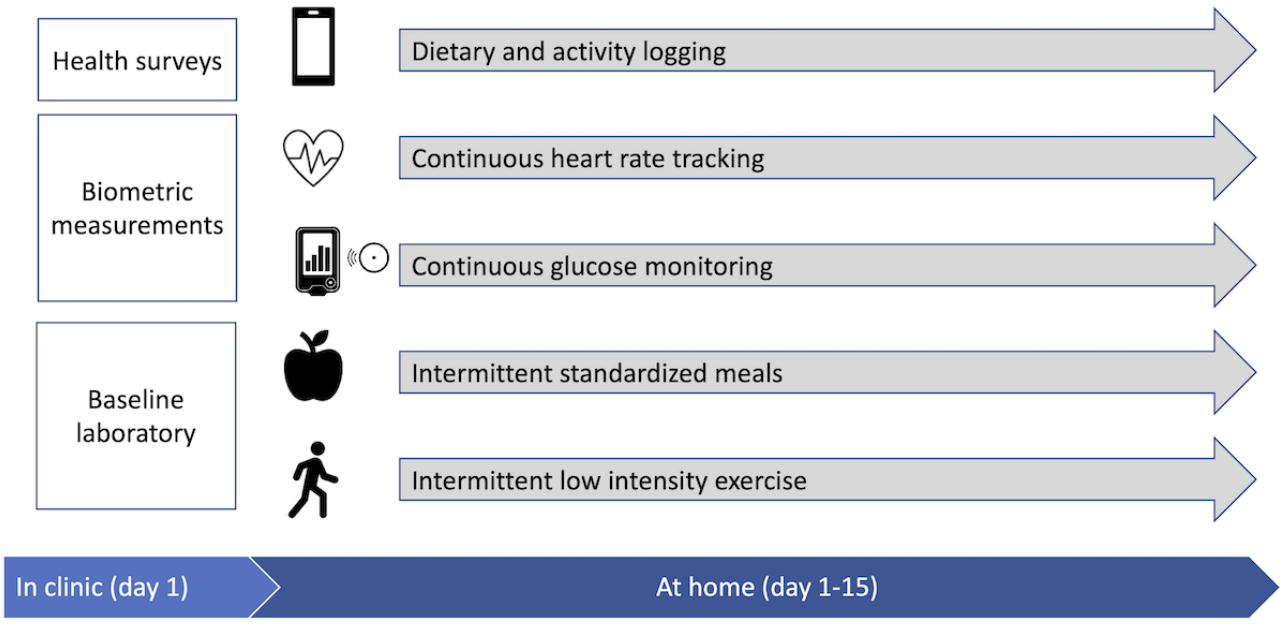
Guidelines recommend that nutritional guidance be personalized based on nutritional status, lifestyle, and metabolic goals [15]. Despite this, most dietary advice for individuals with T2D remains generic emphasizing reductions in calories and minimization of carbohydrates [16]. However, there are marked interindividual responses in postprandial glucose response (PPGR) [17]. A study conducted in Israel found substantial PPGR variability to standardized meals for individuals without diabetes [18]. Similar data has been generated in the United Kingdom, the United States, and China [19-21].

There have been no studies characterizing food responsiveness among individuals living in India and virtually no published data, from any judication, in the variability in PPGR for individuals with T2D [22]. Given the unique Indian diabetes phenotype and differences between Indian and western diets, in specific much higher rates of carbohydrate consumption overall [23] and the centrality of white rice and refined wheat [24], there are very likely to be differences in blood glucose responses to food and exercise in India than observed elsewhere, just as there have been in Indians' responses to diabetes medications [25]. Accordingly, the goal of this study is to characterize and identify factors associated the variability in PPGR among individuals with T2D in India.

Methods

This prospective cohort study seeks to evaluate the relationship between PPGR and self-management activities including diet, exercise, and other daily routines, for individuals with T2D in India (Figure 1).

Figure 1. Overall study design.



Study Setting

This trial is being conducted at 14 outpatient clinics in geographically distinct regions across India with population sizes ranging from 1.2 to 34 million. Sites were identified and managed by IQVIA, a multinational contract research organization, and were included if they specialized in the care of individuals with diabetes, had an established research infrastructure for the conduct of diabetes-related studies including a site principal investigator who is a diabetologist (with clinical training in endocrinology or internal medicine), a local ethics committee to provide study oversight, and a sufficient volume of potentially eligible patients. Study enrollment began in May 2022.

Eligible Participants and Enrollment

The study population consists of adults with diabetes and suboptimal disease control, classified as HbA_{1c} ≥7. Complete inclusion and exclusion criteria are summarized in Textbox 1.

Textbox 1. Eligibility criteria required for participants to be enrolled in the study.

Inclusion criteria

- Age ≥ 18 and <75 years.
- Physician-diagnosed type 2 diabetes treated with ≥1 oral hypoglycemic agents
- Hemoglobin A_{1c}≥ 7.0% recorded within the past 30 days.
- Mobile phone capable of running protocol-specified apps.
- Functional English literacy.

Exclusion criteria

- Unable or unwilling to provide informed consent or comply with the study-specified procedures.
- Current use of prandial insulin including a continuous insulin infusion pump.
- Currently pregnant or planning to become pregnant.
- Estimated life expectancy of ≤12 months.
- Active cancer.
- Myocardial infarction or stroke in the last 6 months.
- Receiving or planned to initiate dialysis for end-stage renal disease.
- Receiving oral or intravenous steroids.
- Any contraindication to using a continuous glucose monitor.

Potentially eligible patients are identified from clinic records and are invited to attend an in-person screening visit at which time eligibility is confirmed and written informed consent obtained. Consenting patients are asked to provide sociodemographic and medical information (specifically, age, sex, predominant diet, health conditions, family history, and current medications) and to complete baseline surveys including the World Health Organization's STEPwise Approach to Non-Communicable Disease Risk Factor Surveillance (STEPS) survey [26], World Health Organization-Five Well-Being Index (WHO-5) [27]. Diabetes Distress Scale [28], Wilson Adherence Scale [29], and the Pittsburgh Sleep Quality Index [30].

Biometric data including blood pressure, heart rate, weight, height, and body measurements at the upper arm, thigh, calf, waist, and hips, are collected by study coordinators at each site. Finally, enrolled participants provide blood samples including a complete blood count, HbA_{1c}, blood electrolytes, creatinine, cholesterol, as well as urinalysis.

After completing baseline assessments, participants are fitted with an Abbott Freestyle Libre continuous glucose monitors (CGM) sensor on their upper, nondominant arm and are provided with a Xiaomi Mi Band Smart Wristband (heart rate monitor) and a Roche Accu-Chek glucometer with testing supplies, and dietary supplements to be consumed with their standardized meals (refer to Follow-up Procedures section). Study-specific apps are downloaded on to the participants' smartphones to allow them to log dietary intake and synchronize their continuous glucose and heart rate monitors. As a back-up, participants are given a paper dietary logbook and a Freestyle Libre CGM reader with which to collect protocol-specified data.

Follow-Up Procedures

Participants are followed for 14 days. They are instructed to wear the CGM and heart rate monitor. The heart rate monitor is to be always worn, including during sleep, and only removed for recharging. Participants are also asked to check their capillary glucose on days 2 through 6 before breakfast and dinner.

Participants log their full dietary intake using the study app or logbook over the 14-day study period, including all standardized test meals and free-living foods (including snacks), beverages (including water), and medications. Participants also log all exercise.

Participants are required to consume protocol-specified meals and to perform light activity, as described in Table 1. The standardized meals consist of vegetarian breakfast foods which participants are to prepare in their homes.

The meals vary in their proportion of carbohydrate, fiber, protein, and fat (refer to Table 2).

Table 1. Meal schedule during the at-home study period.

Day and timing	Meal type
1	
Breakfast	Fasting
Lunch	As desired
Dinner	As desired
2	
Breakfast	Perceived healthy meal
Lunch	Post meal exercise
Dinner	Typical mixed protein with dinner
3	
Breakfast	Fiber supplement with standardized test meal
Lunch	Premeal exercise
Dinner	Alternative mixed protein with dinner
4	
Breakfast	Fiber supplement before standardized test meal
Lunch	As desired
Dinner	As desired
5	
Breakfast	Protein supplement with standardized test meal
Lunch	As desired
Dinner	Alternative mixed protein with dinner
6	
Breakfast	Protein supplement before standardized test meal
Lunch	Added fiber with lunch
Dinner	Alternative mixed protein with added protein
7	
Breakfast	Regular breakfast
Lunch	Added fruit
Dinner	Cooled carbohydrate
8	
Breakfast	Regular breakfast with added protein
Lunch	Added fruit with protein
Dinner	Regular carbohydrate
9	
Breakfast	Protein followed by carbohydrate
Lunch	Water 30 minutes before lunch
Dinner	As desired
10	
Breakfast	Standardized test meal
Lunch	As desired including dessert
Dinner	Protein followed by carbohydrates and vegetables
11	
Breakfast	Standardized test meal with postmeal exercise

Day and timing	Meal type
Lunch	As desired including desert and cinnamon
Dinner	Vegetables followed by protein then carbohydrates
12	
Breakfast	Standardized test meal with postmeal exercise
Lunch	As desired
Dinner	As desired finishing eating by 8 PM
13	
Breakfast	Water before late breakfast + postmeal exercise
Lunch	Low glycemic index lunch
Dinner	Low glycemic index dinner + finish dinner by 8 PM + exercise after meal
14	
Breakfast	Water before late breakfast + exercise after meal
Lunch	Low glycemic index lunch + exercise after meal
Dinner	Low glycemic index dinner + finish dinner by 8 PM + exercise after meal

Table 2. Nutritional composition of standardized test meals.

Meal characteristics	Meal type		
	Carbohydrate	Added fiber	Added protein
Example meal	2 aloo parathas with curd	2 aloo parathas with curd + fiber supplement	2 aloo parathas with curd + protein supplement
Energy (kcal)	474.4	506.4	594.4
Carbohydrate (g)	61.5	64.1	62.9
Fat (g)	12.5	12.5	14.6
Protein (g)	7.7	7.8	31.9
Fiber (g)	8.3	21.9	8.3
Carbohydrate (% energy)	51.9	50.6	42.3
Fat (% energy)	23.8	22.3	22.1
Protein (% energy)	6.46	6.05	21.4

Participants are instructed to fast for a minimum of 8 hours before and 3 hours after consuming the standardized breakfast meal; during these fasting periods, limit exercise and drink only still (not sparkling) water, tea, or coffee in moderation; and eat the meal, in its entirety, within 20 minutes. After completing the postmeal fasting period on standardized test meal days, participants may consume other foods as they normally would unless there are other meal modifications specified by the protocol later the same day.

On other days, participants are asked to consume normal foods with protocol-specified constraints. For example, on different days, participants vary the types of mixed protein (eg, different types of lentils with or without added protein), ordering with the type of foods consumed (eg, protein before carbohydrate vs protein with carbohydrate), consume water before their meal, go for a walk after eating, or eat what they perceive to be a healthy meal. Where applicable, participants are given several options as to which of their usual foods are acceptable for each protocol specified food modification.

During the follow-up period, participants are contacted by phone and text messages to ensure protocol compliance. For participants using the study-specific smartphone apps, a web dashboard is used to monitor the completeness of dietary logging and CGM scanning, with outreach to participants initiated when missing data is detected. Participants using paper logs and a CGM reader, and therefore for whom no dashboard information is available, are contacted daily to ask about protocol compliance. Ad hoc midstudy visits are used to further ensure accurate data collection. If the outreach identifies a problem with a CGM (ie, it was damaged, fell off, or malfunctioned), study staff provide a replacement within 24 hours during which time participants are asked to pause their meal protocol and restart once their CGM has been reapplied and recalibrated. If a test meal was not consumed as intended, participants are provided with the option to repeat the meal.

On day 15, participants are asked to remove their CGM. If need be, study staff help record or correct missing or inaccurate food, activity, and medication data.

Statistical Analysis Plan

The study's primary outcome is PPGR. Following the Wolever and Jenkins method [31], as adapted by Zeevi et al [18], Mendes-Soares et al [20], and Berry et al [32], logged meal times and continuous glucose measurements will be used to calculate the incremental area under the curve. Before conducting analyses, meals logged less than 30 minutes apart will be merged and meals logged within 90 minutes of other meals will be removed. Meals that are very small (<15 g and <70 calories), very large (>1 kg), with implausibly low PPGR values (ie, a PPGR < 5 mg/dL·h after consuming ≥ 40 g of carbohydrates), that are incompletely logged, and which are consumed in the first and last 12 hours of the CGM connection will also be removed. To reduce noise, the median of all glucose values from the 30-minute period before the meal will be taken as the initial glucose level, above which the incremental area will be calculated. Meals that had incomplete glucose measurements in the time window of 30 minutes before and 2 hours after the logged mealtime will be filtered out.

Descriptive statistics will be used to plot the range of PPGRs responses to standardized test meals as well as the correlation between PPGR and the nutritional composition of the logged meals (ie, carbohydrates, fat, and protein).

A machine learning predictor will be developed based on stochastic gradient boosting regression (XGBoost, version 2.2.1; The XG Boost Contributors) [33] using the XGBRegressor class. PPGR will be predicted as the sum of predictions from thousands of decision trees. Trees will be inferred sequentially, with each trained on the residual of all previous trees. The features incorporated in each tree are selected by an inference procedure from features representing meal content (ie, calorie, protein, carbohydrate, and fiber content), meal timing, baseline demographics (ie, age, sex, predominant diet, health conditions, family history, and current medications), baseline survey results (ie, WHO STEPS, WHO-5, Diabetes Distress School, Wilson Adherence Scale, and Pittsburgh Sleep Quality), baseline biometric values (ie, blood pressure, heart rate, weight, height, and body measurements at the upper arm, thigh, calf, waist, and hips), baseline laboratory values (complete blood count, HbA_{1c}, blood electrolytes, creatinine, cholesterol, and urinalysis), as well as CGM, heart rate, and activity data.

Performance will be assessed by holding out 30% of the sample and using 5-fold cross-validation in which cross-validation participants are divided into 5 groups, the model will be trained on the other 4 parts. Random datasets of the same size as the original will be sampled with replacement from the original dataset, and the entire training and validation process will be repeated. The performance will be measured by the ability to accurately predict meals reported by the held-out participants. Prediction results will be aggregated, and Pearson product moment correlation with the measured PPGRs will be reported. The SE for the calculated performance will be assessed using at least a thousand iterations of bootstrapping until the errors stabilize. Model discrimination will be assessed using a binary cut-point for PPGR, set at the 50th percentile of all observed PPGR values, plotting a receiver operating characteristic curve (ROC) and then calculating the area under the ROC.

Sample Size Considerations

A total of 1050 individuals will be targeted for recruitment. Assuming a 5% loss to follow-up, this corresponds to 1000 evaluable individuals at the end of the study. The study has been designed to predict postprandial glucose responses based on individual characteristics and 1000 participants followed for 14-days will result more than 4 million glucose readings (assuming glucose readings from the CGMs every 5 minutes) and 42,000 meals (assuming 3 meals per participant per day). This volume of data will also provide more than 80% power to detect correlations of a magnitude of r=0.13 (R^2=0.02) with P<.005. We will also be sufficiently powered to detect effects of r=0.17 (R^2=0.03, ie, explaining 2.7% of interindividual variation) with P<.001, that is, accounting for 5000 independent hypothesis tests.

Ethical Considerations

This study was approved by the following ethics committees at all institutions enrolling patients: SShrey Hospital Institutional Ethics Committee (DHINDIA_2021_01A04), Inamdar Multispecialty Hospital Ethics Committee (DHINDIA_2021_01A04), Neelima Hospitals Institutional Ethics Committee (DHINDIA_2021_01A04), Jaipur National University Institutional Ethics Committee (JNUIMSRC/IEC/2022/06), Maharaja Agrasen Hospital Institutional Ethics Committee EP/F-174), Ganesh Shankar Vidyarthi Memorial Medical College Ethics Committee (EC/72/March/2022), Mar Augustine Golden Jubilee Hospital Institutional Ethics Committee (DHINDIA_2021_01A04), Medisys Clinisearch Ethical Review Board, Dayanand Medical College and Hospital Drug Trials Ethics Committee (DMCH/DTEC/2020/1242), Chennai Meenakshi Multispecialty Hospital Ethics Committee (CMMHEC/22/02), Sparsh Hospital Institutional Ethics Committee (ZZA78309), Medical College of Kolkata Institutional Ethics Committee (MC/KOL/IEC/SPON/1296/03/22), Ethics Committee Downtown Hospital, and CHL-Hospitals Integrity Ethics Committee.

Results

Data collection commenced in May 2022, and the results will be ready for publication by October 2025. Results from our study will generate data to facilitate the creation of machine learning models to predict individual PPGR responses and to facilitate the prescription of personalized diets for individuals with T2D.

Discussion

Study Implications

This study will provide the first large scale examination of variability in blood glucose responses to food in India and will be among the first to estimate PPGR variability for individuals with T2D in any jurisdiction. We hypothesize that there will be substantial interindividual variability in PPGR and that, based on the data collected from this study, machine learning models will be able to accurately predict individual PPGR responses.

This will facilitate the prescription of truly personalized diets for individuals with T2D.

These results will be particularly important in the context of the rapidly rising prevalence of T2D in India [34]. Along with medications and physical activity, diet is a key tenant of effective blood glucose control [15]. Like in other jurisdictions, guidelines call for individualization of meal planning, which is sometimes referred to as "Medical Nutritional Therapy." Despite this, personalization of dietary plans are generally based upon broad constructs like age, activity level, health status, and preferences, and, for all patients, tend to emphasize overall calorie reductions and minimization of carbohydrate [16]. especially added sugars and refined grains, in favor of the consumption of nonstarchy vegetables and foods that are high in protein [35].

However, emerging data demonstrates that there are marked interindividual responses to food [17], attributed to differences in physical activity [36], gut microbiome [18,19,37], and genetics [38], including in variations in skeletal glucose transporters related to insulin resistance [39]. For example, a study conducted in the United States among nondiabetic individuals with a mean BMI of 27 found PPGR to a standardized meal of bagel and cream cheese ranged from 6 to 94 mg/dL·h [20]. A similar study conducted in Israel enrolled nondiabetic individuals of whom 3-quarters had a BMI ≥ 25 and found mean PPGR to bread and butter of 44 mg/dL·h but the bottom decile had responses of ≤ 15 mg/dL·h and the top decile has responses ≥ 79 mg/dL·h [18]. Similar data have been generated for individual without diabetes in the United Kingdom and the United States [19,20], and for individuals with type 1 diabetes in Israel [40].

There is exceptionally limited data for variability in PPGR for individuals with T2D in the peer-reviewed although it is highly likely that such variability exists [22]. The primary goal of our study is to fill this void and to generate an India-specific machine-learning models on the basis of which PPGR can be predicted with high accuracy for T2D. Similar models have been built in other jurisdictions. For example, a machine learning algorithm trained on CGM data, dietary, activity, anthropometrics, and gut microbiota for nondiabetic individuals in Israel was much more accurate at predicting PPGR than generic models based on the carbohydrate content or the amount of calories in a meal [18]. A separate US-based study had similar findings [20].

Among individuals with diabetes, a study in the Netherlands that included a small number of individuals with T2D along with individuals with prediabetes and normal glucose metabolism, a machine learning model based on CGM data was highly accurate in predicting future glucose values but this study did not specifically evaluate the ability to predict PPGR [41]. A US study of 1000 patients of whom 1-quarter had T2D found that a machine learning model trained on CGM, HRM data and food logs was highly accurate at predicting PPGR but this study has, to our knowledge, only been published in abstract form [22]. These studies have all relied on CGM data to make their predictions. While these devices are increasingly used, practice guidelines do not recommend their long-term use for most individuals with T2D [42]. Accordingly, a key goal of our study will be to explore the ability to predict PPGR response without reliance on CGM data or with very limited blood glucose data from patients.

Limitations

There are several limitations to our approach. Our approach is purposely pragmatic and is intended to simulate real-world circumstances for individuals with T2D living in India. Similar to studies conducted in other jurisdictions, we rely on self-reported dietary and activity information. And, while we are auditing patient logs on an ongoing basis, there may nevertheless be issues with protocol adherence that may undermine the accuracy of the data we collect. Participants are being recruited from clinics, predominantly caring for individuals with diabetes, are required to have functional English literacy and a cellphone capable of running study specific devices. Thus, our results may not be fully generalizable to patients who do not fulfill these criteria. Finally, some of the enrollment has overlapped with the COVID-19 pandemic, which may have influenced access to health care, dietary practices, and glucose control for individuals with T2D.

Conclusion

In conclusion, this study will provide the first large scale examination variability in blood glucose responses to food in India and will be among the first to estimate PPGR variability for individuals with T2D in any jurisdiction. Results from our study will generate data to facilitate the creation of machine learning models to predict individual PPGR responses and to ultimately facilitate the prescription of truly personalized diets for individuals with T2D.

Acknowledgments

The authors wish to thank the site investigators and patients participating in the study as well as IQVIA for their assistance identifying study sites and overseeing the study conduct. This work is supported by Decipher Health, Inc.

Data Availability

The datasets generated during and analyzed during this study are not publicly available as they will be used for commercial application. Data may be available on reasonable request after executing appropriate data use and licensing agreements.

Authors' Contributions

All authors meet International Committee of Medical Journal Editors (ICMJE) criteria. NKC had overall responsibility for the study design and drafted the trial protocol and manuscript. MM is the co-principal investigator, had overall responsibility for the study design, and helped draft the study protocol and manuscript. SP and JS contributed meaningfully to study design and implementation as well as the manuscript. All authors contributed to the refinement of the study protocol and approved the final manuscript.

Conflicts of Interest

NKC and JS receive consulting fees and hold equity in Decipher Health. SP is an employee of Decipher Health. MM is an employee and holds equity in Decipher Health.

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Abbreviations

CGM: continuous glucose monitor
HbA_{1c}: hemoglobin A1c
PPGR: postprandial glucose response
ROC: receiver operating characteristic
STEPS: STEPwise Approach to Non-Communicable Disease Risk Factor Surveillance
T2D: type 2 diabetes mellitus
WHO-5: World Health Organization-Five Well-Being Index

Edited by T Leung; submitted 08.04.24; peer-reviewed by C Xiang, B Reshmi; comments to author 29.07.24; revised version received 15.09.24; accepted 27.09.24; published 23.01.25.

Please cite as:
Choudhry NK, Priyadarshini S, Swamy J, Mehta M
Use of Machine Learning to Predict Individual Postprandial Glycemic Responses to Food Among Individuals With Type 2 Diabetes in India: Protocol for a Prospective Cohort Study
JMIR Res Protoc 2025;14:e59308
URL: https://www.researchprotocols.org/2025/1/e59308
doi:10.2196/59308
PMID:39847416

Protocol

Digital Home-Based Self-Monitoring System for People with Heart Failure: Protocol for Development of SmartHeart and Evaluation of Feasibility and Acceptability

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Abstract

Background: Heart failure (HF) is a chronic, progressive condition where the heart cannot pump enough blood to meet the body's needs. In addition to the daily challenges that HF poses, acute exacerbations can lead to costly hospitalizations and increased mortality. High health care costs and the burden of HF have led to the emerging application of new technologies to support people living with HF to stay well while living in the community. However, many digital solutions have not involved consumers and health care professionals in their design, leading to poor adoption. The SmartHeart project aimed to codevelop a smart health ecosystem to support the early detection of HF deterioration and encourage self-care, potentially preventing hospitalizations.

Objective: This study aims to provide an overview of the SmartHeart project by describing our approach to designing the SmartHeart system, outlining its features, and describing the planned pilot study to determine the feasibility of the system.

Methods: We used the Integrate, Design, Assess, and Share (IDEAS) framework to guide the development of the SmartHeart system, involving users (people with HF and their caregivers) and stakeholders (health care providers involved in the management of HF) in its design. SmartHeart is a complete remote heart health monitoring and automated feedback delivery system. It includes 2 user interfaces for patients: an Amazon Alexa conversational agent and a smartphone app. The system collects physiological, symptom, and behavioral data through wireless sensors and self-reports from users. These data are processed and analyzed to provide personalized health insights, self-care support, and alerts in case of health deterioration. The system also includes a web-based user interface for health care professionals, allowing them to access data, send messages to users, and receive notifications about potential health deterioration. A single-arm, multicenter pilot trial (N=20) is planned to determine the feasibility and acceptability of SmartHeart before evaluation through a randomized controlled trial. The primary outcome will be a description of the study's feasibility (recruitment, attrition, engagement, and changes in self-care).

Results: The SmartHeart study started in January 2021 on procurement of funding. Recruitment for the pilot trial started in August 2024 and will be completed by March 2025. We have currently enrolled 12 participants. Follow-up of all participants will be completed by the end of May 2025.

Conclusions: We have co-designed and developed a complete remote heart health monitoring and automated feedback delivery system for the early detection of HF deterioration and prevention of HF-related hospitalizations. The next step is a pilot study, which will provide valuable information on feasibility and preliminary effects to inform a larger evaluation trial. SmartHeart has the potential to augment existing health services and help people with HF stay well while living in the community.

International Registered Report Identifier (IRRID): DERR1-10.2196/62964

(JMIR Res Protoc 2025;14:e62964) doi:10.2196/62964

KEYWORDS

smart home; health; chronic conditions; digital health; technology; behavior change; wearables; methodological considerations

Introduction

Burden of Heart Failure and Importance of Self-Care

Heart failure (HF) is a complex life-threatening syndrome associated with high mortality and morbidity, poor quality of life, diminished functional capacity, and substantial health care burden [1,2]. HF affects over 64 million people worldwide [1]. People with HF experience debilitating symptoms, including shortness of breath and fatigue, which significantly impact their daily activities and quality of life [3]. Beyond these persistent daily challenges, individuals experience acute exacerbations, that frequently necessitate hospitalization [4]. These hospitalizations are strongly correlated with increased mortality. In Australia, data indicates that individuals experiencing acute HF exacerbations requiring hospitalization face a 50% reduction in their remaining life expectancy (10 years for those aged 65-75 years) [5]. Research suggests that two-thirds of HF-related hospital admissions could be prevented by enhanced coordination of postacute care and improved self-care [3]. Self-care refers to the process of maintaining health through health promotion and preventive practice [3]. While international guidelines make self-care integral for HF management, people find managing their condition while living in the community difficult, and adherence to clinical guidelines is poor [3].

Toward a Smart Health Ecosystem

There is an urgent need for new scalable models of person-centered health care in which care for long-term conditions such as HF shifts from the clinic to the home [6]. The COVID-19 pandemic was a catalyst for swift, wholesale change to the way we view and provide health care; there has been a significant increase in the use of telehealth and online care services, increased acceptance of digital health technologies by the medical community and the public, and broader recognition of the need to embrace digital health approaches to create a resilient health care system [6]. However, despite the potential for digital health to improve HF management [7], previous approaches to designing digital health interventions have largely failed to include patients and clinicians [8]. This can lead to lower levels of program adoption by users and increased dissatisfaction, stress, and nonadherence [9].

We previously argued for a smart health ecosystem, a holistic approach to support people living with long-term conditions that incorporate sensing, processing, and communication technologies [7]. Such an ecosystem uses a comprehensive network of internet-connected sensors (referred to as the Internet of Things) to collect data about the patient in the home [10,11] and processes these data to provide near–real-time individualized monitoring. It also uses predictive models to anticipate the need for medical intervention (eg, when detecting warning signs of decompensation) and support with self-care activities. While many of these discrete technologies exist, we bring them all together into a single system (named SmartHeart) to support people to better manage their HF at home and in the community. It is proposed that such a system can help maintain health outcomes, improve quality of life, promote independence, and reduce carer burden [12,13].

In this article, we present an overview of the SmartHeart project and describe its design and development approach. We provide a detailed description of the SmartHeart system and outline the planned pilot study to evaluate its feasibility and acceptability.

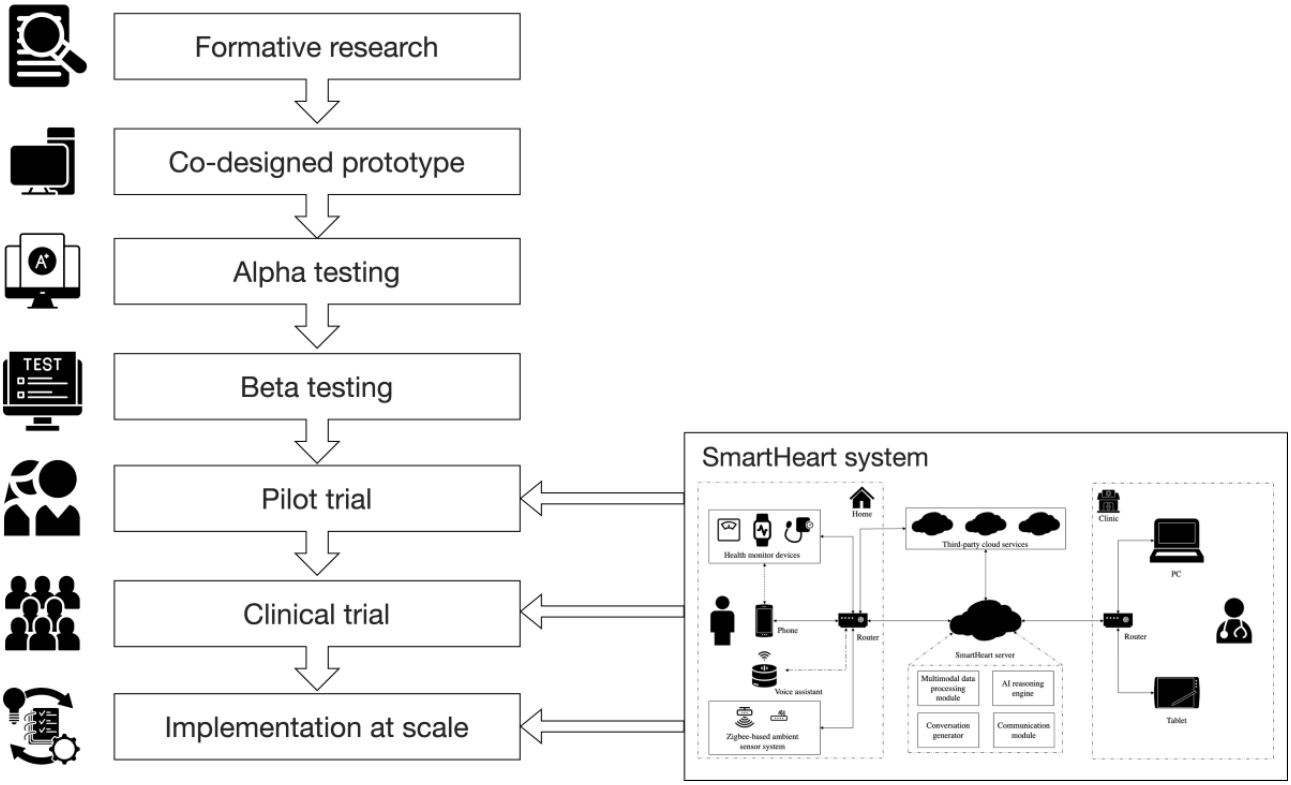
Methods

SmartHeart Project

To guide the SmartHeart project, we used the Integrate, Design, Assess, and Share (IDEAS) framework [14]. The IDEAS

framework is an intervention-specific framework for the development of digital interventions, fitting the nature of our proposed intervention [15]. Moreover, the framework combines behavioral theory with design thinking, which are complementary perspectives that can promote the acceptance and adoption of an intervention [15]. The IDEAS framework proposes ten steps: (1) empathize with target users, (2) specify target behavior, (3) ground in behavioral theory, (4) ideate implementation strategies, (5) prototype potential products, (6) gather user feedback, (7) build a minimum viable product, (8) pilot potential efficacy and usability, (9) evaluate efficacy in a randomized controlled trial (RCT), and (10) share intervention and findings [14]. In addressing steps 1-7 of the IDEAS framework, we undertook a range of studies to co-design and develop the SmartHeart system. As part of step 7, build a minimum viable product, we undertook an additional alpha- and beta-testing phase. The methods and results of these studies are briefly described in this article and the development studies are reported in full elsewhere [16,17]. The protocol for step 8 of the IDEAS framework, pilot potential efficacy and usability, is presented later in this article and will inform the design of a larger hybrid RCT to assess the effectiveness and implementation of SmartHeart, which we hope will guide subsequent delivery at scale. Figure 1 presents the phases of the overall SmartHeart project.

Figure 1. Phases of the SmartHeart project.



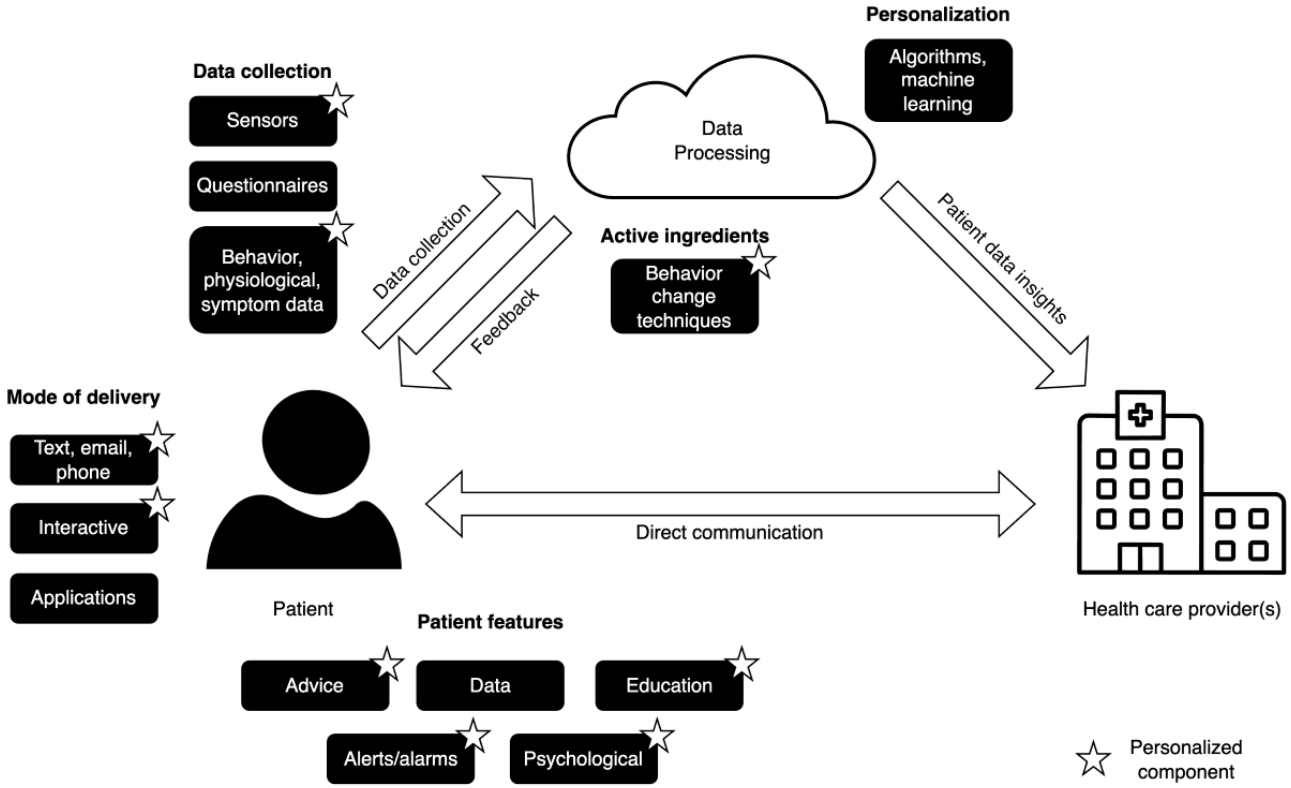
Approach to Designing the SmartHeart System

As part of the formative research phase, we conducted a scoping review of existing smart health ecosystems to support people with HF [18]. This study allowed us to identify data collection, personalization, behavior change, patient-facing, and mode of delivery features of similar interventions (refer to Figure 2). These features provided us with initial ideas for the SmartHeart system.

Then, we sought to better understand the lived experiences of individuals with HF in the community and the self-care strategies they used. This involved conducting in-depth interviews with individuals living with HF (n=9) [17]. Following this, we explored potential components and features for SmartHeart from the user perspective through workshops with individuals living with HF (n=16) and their caregivers (n=4) [16]. To identify consensus-based recommendations for potential intervention features, we used the Delphi method with 15 health care providers with experience caring for people with HF (eg, general practitioners (GP), cardiologists, nurses, pharmacists, and physiotherapists) [19]. We also conducted in-depth interviews with health care providers (n=9) [20].

Building upon these findings, we refined the SmartHeart prototype through a series of co-design workshops. Specifically, we conducted 4 co-design workshops with health care providers (n=15) to gain insight into how the system would work in practice and to refine the initial prototype [16]. Subsequently, 2 further co-design workshops were conducted with people with HF (n=6) to inform the user-facing app features, and optimize the overall design look, feel, and navigation logic.

Figure 2. Intervention features identified in the scoping review.



On completion of the SmartHeart prototype, we conducted alpha testing to evaluate the system's core functionalities, user interface, and performance under controlled conditions. For alpha-testing, four members of the research and development team used the system for 6 weeks, which allowed us to assess the system's responsiveness and identify and resolve any technical issues. Then, beta testing was undertaken to assess the system's responsiveness, data accuracy, and user experience. For beta testing, 5 people with HF used the prototype system for 4 weeks. Participant feedback from this testing was used to improve system onboarding, app performance, and data visualization.

SmartHeart System

In undertaking the design and development process outlined above, we developed the SmartHeart system (herein, SmartHeart), a smart health ecosystem to support the early detection of HF deterioration and prompt action by users with the aim of preventing HF-related hospitalizations. SmartHeart comprises components for patients (and their caregivers) and healthcare providers (ie, cardiologists, HF nurse practitioners, or other nurses).

Patient Components

User interface: Patients and caregivers interact with SmartHeart through an Amazon Alexa Echo Show 8 (second generation), featuring an 8-inch HD touchscreen, which serves as the primary user interface and conversational agent (Figure 3). In addition, a bespoke smartphone app (Figure 4), offers an alternative interface when Amazon Alexa is not available, such as when users are away from home. Amazon Alexa was selected based on access, ease of deployment, and programmability. In its current form, Amazon Alexa can facilitate interaction with people in their own language (currently 9 languages available). The smartphone app also supports multiple languages (for initial testing, we have included Hindi and Mandarin) and time zones.

Figure 3. Screenshots of SmartHeart conversational agent.

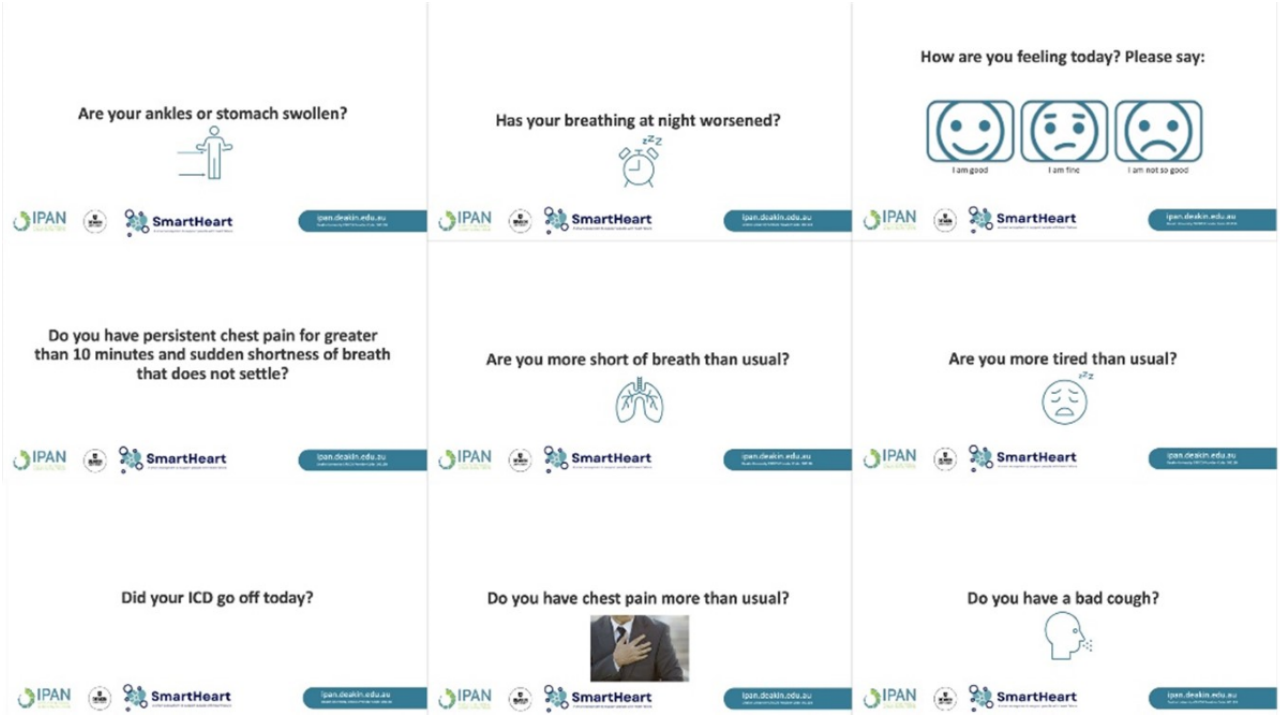
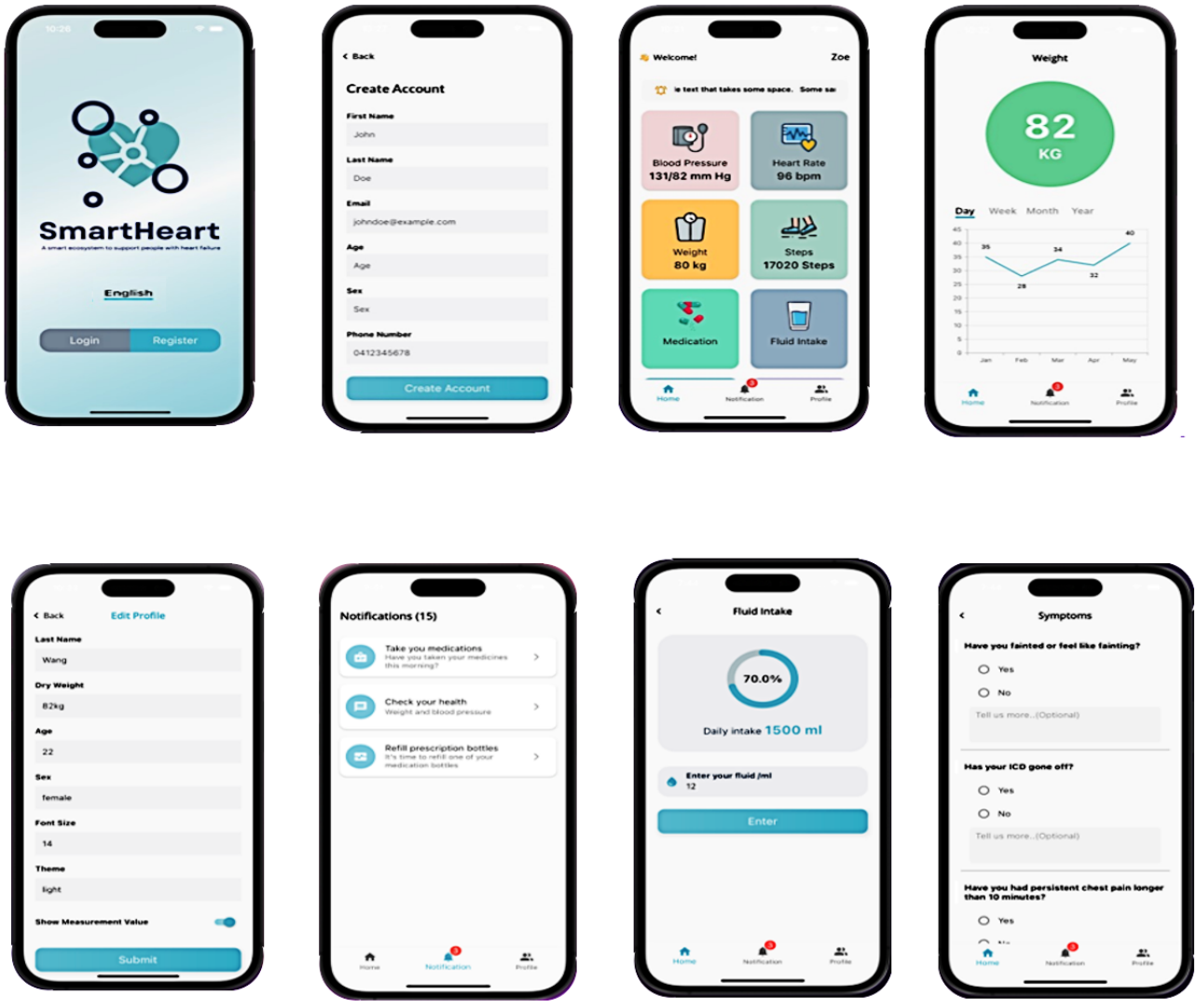


Figure 4. Screenshots of the SmartHeart app.



Data Collection

SmartHeart will collect physiological, symptom, and behavioral data through wireless sensors and self-reports. The sensors included and the parameters they measure are outlined in Table 1. Users can also self-report symptoms at any time through the Amazon Alexa or smartphone app. Amazon Alexa will also periodically check in with users through timed ecological momentary assessments to gather feedback on symptoms [21]. The symptom questions are based on current practice, which involves people with HF completing a paper and pencil diary on standard symptoms (eg, shortness of breath, dizziness, cough).

To collect data on medication use, we use a proxy measure of medication access, as measured through a Philips Hue infrared motion sensor placed at the site of medication storage (eg, cupboard, drawer). This sensor will timestamp potential medication access. This approach was adopted to account for the heterogeneity of medications taken and strategies used by participants in managing their medications [16,17]. The pilot study described below will allow us to determine the feasibility of this approach. The motion sensor is connected to the Philip hub using Zigbee, a low-power wireless mesh network for connected devices. The Philips hub handles data transmission to the cloud.

Table 1. Wireless sensors and parameters measured.

Sensor	Parameter
Withings blood pressure monitor connects wireless blood pressure monitor	Blood pressure
Samsung Galaxy Watch Pro 5	Heart rate; activity levels (including physical activity, inactivity, and activities of daily living)
Withing's Body Smart Bluetooth scales	Weight
Phillips Hue infrared motion sensors	Medication access (as a proxy for medication use)

Support Features

The SmartHeart system offers a wide range of features aimed at supporting the early detection of HF deterioration and encouraging proactive self-care.

Through Amazon Alexa, users can access educational materials on topics such as healthy eating and heart health, and a home-based physical activity program. They can also set their own reminders for tasks such as taking medication, monitoring weight and blood pressure, monitoring mood, and attending health care appointments. Health data are presented to users in the form of graphs and charts, allowing them to track and self-monitor their health over time.

SmartHeart delivers alert messages according to a matrix of possible outcome states from all combinations of sensor and symptom measurements and a corresponding rule set to define conversational agent actions. We developed the matrix based on previous work [22], but it was modified to align with the Australian HF Guidelines [2]. Alert messages and actions associated with each outcome state were validated during a face-to-face user panel workshop with health professionals (cardiologists, HF nurses, physiotherapists) at 3 hospitals (Royal Brisbane and Women's Hospital, Bendigo Hospital, and Austin Hospital). For example, combinations of blood pressure, weight gain, and symptoms corresponding to a critical or urgent outcome state (Figure 5) will notify patients via the conversational agent (or smartphone app) to seek immediate medical support and prompt a text message to HF nurses to review data via the health care provider interface.

The numbers represented in Figure 5 are various patient alert messages (see Table 2).

Based on HF guidelines [2] and previous text messaging research in heart disease [23], we also developed a package of self-care support comprising data-driven and nondata-driven messages. In response to sensor data and self-reported symptoms, users will receive educational support and prompts to modify key self-care activities. For example, if the combinations of blood pressure, weight, heart rate, and symptoms correspond to a normal outcome state (Figure 5) users would receive personalized HF education. Alternatively, if low physical activity levels and high fluid intake were recorded, SmartHeart would prompt users to reduce fluid intake and increase their step count. This educational support and prompts will be delivered by the conversational agent or smartphone app.

In addition, users will receive regular unidirectional push notifications through the SmartHeart app only. These push notifications, delivered twice a week (1 message per day on Monday and Friday) are not data-driven and aim to encourage users to take their medication, eat a healthy diet (eg, low salt), manage their fluid intake, participate in physical activity, and reduce sedentary behavior (Textbox 1). Content for these nondata-driven notifications was adapted from our previous interventions [24,25]. Participants can opt in or out of receiving push notifications by toggling this feature on or off through the smartphone app.

Figure 5. Matrix of outcome states from possible combinations of measurements. The numbers represented in Figure 5 are various patient alert messages (refer to Table 2). Ab: abnormal; BP: blood pressure; HR: heart rate; N/A: not applicable; N: normal.

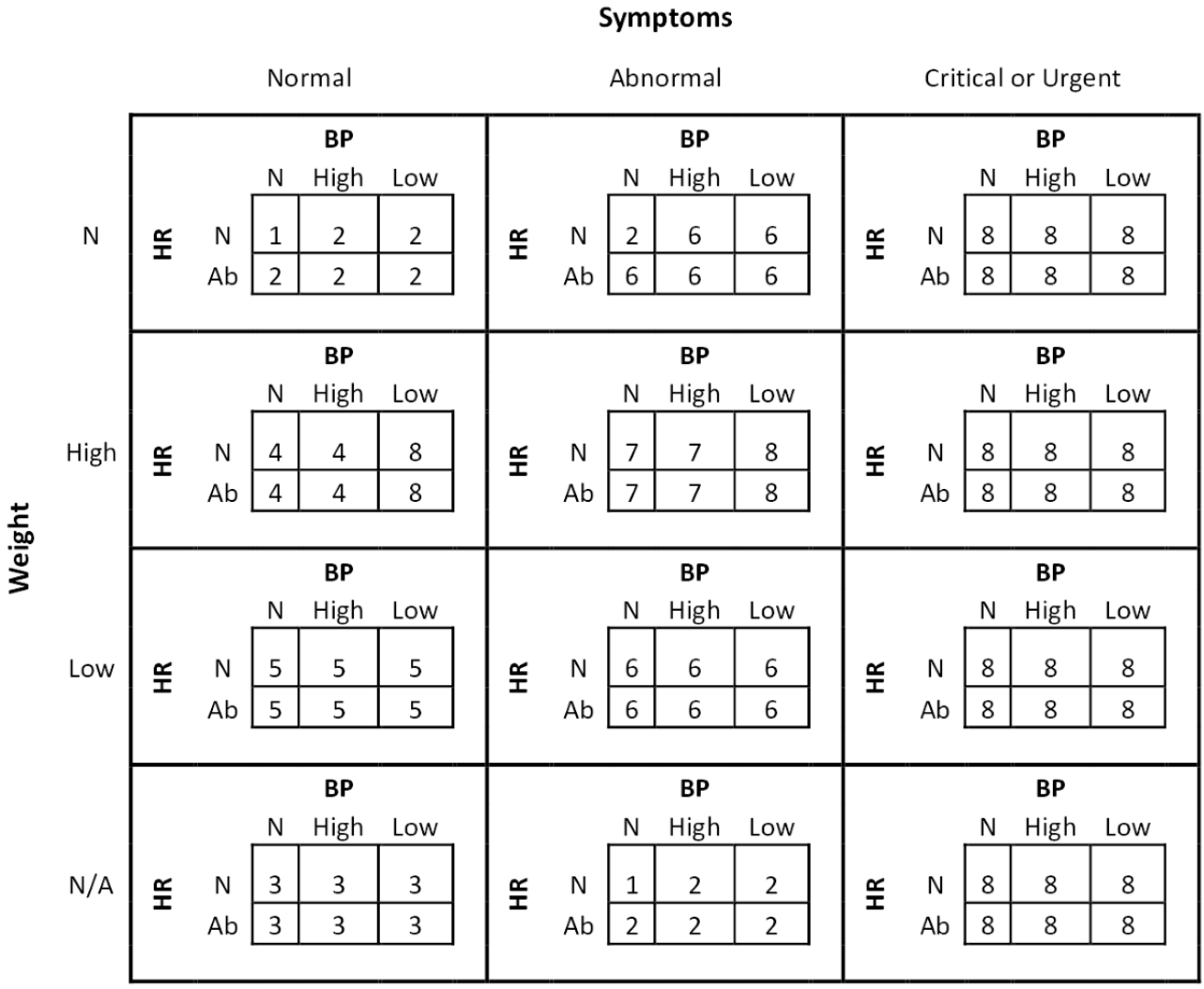


Table 2. Examples of alert messages provided through SmartHeart.

Message number	Example message
1	“Your measurements are fine today”
2-3	“If you feel worse later today, use the system to record your symptoms”
4-5	“Contact your Heart Failure Nurse or General Practitioner (GP). Follow doctor’s orders. Restrict salt and fluids.”
6-7	“Contact your GP now or go to the emergency department if you feel you should. Follow doctor’s orders. Restrict salt and fluids”
8	“Call 000 now”

Textbox 1. Examples of regular SmartHeart unidirectional push notifications by category.

Health

- How much time do you spend sitting every day? Decreasing the amount of time you spend sitting can improve your heart health, even if you engage in regular exercise.
- Although physical activity is useful for heart health, taking the first step can be the biggest challenge. Choose a physical activity that you like, anything that makes you more active.
- Think about barriers that can stop you from being active. Choose an activity that is more fun. Some people find it useful to invite a friend or a family member to join their daily exercise.

Medication adherence

- Encountering obstacles with your medication regimen? You don't need to tackle these challenges by yourself. Your doctor is there to provide assistance.
- Consistently taking your medications is essential for effectively managing your heart condition and preserving the associated benefits.
- Consistently adhering to your medication regimen is essential in managing your condition. If you believe you're having side effects, it's crucial to discuss it with your doctor. They could recommend a different medication that suits you more effectively.

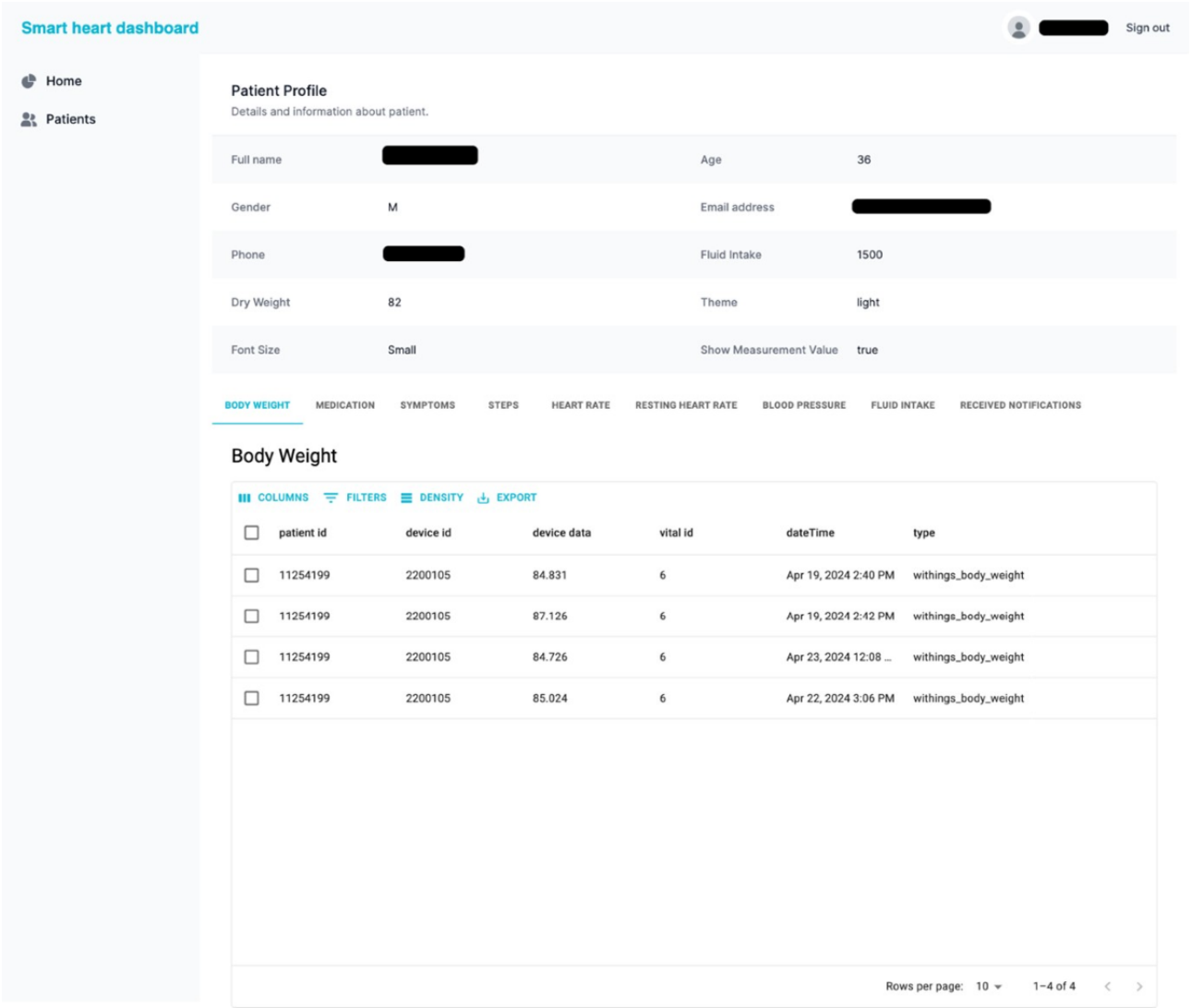
Refill prescription bottles

- Running out of your medication could lead to a few days without it, but this is a preventable situation. Stay prepared by marking your next prescription refill date on your calendar or setting a reminder on your mobile phone.
- Ensuring the continuous availability of your medications is a crucial measure, so be certain you're aware of the upcoming refill date. Incorporating a calendar reminder can be a valuable prompt when required.
- Think about where it would be most suitable for you to store extra medications as a backup strategy.

Health Care Provider Components

Health care providers (ie, cardiologists, HF nurse practitioners, or other nurses) access the SmartHeart web-based user interface to register participants, review health data, and view notifications patients have received. If necessary, and according to clinical practice, health care providers will contact patients directly by telephone (Figure 6).

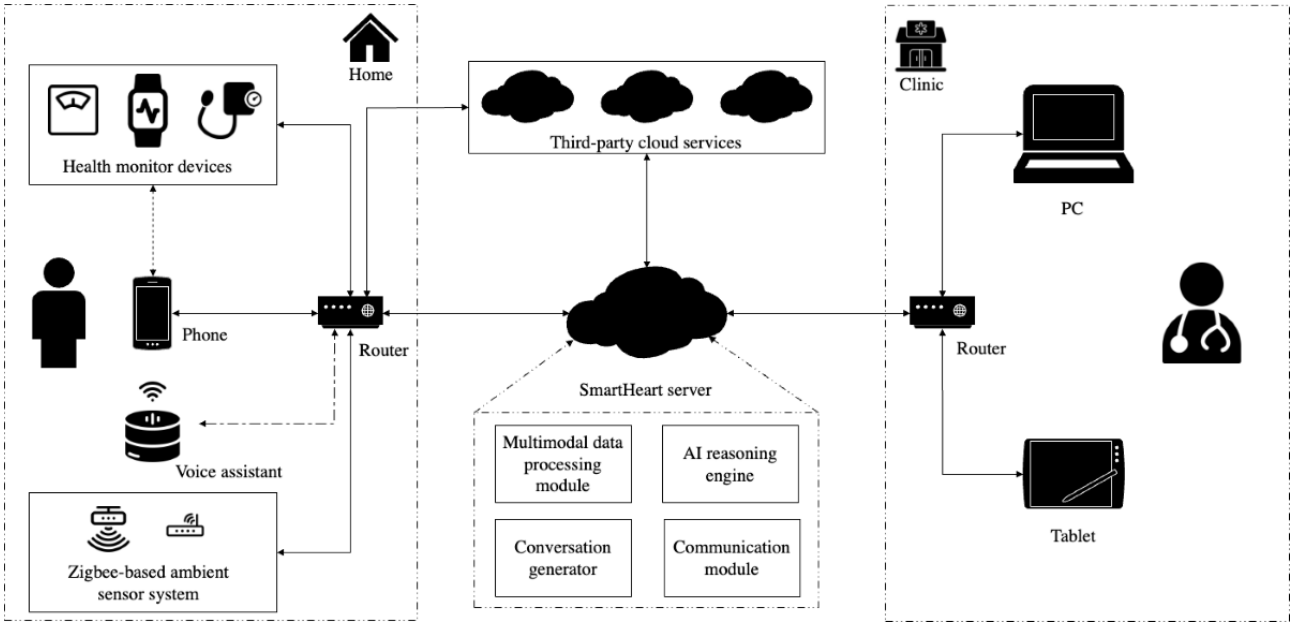
Figure 6. Health care provider interface.



System Architecture and Functions

Cloud-to-cloud integration connects and transmits users' data from third-party (sensor vendor) clouds to the SmartHeart data processing server (Figure 7). This server processes multimodal data (ie, health monitoring device data and self-reported symptoms), and makes logical inferences to generate personalized recommendations for the users in different formats (ie, conversation and report). It also handles all data transmissions between end users and clinicians. Data collected through SmartHeart are stored in a secure cloud-based server hosted in Australia. All data capture, storage, and transmission are secured using state-of-the-art encryption technologies according to Health Insurance Portability and Accountability Act requirements.

Figure 7. SmartHeart system architecture. AI: artificial intelligence.



SmartHeart Pilot Study Protocol

Objectives

This pilot study aims to assess the feasibility and acceptability of SmartHeart and inform the design of a larger hybrid RCT to assess effectiveness and implementation outcomes.

Sample Size

The sample size for pilot feasibility studies should be based on practical considerations including participant flow, budgetary constraints, and the number of participants needed to reasonably evaluate feasibility goals [26]. For this study we aim to recruit a total of 20 participants, which will be sufficient to determine the feasibility of delivering SmartHeart, allowing for exploration of participant feedback regarding acceptability, usability, and uptake.

Participants and Eligibility Criteria

Participants will be 20 adults (aged 18 years or more) with a documented clinical diagnosis of HF, outpatients at the time of recruitment, with access to the internet, and able to read and understand the English language (for informed consent purposes) will be eligible. SmartHeart support is available in multiple languages, so people for whom English is not a first language can use it. Individuals will be excluded if they have difficulty communicating with study personnel or a conversational agent due to speech or untreated hearing problems; are planning to be away from home for ≥4 weeks during the intervention; have progressive neurological disorders including Parkinson Disease and multiple sclerosis; have schizophrenia or bipolar disorder; have renal disease requiring dialysis; have any other disorder of such severity that life expectancy is less than 12 months; or have any cognitive or physical impairment or disability that in the opinion of either the participants' GP or specialist, or the study investigators would result in the participant having difficulty interacting with SmartHeart without support.

Recruitment Process

Participants will be identified by clinical staff at the 2 participating sites (Austin Health and Bendigo Health in Victoria). Research nurses at study sites will identify eligible individuals before hospital discharge and through outpatient cardiac clinics. Nurses will provide potential participants with information and consent forms and refer interested individuals to the research team. Approximately one week after the provision of study information, a researcher will confirm interest, answer questions, and schedule a baseline assessment if individuals indicate an interest in consent.

Procedures

SmartHeart will be installed in participants' homes and demonstrated by a trained researcher. Written, verbal, and audio-visual support will be provided to help participants engage with the system. A loan phone (Android) will be provided free of charge to those who do not own one. With the help of SmartHeart, participants will be asked to record daily measurements of weight and blood pressure and answer questions about their symptoms. All participants will have access to their usual cardiology and general practice care throughout the course of the study.

For this study, HF nurses will have access to the clinician portal through which they can review participants' data, including notifications. HF nurses will receive email notifications to alert them of potential changes to the participants' HF condition. Australian HF guidelines and best practices will be followed when responding to notifications. HF nurses will be available to review sensed data and respond to notifications during their working hours; however, SmartHeart will alert participants to contact their GP as first contact.

Data Collection

Data will be collected at baseline and the end of the 8-week intervention period using self-reported questionnaires and qualitative interviews (refer to Table 3 for an overview).

In addition, to the items in Table 3, a qualitative researcher will conduct one-to-one in-depth interviews with all participants, their caregivers (if applicable), and health care providers involved in the delivery of SmartHeart. Interviews will be based on the UK National Institute for Health and Care Excellence (NICE) Evidence framework for digital health technologies [27] and will address acceptability, demand, practicality, frequency of monitoring, burden to participants, potential of provoking anxiety, scenarios in which the program would be best employed, compliance with functional components, facilitators, and barriers to participation.

Table 3. Summary of outcome measures.

Items	Description or tool used to measure the item	Baseline	During intervention	Postintervention (8 weeks)
Recruitment and attrition	Study recruitment will be recorded by a trained research assistant and will include the total number of participants referred to the study, numbers who agree to participants, and those who enroll in SmartHeart. The research assistant will also record the number of participants that complete the study as a measure of attrition.	✓	✓	✓
Engagement	System use logs will be collected through the SmartHeart system and will provide data on the frequency of use of SmartHeart features. These will not require user input.	—[a]	✓	—
Weight	Withings Body Smart Bluetooth scales	✓	✓	—
Physical activity	Samsung Galaxy Watch Pro 5	—	✓	—
Heart rate	Samsung Galaxy Watch Pro 5	—	✓	—
Blood pressure	Withings blood pressure monitor Connect wireless blood pressure monitor	—	✓	—
Symptoms	Self-reported HF symptoms through the SmartHeart app	—	✓	—
Self-care	Self-Care of Heart Failure Index [28], version 6 [29]	✓	—	✓
Usability	System Usability Scale [30]	—	—	✓
Health-related quality of life	European Quality of Life 5D 5-level questionnaire [31]; Minnesota Living With Heart Failure Questionnaire [32]	✓	—	✓
Medication adherence	Philips Hue Infrared Motion Sensor (proxy); Medication Adherence Rating Scale [33]	✓	✓	✓
Hospitalization	Data provided by sites or study nurses.	—	✓	✓

[a]Not applicable.

Self-Report Measures

Self-Care will be assessed using the Self-Care Heart Failure Index (SCHFI) [28], version 6 [29]. The SCHFI comprises 22 items and collects data on 3 domains (self-care maintenance, management, and confidence). Scores can be summed, but this is discouraged by the authors of the SCHFI. They recommend that the scales (maintenance, management, confidence) be used individually. Each scale is standardized to a score of 100. A score of ≥70 can be used as the cut-point to judge self-care adequacy, although evidence is provided that benefit occurs at even lower levels of self-care [29]. The reliability and validity of this measure have been well documented [29].

The System Usability Scale (SUS) comprises 10 items (each question with a Likert scale ranging from strongly agree to strongly disagree) and was designed as a "quick and dirty" measure of the usability of either hardware or software or both by end users' system [30]. Five questions are positively framed, and 5 questions are negatively framed. The process for computing an SUS score is as follows: (1) subtract 1 from the user's Likert ratings for odd-numbered items or questions, (2) subtract the user's Likert ratings from 5 for even-numbered items, (3) each item score will range from 0 to 4, and (4) sum the numbers and multiply the total by 2.5. This calculation will provide a range of possible SUS scores from 0 to 100.

Previous research has shown that a mean score of 68 is a useful benchmark [34].

Health-related quality of life will be measured using the European Quality of Life 5D 5-level (EQ-5D-5L) questionnaire [31] and the HF-specific Minnesota Living With Heart Failure Questionnaire (MLWHFQ) [32].

The EQ-5D-5L comprises 5Ds: mobility, self-care, usual activities, pain or discomfort, and anxiety or depression. Each dimension has 5 levels: no problems, slight problems, moderate problems, severe problems, and extreme problems. Participants are asked to indicate their health state by ticking the box next to the most appropriate statement in each of the 5Ds. This

decision results in a 1-digit number that expresses the level selected for that dimension. The digits for the 5Ds can be combined into a 5-digit number that describes the patient's health state. It also includes a visual analog scale that captures the participant's self-rated health. This can be used as a quantitative measure of health outcomes that reflects the participant's own judgment. The EQ-5D-5L has demonstrated excellent psychometric properties across a broad range of populations and health conditions [35].

The MLWHFQ is a 21-item multidimensional questionnaire designed to assess the health-related quality of life of people with HF in adults across physical, socioeconomic, and emotional or psychological dimensions. It is scored through a 6-point Likert scale (0-5), with a sum of item responses for total and dimension scores. The MLWHFQ has very good psychometric properties [36].

The Medication Adherence Rating Scale [33] is a 10‐item self‐report adherence scale that assesses both intentional ("I avoid using it if I can") and nonintentional medication nonadherence ("I forget to use it"). Psychometric properties are well established [37]. Scores range from 0-10 with higher scores indicating better attitudes toward medication.

Feasibility Outcomes

To inform decisions to progress to a definitive trial, there must be evidence of achieving key criteria for recruitment, engagement, self-care, and attrition. For this, the criteria in Textbox 2 will be used. These criteria were not based on published data but were developed following expert discussion with the chief investigator team, which comprised 2 cardiologists, an HF nurse specialist, 2 public health researchers, 2 exercise physiologists, one computer scientist, a health economist, and a biostatistician.

Textbox 2. Feasibility criteria and metrics.

Green: If all four green criteria are met, we will consider the study feasible (unless there is a clear indication from the qualitative interviews and our experience that would improve the study)

- At least 80% of the target sample size is recruited within 3 months.
- At least 50% of participants engaged with SmartHeart.
- At least 60% of participants maintained or improved their Self-Care of Heart Failure Index score.
- Attrition ≤20%. A rule of thumb states that >20% attrition poses threats to study validity [38].

Amber: If one or more of our amber criteria are met, we will consider the study as likely feasible but will consider the results of the feedback from the qualitative interviews and our experience to improve whichever criteria are not at the "green light" level before considering a full trial.

- 50%-79% of the target sample size is recruited within 3 months.
- 35%-49% of participants engaged with SmartHeart.
- 45%-59% of participants maintained or improved their Self-Care of Heart Failure Index score.
- Attrition 20.1%-35%.

Red: If one or more red criteria are met, we would consider the study as likely not feasible with the current protocol.

- <50% of the target sample size is recruited within 3 months.
- <35% of participants engaged with SmartHeart.
- <45% of participants maintained or improved their Self-Care of Heart Failure Index score.
- Attrition >35%.

Analysis

Descriptive statistics (mean and SD for continuous data, N and percentage for categorical) will be presented for all quantitative primary and secondary (eg, self-care behaviors, Health-Related Quality of Life) outcomes and will be the primary form of analysis. The EQ-5D-5L questionnaire will be scored using the Australian value set [39]. Within a person, cross-correlation matrices will also be generated [40].

Interviews will be audio-recorded and transcribed. We will use framework analysis to analyze the interviews, using predefined categories according to the NICE Evidence framework for digital health technologies [27].

Ethical Considerations

The study received ethical approval from the Deakin University Human Research Ethics Committee (HREC/76317/MH-202). A participant information sheet and consent form will be sent to participants during the baseline assessment. Written informed consent will be obtained at the baseline assessment before data collection.

Results

The SmartHeart project, including the proposed pilot study, received funding from the National Health and Medical and Research Council grant (grant number 2018698) and commenced in January 2021. This study was conducted in collaboration with health and academic partners in the states of Victoria and Queensland, Australia. Recruitment for the pilot

trial started in August 2024 and will be completed by March 2025. We have currently enrolled 12 participants. Follow-up of all participants will be completed by the end of May 2025. Once analysis from the pilot study has been completed, we will submit the findings for publication.

Discussion

Principal Findings

This article reports on the formative development of the SmartHeart system, a smart health ecosystem with advanced telemonitoring and behavioral support, offering a comprehensive, integrated, and coordinated approach to HF management. We also outline a protocol for piloting SmartHeart to inform a future RCT.

Consistent with the need to integrate consumers in health research [41], we have undertaken extensive user-centered design and engagement with end users. A comprehensive program of research, following the IDEAS framework was used in developing SmartHeart. Reflecting on the design and development process, we benefited greatly from using the IDEAS framework. Our formative work involving a scoping review, stakeholder interviews, and a Delphi survey was important for ideation and informing the prototype features and functions. Co-design workshops were critical in identifying the needs of users and health care providers. We hypothesize that this will likely maximize the acceptability, engagement, and usability of the SmartHeart system. However, the downside to this co-design approach was the much longer development timeframes to achieve the SmartHeart prototype.

SmartHeart incorporates a conversational agent (Amazon Alexa). With ongoing development, conversational agents have evolved into digital systems that aid the delivery of health interventions for individuals at the places most convenient for them. Using voice to interact with these agents is a more natural user interface than traditional mouse, keyboard, or touch interfaces, which may lower barriers to entry for many people, especially older adults, those culturally and linguistically diverse, and people with low literacy [42]. We also provide access to SmartHeart in multiple languages, increasing the accessibility of support to those who speak languages other than English. Furthermore, in Australia, SmartHeart could have a significant impact by providing greater access to health care, especially in high-priority rural and regional areas.

There are some limitations of the current system that warrant consideration. First, the system is currently Android-based; however, we offer participants an Android phone for the duration of the study, and we are developing an iOS version for future use. Second, the Samsung Galaxy watch used to collect data from participants is also only compatible with the Android system. Our future plans are to support most off-the-shelf smartwatches in the market, including Fitbit (Google; iOS and Android), Apple Watch (iOS), and Garmin. Third and finally, we use a cloud-to-cloud approach, which can be problematic when third-party providers (eg, Withings) provide updates affecting data capture. Our team will check and maintain the system on a regular basis to ensure all components are up to date, helping to mitigate this issue.

A risk mitigation strategy plan was developed for the funding application that supported this project. A key risk is the slow recruitment of participants. Our current recruitment strategy includes recruitment from participating partner hospital sites; however, we will mitigate risk by also recruiting from community HF support groups, general practices, and online through social media. The small number of participants may also be a risk as this may not be sufficient to inform feasibility; however, we have indicated in our ethics application that we may extend recruitment to mitigate this risk. Data security is another risk, which will be addressed by ensuring all data are anonymized, and data storage meets Melbourne and Deakin's Research Conduct Policy and the Research Data and Primary Materials Management Procedure. As mentioned earlier, all data will be stored securely on password-protected servers and in accordance with ethical procedures. Finally, because participants are required to provide consent in English, it is possible that the benefit of SmartHeart being available in different languages will not be realized. The requirement for consent in English is based on logistics; we do not have a resource to pay for interpreters; however, most participants in Australia for whom English is not a first language can read English for consent purposes.

The SmartHeart system has significant potential for future expansion and enhancement. While our current prototype uses desktop smart speakers, the integration of conversational agents on mobile devices (eg, phones, tablets, smartwatches) could extend the system's reach beyond the home environment. Furthermore, we are exploring the integration of generative artificial intelligence to enhance user engagement through more natural dialogue and personalized responses, leveraging a curated guideline-based database and retrieved augmented generation techniques. While the project's initial focus targets people living with HF, the system's architecture supports broad applicability to other long-term conditions. This versatility will be particularly beneficial for the increasing number of people managing more than one long-term condition. The system's adaptability is enhanced by the fact that challenges associated with HF significantly overlap with other health conditions, such as other cardiovascular conditions, chronic obstructive pulmonary disease, and diabetes, making the core functionality transferable. Potential adaptations include customizing symptom questionnaires for one or more conditions, implementing different wireless sensors, and refining the algorithms and support messages.

The next step is to assess the feasibility of this version of the SmartHeart system with both people with HF and health care providers. A pilot study will provide valuable information on feasibility and preliminary effects, which will inform the design of a larger proposed RCT. If clinical and cost-effectiveness are subsequently demonstrated, SmartHeart could augment existing health care services to support people with HF to stay well living in the community and living independently. The primary benefit of this solution is to empower people with HF to be more actively engaged in self-care and realize the unfulfilled potential for digital health to transform health care delivery. If proven

feasible, it could improve clinical outcomes (hospital admissions, self-care, health-related quality of life) and reduce the cost burden of the health care system. The SmartHeart concept aligns with recent calls for a health care shift from clinics to the home, with digital health support [6] and a recent European Society of Cardiology position statement [43] to address key elements of digital health implementation.

Conclusion

The SmartHeart system represents a promising, user-centered approach to HF management through advanced telemonitoring and behavioral support, with significant potential for expansion to other chronic conditions. Future research, including a pilot study and larger RCT, will be crucial in assessing its feasibility, effectiveness, and impact on both clinical outcomes and health care costs.

Acknowledgments

We would like to acknowledge all participants who have contributed to the development of SmartHeart as well as the clinical sites who have provided input on the study to date and will help with recruitment for the proposed pilot study.

This study was funded by a National Health and Medical and Research Council grant (grant number 2018698). However, the funding agency did not play a part in the design, execution, analysis, or interpretation of this study.

Data Availability

The datasets generated and analyzed in this study will be made available upon publication of the principal findings.

Authors' Contributions

RM led the conceptualization of this study, procured funding, and provided oversight for the whole study. RN, PJ, and RD led the formative and co-design work. YZ oversaw architecture development. YJ, RV, and RM led the software conceptualization and development. RM wrote the original draft. All authors provided feedback and edits on several revisions of the manuscript and gave final approval before submission. No artificial intelligence was used to support any portion of the manuscript creation.

Conflicts of Interest

None declared.

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Abbreviations

EQ-5D-5L questionnaire: European Quality of Life 5-Dimension 5-Level questionnaire
GP: general practitioner
HF: heart failure
IDEAS: Integrate, Design, Assess, and Share
MLWHFQ: Minnesota Living With Heart Failure Questionnaire
NICE: UK National Institute for Health and Care Excellence
RCT: randomized controlled trial
SCHFI: Self-Care of Heart Failure Index
SUS: System Usability Scale

Edited by T Leung; submitted 06.06.24; peer-reviewed by H Holmen, I Wilson; comments to author 12.09.24; revised version received 08.11.24; accepted 05.12.24; published 28.01.25.

Please cite as:
Maddison R, Nourse R, Daryabeygikhotbehsara R, Tegegne TK, Jansons P, Rawstorn JC, Atherton J, Driscoll A, Oldenburg B, Vasa R, Kostakos V, Dingler T, Abbott G, Scuffham P, Manski-Nankervis JAE, Kwasnicka D, Kensing F, Islam SMS, Maeder A, Zhang Y Digital Home-Based Self-Monitoring System for People with Heart Failure: Protocol for Development of SmartHeart and Evaluation of Feasibility and Acceptability
JMIR Res Protoc 2025;14:e62964
URL: https://www.researchprotocols.org/2025/1/e62964
doi:10.2196/62964
PMID:

Protocol

Adolescent Youth Survey on HIV Prevention and Sexual Health Education in Alabama: Protocol for a Web-Based Survey With Fraud Protection Study

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Abstract

Background: In Alabama, the undiagnosed HIV rate is over 20%; youth and young adults, particularly those who identify as sexual and gender minority individuals, are at elevated risk for HIV acquisition and are the only demographic group in the United States with rising rates of new infections. Adolescence is a period marked by exploration, risk taking, and learning, making comprehensive sexual health education a high-priority prevention strategy for HIV and sexually transmitted infections. However, in Alabama, school-based sexual health and HIV prevention education is strictly regulated and does not address the unique needs of sexual and gender minority teenagers.

Objective: To understand knowledge gaps related to sexual health, HIV prevention, and pre-exposure prophylaxis (PrEP), we conducted the Alabama Youth Survey with individuals aged 14-17 years. In the survey, we also evaluated young sexual and gender minority individuals' preferences related to prevention modalities and trusted sources of health information.

Methods: Between September 2023 and March 2024, we conducted a web-based survey with 14- to 17-year-olds who are assigned male at birth, are sexually attracted to male youth, and lived in Alabama. Half of the study's participants were recruited through community partners, the Magic City Acceptance Academy and Magic City Acceptance Center. The other half were recruited on the web via social media. A 7-step fraud and bot detection protocol was implemented and applied to web-based recruitment to reduce the likelihood of collecting false information. Once data are ready, we will compute frequencies for each measure and construct summary scores of scales, such as HIV and PrEP knowledge, to determine internal consistency. Using multivariable logistic regression, we will examine associations between personal characteristics of survey respondents and key constructs using SPSS 29 (IBM Corp) or SAS 9.4 (SAS Institute).

Results: Analyses are ongoing (N=206) and will conclude in June 2025. Preliminary results include a sample mean age of 16.21 (SD 0.88) years; about a quarter identified as transgender or gender nonconforming, with 6% stating their gender as a transgender woman. A total of 30% self-reported their race as African American or Black; 12% were Hispanic or Latinx. More than half reported being sexually active in the past 6 months. Primary data analyses will be completed in mid-2025. If findings are promising, results will be used as preliminary data to support the development of an intervention to address knowledge gaps and prevention preferences.

Conclusions: If the study is successful, it will yield information on HIV knowledge, PrEP awareness, PrEP preferences, and related outcomes among sexual and gender minority teenagers in Alabama, an underserved, hard-to-reach, but also high-priority population for public health efforts to Ending the HIV Epidemic.

International Registered Report Identifier (IRRID): DERR1-10.2196/63114

(JMIR Res Protoc 2025;14:e63114) doi:10.2196/63114

KEYWORDS

HIV knowledge; PrEP; pre-exposure prophylaxis; adolescents; teenagers; transgender; MSM; men who have sex with men; south; bot protection; bots; fraud protection; survey protocol

Introduction

Background

In Alabama, the undiagnosed HIV rate is over 20%; youth and young adults, particularly those who identify as sexual and gender minority individuals, are at elevated risk for HIV acquisition and are the only demographic group in the United States with rising rates of new infections [1,2]. Adolescence is a period marked by exploration, risk taking, and learning [3], making comprehensive sexual health education, typically delivered in school systems, a high-priority prevention strategy for HIV and sexually transmitted infections [4,5]. However, in Alabama, school-based sexual health education is strictly regulated [6]; school-based sexual health education must adopt an abstinence orientation, and HIV prevention is typically discussed within the context of heterosexual marriage [7,8]. In response to these structural limitations, community-based organizations have developed their own sexual health and HIV prevention education programs [9]. However, their content is typically delivered inconsistently, relies on funding availability, and is offered only to youth engaged in services. In 2019, pre-exposure prophylaxis (PrEP) was established as safe and effective in preventing HIV among adolescent-aged men who have sex with men (MSM), and the US Food and Drug Administration approved PrEP for individuals weighing at least 77 pounds (~34.9 kg), thereby making it available to adolescents [10,11]. Nevertheless, prescribing PrEP to adolescents remains under ideal levels [12]. Potentially, due to the lack of comprehensive HIV prevention and sexual health education in Alabama schools, there are high rates of HIV among sexual and gender minority youth and low rates of PrEP uptake. This leads to unanswered questions about what adolescents know or do not know about HIV and sexually transmitted infections (STIs) and about characteristics of their psychosocial profile, which may influence the acceptance of PrEP. Furthermore, new PrEP modalities are being developed, and clinicians and researchers alike are interested in learning about what PrEP options may be more acceptable to adolescents.

While the National Institutes of Health–funded Adolescent Medicine Trials Network for HIV/AIDS Interventions and HIV Prevention Trials Network have supported studies that assess PrEP preferences among sexual and gender minority adolescents and young adults [13,14], the age range usually begins at 15 or 16 years, with few studies enrolling as young as 14 years, even though sexual debut is thought to be younger in MSM as compared to the public [15]. There also continues to be a need to examine PrEP preferences of sexual and gender minority adolescents in the southern United States, where stigma related to HIV, sexual orientation, and gender identity is high and resources are limited [16,17]. Some research on adolescent knowledge and preferences related to HIV prevention has been conducted in the region [18,19]; however, studies more often occur with adolescents' support persons, including guardians and providers, rather than the adolescents themselves and occur in clinical settings. Web-based surveys offer adolescents a comfortable and confidential way to share their essential opinions without feeling judged, especially since they heavily rely on digital technologies to build their social networks, receive social support, and obtain health information [5,20-22]. Engaging sexual and gender minority adolescents in research to understand their HIV and STI prevention is critical to reducing rates of HIV transmission but is challenging to do, making this protocol a high public health priority project.

While increasing PrEP uptake among young sexual and gender minorities is urgently warranted [23], and federal and local agencies are supporting behavioral interventions to reach this group [24], adolescent sexual and gender minority individuals will not engage in HIV biomedical prevention if (1) they do not know about PrEP, (2) PrEP options are not acceptable for their developmental period, or (3) they do not understand their risk [25-27]. There is an unmet need to deliver tailored HIV prevention for diverse sexual and gender minority youth, built upon adolescents' existing knowledge and preferences [28,29]. To understand existing knowledge gaps and specifically address them via intervention, we conducted the Alabama Youth Survey to evaluate 14- to 17-year-old sexual and gender minority individuals' preferences and knowledge related to HIV prevention, PrEP, and STIs. The aim of this study was to elucidate knowledge, beliefs, and preferences related to HIV and STI prevention from sexual and gender minority adolescents in Alabama through a web-based survey to inform future intervention development. Because this study is exploratory, no hypotheses are proposed.

Objectives

In this study, we aim to elucidate knowledge, beliefs, and preferences related to HIV and STI knowledge and prevention among sexual and gender minority adolescents in Alabama through a web-based survey to inform future intervention development. If this study yields informative results, we will develop or adapt digital health intervention modules [30,31], a preferred and effective modality for reaching youth to address PrEP uptake while considering preferences and levels of knowledge.

Methods

Ethical Considerations

All study materials and procedures were reviewed and approved by the University of Alabama at Birmingham Institutional Review Board (IRB; IRB-300009255) and the Florida State University IRB (STUDY00003480). Informed assent was collected digitally from all study participants before data collection. Potential participants were informed of the purpose of the survey and anonymity, confidentiality, and voluntary

principles before responding. We received parental waivers from both reviewing IRBs due to the precarious situation of many sexual and gender minority youth in Alabama. Still, an information sheet for parents was made available. Participation in the study was voluntary. Study data have been deidentified and stored on a secure server. Study participants received an incentive of a US $35 digital gift card.

Eligibility Criteria

All potential participants completed a web-based screening survey via Qualtrics to verify their eligibility. To be eligible for the study, potential participants must have been 14-17 years old, assigned male at birth, report sexual attraction to men, and live in Alabama. MSM, transgender women, and genderqueer individuals were eligible if they met the aforementioned criteria.

Recruitment

We partnered with three local agencies for this study. The Magic City Acceptance Academy is the only trauma-informed charter school for LGBTQIA+ (lesbian, gay, bisexual, transgender, intersex, queer/questioning, asexual) individuals in the US Deep South. Magic City Acceptance Academy recruitment was supplemented by recruitment from the Magic City Acceptance Center [32,33]. While both agencies are independent, they have ties to leadership and are connected to Birmingham AIDS Outreach [8,34]. About half of our sample was recruited in person from these sites. The other half was recruited on the web via social media through targeted advertisements on Facebook, Instagram, and Snapchat. Adolescents could access the survey via QR codes linked to an eligibility screener. Eligible individuals were automatically redirected to the Alabama Youth Survey.

Bot Detection and Data Protection

Fraudulent data and fake responses are commonplace in web-based surveys, especially when a monetary incentive is provided. Examples of data fraud include bad actors, such as eligible individuals who submit surveys multiple times for multiple incentives, ineligible individuals who lie to meet eligibility criteria, and programmed bots. Since half of our sample was recruited on the web, we used extensive screening protocols, including (1) requiring the answering of youth-focused qualitative questions that require a typed response that would indicate residence, such as “What’s your favorite local restaurant?” and “What’s your favorite television show?” during screening [15]; (2) embedding multiple reCAPTCHAs throughout with review of Qualtrics bot detection; (3) requiring a US-based IP address; (4) locking surveys to disallow multiple submissions from the same IP address or device; (5) requiring all eligible respondents to provide an in-state phone number, which was then pinged for SMS text messaging verification before sharing the survey link—while many people have out-of-state area codes, this is much less likely for 14- to 17-year-old adolescents; (6) checking that all linked surveys were completed sequentially; and (7) using Zoom (Zoom Video Communications)–based verification audits when data seemed suspicious. Suspicious activities or indicators included but were not limited to submitting more than two surveys back to back, surveys received from the same small town in Alabama, and using an AOL or Yahoo (Yahoo Inc) email address. We also changed the survey links weekly to avoid improper circulation. These procedures were completed for all participants who were recruited on the web to ensure data integrity.

Adolescent Youth Survey

The Adolescent Youth Survey was developed and implemented following the CHERRIES (Checklist for Reporting Results of Internet E-Surveys) checklist [35]. The web-based survey was programmed in Qualtrics to collect data on HIV knowledge, perceived HIV risk, actual HIV risk, PrEP knowledge, preferences related to PrEP modalities, stigmas, and characteristics that are known to be related to HIV prevention among sexual and gender minority individuals. Some constructs were explicitly developed for this study, such as PrEP modality preference, while in other cases, we used validated scales. The measures are shown in Table 1 below. The question order was not randomized. Questions were adaptive, and questions that were not applicable were not presented. For example, if a participant was not sexually active, questions about using protection during sexual intercourse were not presented. Respondents were allowed to go “back” in the survey. However, they could not adjust their responses after pressing the final submit. We aimed to recruit 200 participants and were able to recruit a total of 206 participants between September 2023 and March 2024 via a convenience sample that was shared by those recruited via the Magic City Acceptance Academy, the Magic City Acceptance Center, and the web.

Table 1. Measures collected

Construct	Description or examples	Questions, n
Demographics	Age, gender, sex, race, ethnicity, sexual orientation, residence in Alabama, parental education, and income	10
HIV risk and prevention	Sexually active [36,37], injectable substance use, on PrEP[a], and previous STI[b] diagnosis [38]	10
HIV knowledge	HIV-KQ-18[c] [39]	18
STI knowledge	STI Knowledge Scale [40]	27
Medication experience and preferences	Oral pills, shots, suppositories, patches, etc	13
PrEP familiarity	Seen commercials, types of PrEP, and PrEP brands	6
PrEP awareness	PrEP-COL[d] Scale [41]	10
PrEP preferences	PrEP modalities, PrEP delivery locations, etc	20
Trusted sources	Types of information sources and people	24
Stigma	IHP-R[e] [42] and Everyday Discrimination Scale [43]	14
Depression	PHQ-8[f] [44]	8
Resilience	MOS Social Support Survey [45], GSE[g] [46]	29

[a]PrEP: pre-exposure prophylaxis.

[b]STI: sexually transmitted infection.

[c]HIV-KQ-18: HIV knowledge questionnaire.

[d]PrEP-COL: PrEP Columbia Scale

[e]IHP-R: Revised Internalized Homophobia Scale.

[f]PHQ-8: Personal Health Questionnaire Depression Scale.

[g]GSE: General Self-Efficacy Scale.

Pilot Testing

Study team members aged 20-24 years pilot-tested the survey multiple times to assess its completion time. It was determined to be about 20-25 minutes, depending on how slowly one reads the questions and the time to consider response options. We then pilot-tested the survey with the first 10 respondents and found similar completion metrics, with no complaints or concerns reported.

Data Storage and Analysis

Encrypted data are saved on a Florida State University server with password protection. The database and associated data structures were developed before survey distribution and were not adjusted during the protocol. We asked participants to voluntarily provide emails and cell phone numbers to facilitate the provision of incentives. These personal data were only known to the incentive processors and were kept separate from survey responses. During data collection, we examined data quality weekly (eg, missing data, assessment of distributional assumptions, and identification of outliers) and will do so before statistical analysis is conducted. As a pilot study, missing scale data will not be estimated. Once data are ready, we will compute frequencies for each measure and for each scale to assess variability and internal reliability. We will construct summary scores of scales, such as HIV and PrEP knowledge, to determine if these have adequate internal consistency (Cronbach $\alpha \geq 0.70$) [47]. Using multivariable logistic regression, we will examine associations between the personal characteristics of survey respondents and key constructs. We will use SPSS 29 (IBM Corp) or SAS 9.4 (SAS Institute) for quantitative analyses.

Results

While this study was approved in 2021, data collection began in September 2023 and concluded in March 2024. Since the survey was open, the system could not record the number of unique visitors; thus, a formal response rate cannot be calculated. Data analysis is underway and will conclude in June 2025. The sample included 206 participants aged 14-17 years with a mean age of 16.21 (SD 0.88) years; about a quarter identified as transgender or gender nonconforming, with 6% explicitly stating their gender as a transgender woman. A total of 30% self-reported their race as African American or Black; 12% were Hispanic or Latinx. About half of them reported being sexually active in the past 6 months.

Discussion

Principal Findings

In this study, we aim to elucidate knowledge, beliefs, and preferences related to HIV and STI prevention among sexual and gender minority adolescents in Alabama through a web-based survey to inform future intervention development. If this study yields informative results, data could inform the adaptation or creation of a sexual health and HIV prevention intervention for sexual and gender minority adolescents who

live in southern states, where school-based sexual health education may be unavailable or strictly limited.

While hypotheses were not proposed, based on preliminary analyses and the extant literature, we anticipate finding low levels of knowledge and high levels of poor mental health outcomes. Little is known about PrEP modality preference in this population, so we cannot anticipate findings related to this topic. Findings will provide intervention targets (eg, PrEP education) and the needed dose; very low knowledge will necessitate more significant emphasis on PrEP education. When recruiting on the web, we encountered an enormous amount of fraud and ultimately needed to implement SMS text messaging verification, wherein eligible participants would only be routed to the survey after their unique phone number, with in-state area code, was verified. Even after verification, since Google phone numbers can be created, we audited suspicious submissions, such as surveys that were completed too quickly. A total of 10% of web-recruited submissions were audited via a Zoom call with a trained study coordinator. The web-based survey and fraud detection strategies were feasible; however, completing this survey with data protection and scientific integrity was much more costly and time-intensive than expected. For future web-based survey studies, we recommend implementing SMS text messaging verification at study onset with a random audit of 20% of records. Audits should include a video call (preferred) or a voice call (acceptable). Email verification, while simple, was not reliable, likely due to the ease of creating email accounts.

As noted in the *Introduction*, little is known about 14- to 17-year-olds' knowledge, beliefs, and preferences related to HIV and STI prevention in the United States; thus, comparison to other studies is challenging. Recent research on these topics has been conducted in global settings with mixed findings [48-50]. A unique feature of our survey study is the assessment of PrEP modality preference, including options currently in clinical trials or may be available outside of the United States. Findings on modality preference have the potential to inform clinical care and how providers offer PrEP to sexual and gender minority adolescents.

While the study team was meticulous in bot detection and other fraud measures, some participants did not receive face-to-face interaction, and thus, those recruited on the web may be different from participants recruited from our local community partners. Second, the study may be susceptible to desirability bias, especially from participants recruited via in-person venues. While our sample is large for sexual and gender minority adolescents, a larger sample would increase generalizability. Some domains would have been valuable to assess, such as living circumstances and previous experiences with adverse life events; however, in pilot testing, adolescents felt the survey could not be lengthened.

Conclusions

If the study is successful, we will yield information on HIV knowledge, PrEP awareness, PrEP preferences, and related outcomes among sexual and gender minority teenagers in Alabama, an underserved, hard-to-reach, but also high-priority population for public health efforts to Ending the HIV Epidemic. Data can inform the development of a culturally appropriate (for southern contexts, to be adolescent-friendly) and modular HIV prevention intervention, targeting behavior change related to HIV prevention for sexual and gender minority adolescents, that can be seamlessly integrated into amenable community settings in the southern United States.

Acknowledgments

We thank Dr. Patton Furman, Principal of the Magic City Acceptance Academy, and Amanda Keller and Lauren Jacobs, leadership at the Magic City Acceptance Center, for their support with recruitment. This study was supported by a research grant from Merck Sharp & Dohme LLC Investigator-Initiated Studies Program (MISP) under award 60819. The opinions expressed in this paper are those of the authors and do not necessarily represent those of Merck Sharp & Dohme LLC.

Data Availability

Data are available upon reasonable request through this study's lead author (HB).

Authors' Contributions

HB is the principal investigator and lead author of the study and is involved in all aspects of the study from conceptualization and funding acquisition to writing. IY is the lead statistician and led the formal analysis. JB led data collection efforts with the support of CLB and AJ. JB, CLB, and AJ were involved with project administration and writing the original draft.

Conflicts of Interest

None declared.

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Abbreviations

IRB: institutional review board
LGBTQIA+: lesbian, gay, bisexual, transgender, intersex, queer/questioning, asexual
MSM: men who have sex with men
PrEP: pre-exposure prophylaxis
STI: sexually transmitted infection

Edited by A Schwartz; submitted 10.06.24; peer-reviewed by K Kidd, N Gleason; comments to author 09.10.24; revised version received 17.10.24; accepted 18.12.24; published 29.01.25.

Please cite as:
Budhwani H, Yigit I, Bruce J, Bond CL, Johnson A
Adolescent Youth Survey on HIV Prevention and Sexual Health Education in Alabama: Protocol for a Web-Based Survey With Fraud Protection Study
JMIR Res Protoc 2025;14:e63114
URL: https://www.researchprotocols.org/2025/1/e63114
doi:10.2196/63114
PMID:

Protocol

Detecting Freezing of Gait in Parkinson Disease Using Multiple Wearable Sensors Sets During Various Walking Tasks Relative to Medication Conditions (DetectFoG): Protocol for a Prospective Cohort Study

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Abstract

Background: Freezing of gait (FoG) is one of the most disabling symptoms of Parkinson disease (PD). Detecting and monitoring episodes of FoG are important in the medical follow-up of patients to assess disease progression and functional impact and to adjust treatment accordingly. Although several questionnaires exist, they lack objectivity. Using wearable sensors such as inertial measurement units (IMUs) to detect FoG episodes offers greater objectivity and accuracy. There is no consensus on the number and location of IMU, type of algorithm, and method of triggering and scoring the FoG episodes.

Objective: The objective of this study is to investigate the use of multiple wearable sensors sets to detect FoG in patients with PD during various walking tasks under different medication conditions.

Methods: This single-center, prospective cohort study (DetectFoG) will include 18 patients with PD. Patients will be fitted with 7 IMUs and will walk a freezing-provoking path under different tasks—"single task," "dual motor task," or "dual cognitive task"—and medical conditions corresponding to levodopa medication ("on" or "off"). Passages will be videotaped, and 2 movement disorder specialists will identify FoG episodes in the videos. The accuracy, sensitivity, specificity, positive predictive value, and negative predictive value of the most effective combination of wearable sensors for detecting FoG episodes will be studied.

Results: The study is currently in the data collection phase, having commenced recruitment in February 2024. Once all data have been gathered, the data analysis will commence. As of August 2024, 3 patients have been recruited. It is anticipated that the results will be published by the end of 2025.

Conclusions: Detecting FoG episodes in various medical and clinical settings would provide a more comprehensive understanding of this phenomenon. Furthermore, it would enable reliable and objective monitoring of the progression of this symptom based on treatments and the natural course of the disease. This could serve as an objective tool for monitoring patients and assessing the severity and frequency of FoG.

Trial Registration: Clinicaltrials.gov NCT05822258; https://www.clinicaltrials.gov/study/NCT05822258

International Registered Report Identifier (IRRID): DERR1-10.2196/58612

(JMIR Res Protoc 2025;14:e58612) doi:10.2196/58612

KEYWORDS

Parkinson; detection; freezing of gait; sensor; wearable; freezing; walk; neurodegenerative; movement

Introduction

Affecting more than 8.5 million people worldwide in 2019, Parkinson disease (PD) is the second most common neurodegenerative disease [1]. PD is diagnosed using criteria from the UK Parkinson's Disease Society Brain Bank [2] and is defined by the cardinal symptoms of tremor, bradykinesia, rigidity, and postural instability, along with other motor and nonmotor symptoms [3].

Among the various motor symptoms, freezing of gait (FoG), defined as a "brief and episodic absence or marked reduction in the forward progression of the feet despite the intention to walk" [4], is one of the most disabling symptoms of PD. In advanced and severe forms of PD, FoG occurs in 50% to 80% of cases [5]. FoG is correlated with PD severity and disease duration [6]. It increases the risk of falls [7] and loss of independence and affects patients' quality of life [8].

The detection of FoG episodes is an important issue for patient follow-up and treatment adjustment. Various subjective and objective methods can be used to assess these symptoms. Daily completion of a motor diary by the patient is one possibility for assessing these symptoms, but it relies on the patient's subjective judgment and is often discontinued after a few days or is not feasible in the presence of cognitive impairment [9]. Objective scores with predefined exercises (eg, double spot walking, 180° turning, etc) are available to assess FoG episodes during medical consultations; however, these exercises do not always trigger FoG episodes due to several reasons. First, the phenomenon known as the "white coat effect," whereby patients may perform differently in the presence of medical professionals, can alter their natural response and reduce the likelihood of FoG episodes [10]. Second, the structured nature of clinical assessments often causes a switch from automatic to goal-directed pathways, reducing the occurrence of FoG episodes, which typically occurs in more automatic walking scenarios [11]. Finally, the predefined exercises are constrained by time, unfamiliarity, and the artificiality of the clinical environment, which can influence patients' natural gait patterns. Thus, they fail to provide accurate information on the frequency and severity of FoG episodes in daily life [11]. One potential alternative method involves videotaping patients in different contexts and conducting a postscored examination, considered the gold standard, although this approach demands time and expertise [11].

To overcome these limitations, wearable sensors, such as electromyographs, electroencephalography electrodes, or inertial measurement units (IMUs), provide a solution for automatic FoG detection. The combination of accelerometer and gyroscopes data from an IMU seems to be the most widely used solution with high performance (sensitivity: 86%; specificity: 92.9% [12]). This compact sensor is easy to install and allows FoG assessment both in clinical practice and during daily living [9,13].

Despite numerous studies and literature reviews on the use of these wearable sensors for FoG detection, there is as yet no consensus in the literature on the optimal methodology for their use. It is likely that this discrepancy stems from the inherent variability in the protocols used. Indeed, there is considerable heterogeneity in the protocols for triggering [11] (medical condition: "on" or "off" levodopa treatment; freezing-provoking path; and dual-task conditions). In fact, there are few studies that directly compare FoG episodes in "on" and "off" conditions with small cohorts and a low number of participants [11,12,14]. Furthermore, many locations including feet, shin or ankle, thigh, and pelvis have been investigated [15]. The use of multiple sensors provides a more detailed and holistic view of the patient's movements, enabling the capture of subtle changes that may not be detectable with a single sensor [15]. An IMU is cost-effective and straightforward to wear, rendering it suitable for both laboratory evaluation and daily use. Even if patients prefer to wear sensors solely at the wrist, such as a stopwatch, or conceal them beneath clothing at the ankle or on a belt (lower back), as demonstrated by O'Day et al [15], the placement of sensors on multiple body parts could enhance the robustness of FoG detection across various walking tasks and different FoG subtypes. Furthermore, examining FoG under dual-task conditions provides a more comprehensive understanding of how cognitive load impacts freezing episodes, which only a few studies have addressed [16-20]. Finally, several other variables may confound the study, including the wide age range of cohorts (aged 7-118 years) and the diverse range of FoG episodes (50-1110) [21-23]. Therefore, this study is innovative as it stands out for its ability to replicate findings across various conditions, particularly the medical condition. Furthermore, it explores the effects of dual-task scenarios and optimal sensor placement in a larger cohort than those found in the literature, significantly enhancing our understanding of the underlying mechanisms. These multiple dimensions provide a more nuanced and robust perspective, allowing for better generalization of the results and improving practical applications in medical settings.

Regardless of the wearable sensors used or the freezing protocol, the accuracy of detection is sensitive to the type of algorithm [9,11,12,23]. Yet, the algorithms used to detect FoG episodes are controversial, especially for real-time detection. The threshold method provides a straightforward approach to the implementation and interpretation of algorithms. In this context, the freezing index—defined as the ratio between the power bands of freezing (3-8 Hz) and locomotion (0.5-3 Hz)—is the most commonly used feature in threshold-based algorithms [9,11,12,23]. This single feature accurately detects many FoG episodes (sensitivity: 84.3%; specificity: 78.4% [24]), but detection fails when no motion is observed and voluntary stops may be mistakenly classified as FoG [17]. Adding multiple indices can enhance algorithm performance, but it also increases complexity and the difficulty of tuning thresholds [25,26]. To address these limitations, machine learning (ML) algorithms have been developed to improve FoG detection performance. Indeed, ML algorithms could better fit the model to increase the accuracy of the models; this is a subfield of artificial

intelligence that gives an algorithm the ability to learn without being explicitly programmed [12]. Among the various ML algorithms, support vector machine, multilayer perceptron, and ensemble classifiers (eg, random forest or AdaBoost) have proven to be the most efficient. Determining the best ML algorithm is challenging due to the highly heterogeneous nature of the training data. A limitation of ML algorithms is that training the model and processing the data can require high computational cost. Fortunately, advances in computer technology now offer the possibility of early or real-time detection with ML models [12].

The primary objective is to assess the accuracy of the optimal combination of wearable sensors for detecting FoG episodes in patients with PD. The secondary objectives of this study include measuring the specificity, sensitivity, positive predictive value (PPV), and negative predictive value (NPV) of the optimal combination of wearable sensors for detecting FoG episodes. Regarding the setup, we also aim to compare its performance (accuracy, sensitivity, specificity, PPV, and NPV) across various clinical and medical conditions.

Methods

Study Design and Participants

This study is a single-center, prospective cohort trial (DetectFoG) involving patients with PD with FoG at the University Hospital of Rennes. Patients will be recruited from the neurology department of University Hospital of Rennes during their visit to the neurologist. This study aims to include a total of 18 patients. To mitigate potential issues such as withdrawal of consent, absence of FoG during neurologist annotation, loss of follow-up (failure to attend the second visit), or inability to complete the required number of passages (fewer than 6), initially, 20 patients will be enrolled. Participants experiencing any of these issues will be excluded from the study.

Inclusion criteria will include patients older than 18 years diagnosed with PD according to the UK Brain Bank criteria. Patients must self-report as freezers, scoring between 1 and 3 on question 13 of the Movement Disorder Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS) II [27], and be capable of walking 30 m without assistance to complete the freezing-provoking path. Exclusion criteria will apply to patients scoring less than 20 out of 30 on the Montreal Cognitive Assessment [28] who are unable to give informed consent and those with neurological, orthopedic, or rheumatic comorbidities that could impact gait and ability.

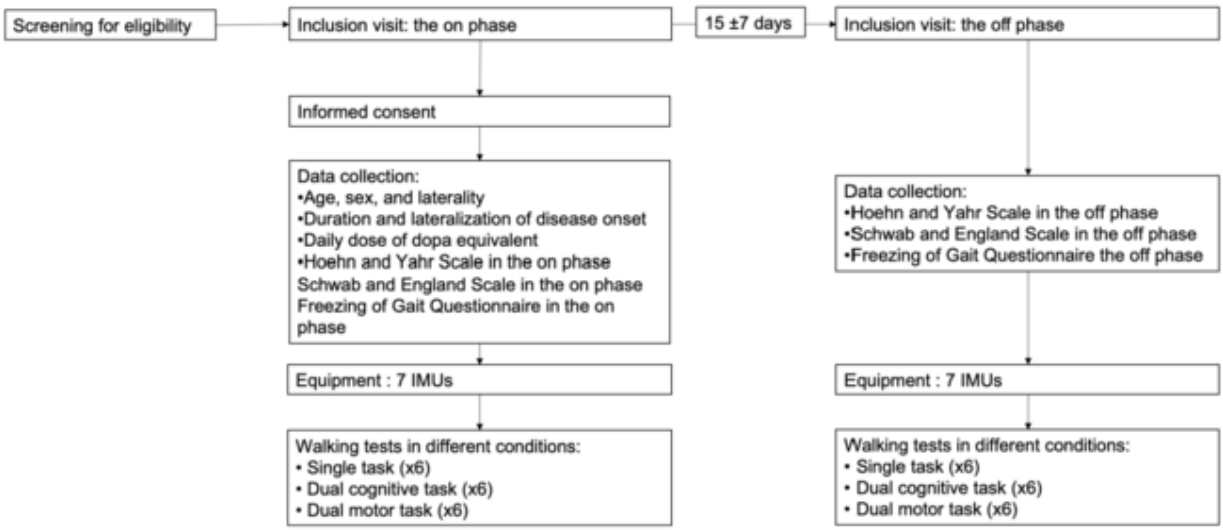
Ethical Considerations

The study design was approved by the ethical committee of Ile de France III (23.01067.000298-MS01) on October 1, 2023. All data collection will adhere to applicable guidelines and regulations. Participants will provide informed consent before enrolling in the study.

Protocol

After verifying the inclusion and exclusion criteria, the neurologist will notify the principal investigator (KJ). The principal investigator will then contact the patients to provide comprehensive and understandable information about the study's objectives, as well as their right to refuse participation or withdraw at any time. If the patients consent and sign the consent form, they will participate in 2 visits separated by 2 weeks (±7 days), encompassing both "on" and "off" phases of levodopa treatment (Figure 1).

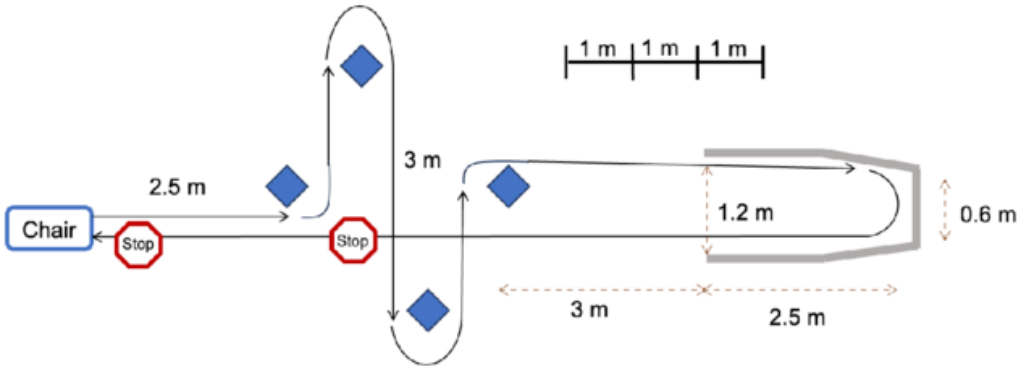
Figure 1. Timeline of study. IMU: inertial measurement unit.



For organizational purposes, the first visit (inclusion visit) will occur during the "on" phase of levodopa medication, while the second visit (follow-up visit) will be during the "off" phase. During the "on" phase, patients will be assessed when oral treatment maximally improves dopa-sensitive PD symptoms (best "on" state, typically 1-2 hours after ingestion). This state will be determined based on patients' subjective assessment, similar to their daily motor self-assessments (home diaries), which has been established as reliable in various studies [29-31]. Assessment during the "off" phase will occur after 12 hours without treatment, preferably in the morning before the first levodopa dose.

During each visit, participants will walk on a freezing-provoking path at a comfortable speed under 3 different clinical conditions (single task [ST], dual cognitive task [DCT], and dual motor task [DMT]). The Pardoel freezing-provoking path, known to induce FoG episodes [32], includes standing up, walking with a slalom (left and right turns), navigating a narrow passage with a 180° turn, and returning straight, with 2 designated stops—one chosen by the patient and another in front of a chair (Figure 2).

Figure 2. Freezing-inducing path (adapted from Pardoel et al [32], which is published under Creative Commons Attribution 4.0 International License [33]).



Participants will undergo testing under different dual-task conditions, which are recognized for promoting FoG episodes [32]. The DMT involves walking with a ball on a tray within a drawn circle, keeping the ball centered. The DCT requires participants to generate as many words as possible starting with a specified letter. Each participant will complete a maximum of 6 blocks, with each block consisting of the 3 conditions (ST, DCT, and DMT), resulting in a total of 18 trials (6 blocks × 3 conditions per block). The sequence of conditions within each block will be randomized to mitigate any order effects. This protocol accommodates varying endurance levels among patients; some may complete each block quickly with few or no FoG episodes, while others may take longer due to frequent tremors that consume energy. This flexible approach ensures that the study is comprehensive and respects each patient's physical limitations. However, participants who complete fewer than 2 blocks (6 trials) will be excluded from the analysis to ensure adequate data collection.

Data Collection (and Preprocessing)

Clinical Data

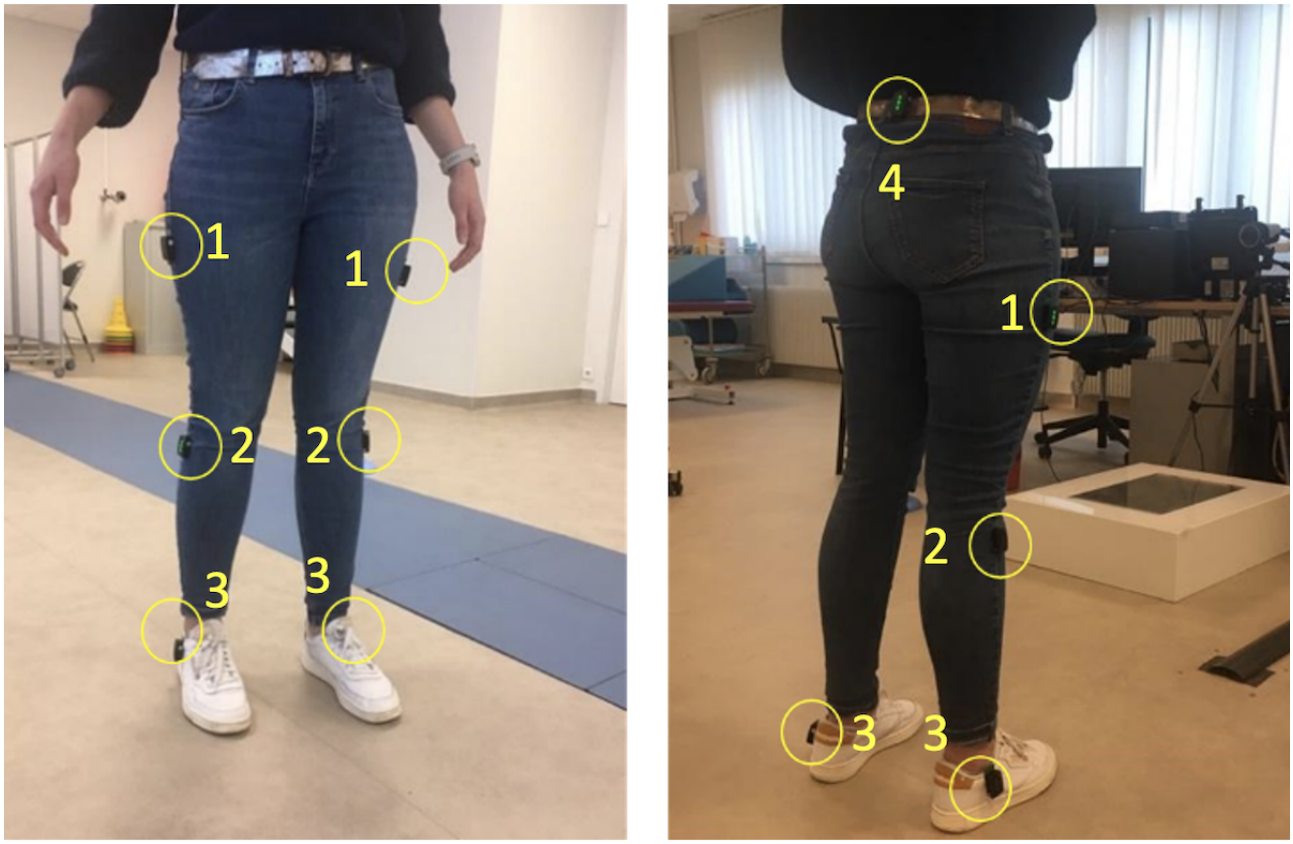
Various patient data are collected, including age, sex, laterality of symptoms, duration of PD, lateralization of symptom onset, daily dose of levodopa equivalent, MDS-UPDRS III score [27], Freezing of Gait Questionnaire (FoGQ; "on" and "off" phases) [34], Hoehn and Yahr Scale ("on" and "off" phases) [35], and Schwab and England Scale ("on" and "off" phases) [36]. The FoGQ is used to assess the characteristics of FoG. The Hoehn and Yahr Scale and the Schwab and England Scale serve as tools for the overall evaluation of patients with PD: the former to gauge disease severity and the latter to evaluate daily life impact, functional status, and level of dependence.

FoG Measurement

IMU Measurements

Patients will wear the Trigno Avanci IMU (Delsys; Figure 3), which includes a triaxial accelerometer, gyroscope, and magnetometer. Data will be transmitted via Bluetooth and collected using the Delsys application programing interface and then transferred to QTM 2020 software (Qualisys). The software manages recording at a sampling frequency of 148.15 Hz and synchronizes with cameras. While this sampling frequency is higher than that in some studies, it has been previously used, similar to the approach taken by Camps et al [37]. This frequency is selected to ensure that all nuances associated with FoG, particularly micromovements, are captured. IMU data will also undergo windowing with a 2-second window length and a 0.4-second shift. A trained operator will position the sensors manually, aligning them with anatomical axes. Seven IMUs will be placed as follows: 1 on each thigh (lateral side, upper third), 1 on each fibula (upper third), 1 on each foot (below the lateral malleolus), and 1 at lumbar level (L5).

Figure 3. Inertial measurement unit placements. 1: Thighs (side, upper third); 2: fibulas (upper third); 3: foot (below lateral malleolus); 4: Lumbar (L5 level).



Video Recording and Window Labeling

During each visit, and during trials designed to induce freezing episodes, patients will be recorded using 14 synchronized Miqus M3 cameras (Qualisys). These cameras will record at a resolution of 1824 × 1088 pixels with a frequency of 25 Hz. FoG episodes will be identified from the videos by 2 movement disorders specialists (FL and SD) independently using QTM 2020 software (Qualisys). The start of a freezing episode is defined as "the moment when the stepping foot does not leave the ground despite a clear intention to step," and the end is defined as "the moment when the stepping foot begins or resumes an effective step" [32]. In cases where there is disagreement about the presence of a FoG episode, the specialists will discuss and reach a consensus. Following the methodology of Pardoel et al [32], the data timeline will be segmented into 2-second windows with a 0.4-second shift between windows (80% overlap). Windows will be labeled as "FoG window" when the entire window corresponds to a period of FoG. Windows not meeting this criterion, either during periods without FoG or during transitions between FoG episodes and non-FoG periods, will be labeled as "no-FoG window." The relative duration of FoG will be assessed by calculating the ratio of FoG windows to the total number of windows. This ratio provides a measure of the freezing time while accounting for the window labeling method used. To ensure comparability with other studies and to mitigate the effect of varying labeling methods across research [32,38], we will also calculate the total number of FoG episodes and the cumulative freezing time based on onset and end events, categorized by task type, session, and patient. This approach will facilitate meaningful comparisons with existing literature on FoG detection methodologies.

Data Management

All data are securely stored in a dedicated folder on a local server with restricted access limited to the research team. Patient's clinical information (such as age, sex, laterality of symptoms, duration of PD, lateralization of symptom onset, daily dose of levodopa equivalent, FoGQ score, Hoehn and Yahr Scale rating, Schwab and England Scale assessment, and MDS-UPDRS III score) along with study results (videos and IMU data) are collected and controlled by the University Hospital of Rennes. A database containing video data is duplicated for each expert responsible for labeling FoG episodes. Time annotations will be exported as events in C3D files along with IMU data before the windowing process, contributing to a final database used for subsequent data analysis. This structured approach ensures the integrity and confidentiality of patient data while facilitating precise event annotation and thorough analysis of collected data.

Data Analysis

Features Extractions

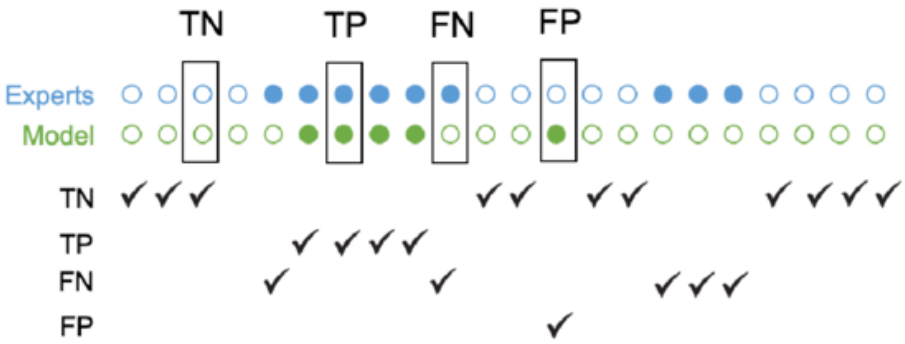
Each window of data will undergo normalization to achieve zero mean and unit variance. Our study distinguishes itself through an exhaustive exploration of features aimed at identifying FoG episodes. From each window, signal features will be extracted from both the time and frequency domains. A comprehensive array of features will be included, such as the number, duration, and length of acceleration or angular velocity

reversals, kurtosis, and skewness [14]. Furthermore, we will incorporate metrics such as the magnitude of mean and SD of signals, as well as specific metrics related to smoothness such as spectral arc length measure [39] and the freezing ratio [40]. Nonlinear modeling features, such as sample entropy or Lyapunov exponent, which quantify gait regularity and complexity, will also be used [41]. Furthermore, measures of inter- and intralimb coordination will be integrated to highlight specific limb dynamics during FoG episodes. Feature selection will be conducted using Relief-F, chosen for its suitability in our application over methods such as minimum redundancy maximum relevance ranking [20]. This approach ensures that the selected features are highly relevant to distinguishing FoG episodes, thereby optimizing the accuracy and effectiveness of our analysis.

Model Training

The top-ranked features identified through Relief-F will be used in a decision tree (DT) model for classifying windows of data. The DT model will be tested using 5 and 10 decision splits and with various sets of top-ranked features ranging from 5 to 20. The performance of the DT model will be evaluated using metrics such as accuracy, sensitivity, specificity, PPV, and NPV. The model's performance will be determined based on the classification of each window as true positive (TP), true negative (TN), false positive (FP), or false negative (FN), comparing the model's classifications with the experts' identification of FoG episodes on video recordings (Figure 4).

Figure 4. Segmentation on true negatives (TNs), true positives (TPs), false negatives (FNs), and false positives (FPs) for each second according to the experts and the model.



The agreement between the model and experts regarding FoG or non-FoG periods will be assessed as follows:

- TP: A FoG period correctly identified by both the experts and the model
- TN: A non-FoG period correctly identified by both the experts and the model
- FP: A FoG period incorrectly identified by the model but not by the experts
- FN: A FoG period incorrectly identified by the experts but not by the model

Performance scores will be calculated using the following equations:

Model Validation

The model validation will use the leave-one-subject-out (LOSO) cross-validation technique to assess its performance across participants and accommodate the considerable variability between participants. While some studies [20,42] advocate for the leave-one-freezer-out (LOFO) cross-validation technique to avoid overrepresentation of patients without FoG in training and validation sets, our study focuses on participants who have experienced at least 1 episode of FoG during their initial visit. Consequently, each patient will have FoG episodes, making the LOSO approach more suitable for our validation process.

Statistical Analysis

Clinical data of the participants will be presented as means (SD) or medians with IQRs for continuous data, depending on their distribution. Categorical data will be reported as counts (with percentages within parentheses).

Primary Outcome

The main objective of our study is to identify the most relevant features and locations of wearable sensors for detecting FoG episodes. The Relief-F technique will rank features extracted from data collected by all sensor segments. The top-ranked features across all subjects will indicate the most critical sensors for detecting FoG episodes, and these features will be used in model training and validation. The LOSO method will be used for validation, and accuracy will be computed for each subject. Furthermore, Relief-F analysis will be conducted individually for each subject to potentially reveal redundancy in the top-ranked features across subjects. Feature extraction, selection, model training, and validation will be implemented using Python 3.0 (PythonLabs) scripts.

Secondary Outcomes

We will investigate the differences in model performance across various conditions to propose recommendations for interpreting the model. Accuracy, sensitivity, and specificity will be evaluated using a mixed-effects model with fixed effects for patients and random effects for the type of condition (ST, DCT, and DMT) and medication state ("on" and "off").

Results

The study is currently in the data collection phase, with recruitment starting in February 2024. Once all data have been gathered, data analysis will commence. As of August 2024, 3 patients have been recruited. We anticipate publishing the results by the end of 2025. The results of this study will be presented at scientific events and published in scientific journals.

Discussion

Strengths and Limitations of This Study

The aim of this study is to assess the accuracy of the most effective combination of wearable sensors in detecting FoG in patients with PD. This setup has been developed following an extensive literature review and clinical evaluation of patients.

To date, consensus on sensor placement remains elusive, necessitating a detailed examination of individual and collective placements [15]. The model used will incorporate a broad array of features from both temporal and frequency domains documented in the literature to maximize accuracy. Moreover, this model will undergo testing on a sizable cohort of patients (n=18), each completing 18 passages on a designated freezing-inducing path, yielding a comprehensive data set. Furthermore, the model will be evaluated on a path known to provoke FoG under different medical ("on" and "off" levodopa medication) and clinical (ST, DMT, and DCT) conditions [32]. This evaluation aims to simulate various walking tasks akin to daily life and assess their potential to induce or alleviate FoG, particularly in dual-task scenarios. Several datasets are available, some with restricted accessibility. Multimedia Appendix 1 outlines several pertinent and comparable datasets. Our dataset's strength lies in its incorporation of multiple sensor placements across varied medication states and task complexities, including cognitive dual tasks. This dataset will be openly accessible or supplied on request, fostering research and collaboration in the field.

One limitation of this study is its reliance on a controlled environment. Despite efforts to simulate ecological tasks that mimic everyday challenges and tend to provoke gait freezes (FoG) under dual-task conditions, it is crucial to acknowledge that the study is conducted under controlled conditions. For future research, conducting tests in real-life settings over prolonged periods would be advantageous. This approach could facilitate the accumulation of larger datasets across diverse situations, thereby enhancing our understanding of FoG in more complex real-world scenarios.

Perspectives

The miniaturization of sensors is unlocking new opportunities for monitoring patients with PD, particularly in detecting episodes of FoG. Extending this capability across all medical and clinical settings would offer a more comprehensive understanding of this phenomenon, which remains incompletely understood. Moreover, it would facilitate dependable and objective monitoring of symptom progression, influenced by treatments and the disease's natural trajectory. This could serve as an objective tool for patient monitoring, assessing both the severity and frequency of FoG.

Objective evaluation is crucial for identifying suitable medical and nonmedical treatments, including rehabilitation or deep brain stimulation [43]. Research has underscored the significance of personalized treatment tailored to individual patient needs and circumstances [44]. Real-time detection facilitates the integration of FoG episode identification with external stimuli, such as sensory, auditory, or visual cues, offering a significant opportunity to mitigate FoG episodes [45].

Conclusions

This study aims to enhance the detection of FoG in patients with PD through the use of multiple wearable sensors. By evaluating various sensor placements and the accuracy of detection algorithms, the study aims to determine the most effective combination of wearable sensors for detecting FoG episodes. Despite the study being conducted in a controlled laboratory environment rather than real-life settings, the findings are expected to significantly advance understanding and monitoring of FoG. The anticipated results will provide crucial insights into optimal sensor configurations and detection methodologies, ultimately supporting the development of more precise and personalized treatment strategies for patients with PD. Publication of these results by the end of 2025 will contribute valuable data to ongoing efforts aimed at improving patient care and enhancing quality of life for individuals affected by PD.

Acknowledgments

This work was supported by the COReSP 2023 of University Hospital of Rennes.

Data Availability

No data are currently available, but the results of the trial will be disseminated either with all the accompanying dataset or on request from the authors.

Authors' Contributions

All authors contributed to designing the experimental protocol. KJ oversaw ethics and dissemination aspects. SC, AD, FB, and KJ will carry out the study. SD and FL will identify FoG episodes from the videos. SC will be responsible for developing and validating the setup. SC, AD, KJ, and IB will analyze the data, and KJ, SC, and IB will interpret the findings. All authors will participate in writing the paper. Finally, all authors have reviewed and approved the final version of the protocol.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Comparative overview of datasets for freezing-of-gait evaluation.
[DOCX File , 21 KB - resprot_v14i1e58612_app1.docx]

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Abbreviations

DCT: dual cognitive task
DMT: dual motor task
DT: decision tree
FN: false negative
FoG: freezing of gait
FoGQ: Freezing of Gait Questionnaire
FP: false positive
IMU: inertial measurement unit
LOFO: leave-one-freezer-out
LOSO: leave-one-subject-out
MDS-UPDRS: Movement Disorder Society-Unified Parkinson’s Disease Rating Scale
ML: machine learning
NPV: negative predictive value
PD: Parkinson disease
PPV: positive predictive value
ST: single task
TF: true negative
TN: true positive

Edited by S Khan; submitted 20.03.24; peer-reviewed by M Goris, EL Tonkin; comments to author 16.05.24; revised version received 28.06.24; accepted 13.08.24; published 06.02.25.

Please cite as:
Cordillet S, Drapier S, Leh F, Dumont A, Bidet F, Bonan I, Jamal K
Detecting Freezing of Gait in Parkinson Disease Using Multiple Wearable Sensors Sets During Various Walking Tasks Relative to Medication Conditions (DetectFoG): Protocol for a Prospective Cohort Study
JMIR Res Protoc 2025;14:e58612
URL: https://www.researchprotocols.org/2025/1/e58612
doi:10.2196/58612
PMID:

Protocol

A Digital Behavior Change Intervention for Health Promotion for Adults in Midlife: Protocol for a Multidimensional Assessment Study

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Abstract

Background: To support lifelong health promotion and disease prevention, Santé publique France studied the methodology for building a social marketing scheme with a digital intervention targeting middle-aged adults, specifically socioeconomically disadvantaged groups. The digital intervention aims to encourage people aged 40-55 years to look after their health in the short and medium terms by adopting small actions relating to 8 health determinants: nutrition, physical activity, smoking, alcohol, stress, cognitive health, sleep, and environmental health. In the long term, the intervention intends to prevent frailty and reduce the burden of multimorbidities in older age, particularly for lower socioeconomic groups.

Objective: This study aims to measure behavior changes among registered users of the future website. The protocol assesses the impact of the website based on users' implementation of small actions relating to the 8 health determinants. Specifically, it intends to evaluate the website's performance in terms of engaging a specific population, triggering behavior change, raising awareness about a multifactorial approach to health, and encouraging user interaction with the website's resources.

Methods: The methodology is based on clinical assessments developed alongside the website according to the functionalities offered to registered users in their personalized space. The assessment tool design draws on logic models for digital interventions, and their consistency for digital applications is verified. The target audience is clearly defined from the outset. The protocol sets out a 3-step assessment: upon registration, after 3 weeks of use, and after 10 weeks of use (end of assessment). Users are divided into 2 groups (socioeconomically disadvantaged users and others) to characterize differences and make corrections. The protocol uses a mixed assessment approach based on website traffic and user login data. Specific and identifiable behavior changes are documented by monitoring the same individuals from T0 to T2, using verbatim comments to classify them into profiles and conducting semistructured individual interviews with a sample of users.

Results: The protocol creates a multidimensional assessment of digital intervention, showing that during a given timeline, interactions with users can reveal their capabilities, opportunities, and motivations to adopt healthy lifestyles. The protocol's principles were integrated into the development of a personal account to assess users' behavior changes. Given the delayed launch of the website, no recruitment or effects analysis of the protocol took place.

Conclusions: As no multidimensional assessment protocol is currently available for digital behavior change interventions, our methods reveal that the different framework stages can strengthen the effect measurement, consolidate the choice of assumptions used within the logic model and steer the digital intervention toward action while reducing the burden of information. The suitability of the assessment protocol remains to be evaluated given the delayed launch of the website.

International Registered Report Identifier (IRRID): PRR1-10.2196/60559

(JMIR Res Protoc 2025;14:e60559) doi:10.2196/60559

KEYWORDS

digital behavior change intervention; assessment protocol; middle-aged adults; health promotion; user account; mixed assessments; health information technologies

Introduction

Background

Today, expert consensus recommends that people should strengthen disease prevention actions from the age of 40 years [1-3] to avoid loss of independence due to the accumulation of chronic diseases. Different studies show a correlation between the number of healthy behaviors (physical activity, diet, stop smoking, and reduction of alcohol consumption) and healthy aging. Santé publique France has been working on the planning stages of a social marketing scheme that includes a digital behavior change intervention. The digital intervention was designed in tandem with its assessment protocol in the hope that engineering feedback would improve its applicability. An overview of the literature on the assessment of digital tools for health promotion and disease prevention found proven evidence for the following: (1) the added value of a multidimensional assessment of a digital intervention [4,5], (2) the challenge of distinguishing between effect measurement and implementation measurement [6] since "a crucial implication of explicitly recognizing the distinction between engagement with the technological and behavioral aspects of the intervention is that intervention usage alone cannot be taken as a valid indicator of engagement" [7], (3) the importance of being able to qualify the maintenance of a target behavior over time [8], and (4) the absence, to our knowledge, of a mixed quantitative and qualitative assessment protocol [4,9-11].

It was precisely this gap that prompted the drafting of this assessment protocol for a nonclinical intervention. We explored the literature on assessments in the fields of medicine and medical informatics as a basis for consolidating some of our following methodological choices.

- The framework stages to develop an assessment protocol: preliminary diagram, study design, operationalization of the methods, project schedule, execution, and conclusion [12-14].
- The lesson that an evaluable result consists of the internet user's loyalty to the logic models used and not the loyalty necessary for a program to be effective [15]: "The distinction in digital health evaluation from traditional evaluation is that there is not always a need to evaluate health outcomes as direct effects of the digital health intervention" [13].
- The decision to document the initial impact of an intervention as well as its additional impact compared to existing digital interventions by Santé publique France [13].
- The decision to take into account the unexpected effects of health IT [16].

Digital Intervention for Behavior Change in Midlife

Based on a holistic and person-centered approach, the digital intervention provides information on the main risk factors for health, taking into account the barriers to and drivers for adopting healthy behaviors as well as the specific living conditions and environments of those aged 40-55 years. This digital intervention is based on the quantified self to support behavior transformation [17,18]. The design of the intervention is explained in a separate study (under review) that illustrates the complementary nature of the theories used in relation to the targeted behavior changes. To become familiar with the user and guide them toward behavior changes, the initial access to the site requires them to fill out a questionnaire on their lifestyle habits, which generates personalized feedback according to a traffic light system in order to introduce recommendations for protective behaviors. At this stage, the user has the option of downloading their report with an overview of the feedback in the form of a table. The next click opens a feed page with action cards and studies that the user can "like," save to their account, and use to navigate further around the site. The personal account is designed as a self-coaching tool intended to support motivation, increase the power to act, and help the user understand health as an interaction between several health determinants applying to all life areas (Table 1).

Table 1. Personalized space of the digital intervention with the available resources and functionalities.

Sections of the personalized space	Resources or functionalities available
Home page	The following items are displayed as a dashboard: answers to the "lifestyle habits" questionnaire, feedback in a traffic light system, feed page with action cards and study pages that can be liked, and liked actions and study pages following website navigation.
My favorite content and goals	A list of liked actions automatically categorized by determinants—users have total freedom to use drag-and-drop to modify the layout according to their needs (eg, from the easiest to the most difficult; based on a time frame) and to delete or add material; and a list of liked studies automatically categorized by determinant—users have total freedom to use drag-and-drop to modify the layout according to their needs (eg, from the easiest to the most difficult; based on a time frame) and delete or add more.
My assessment	An option to repeat the "lifestyle habits" questionnaire to see how habits have changed with the traffic lights and feed page being updated and a history of previous questionnaires is displayed.
My successes	A list of actions that have become everyday behavior.

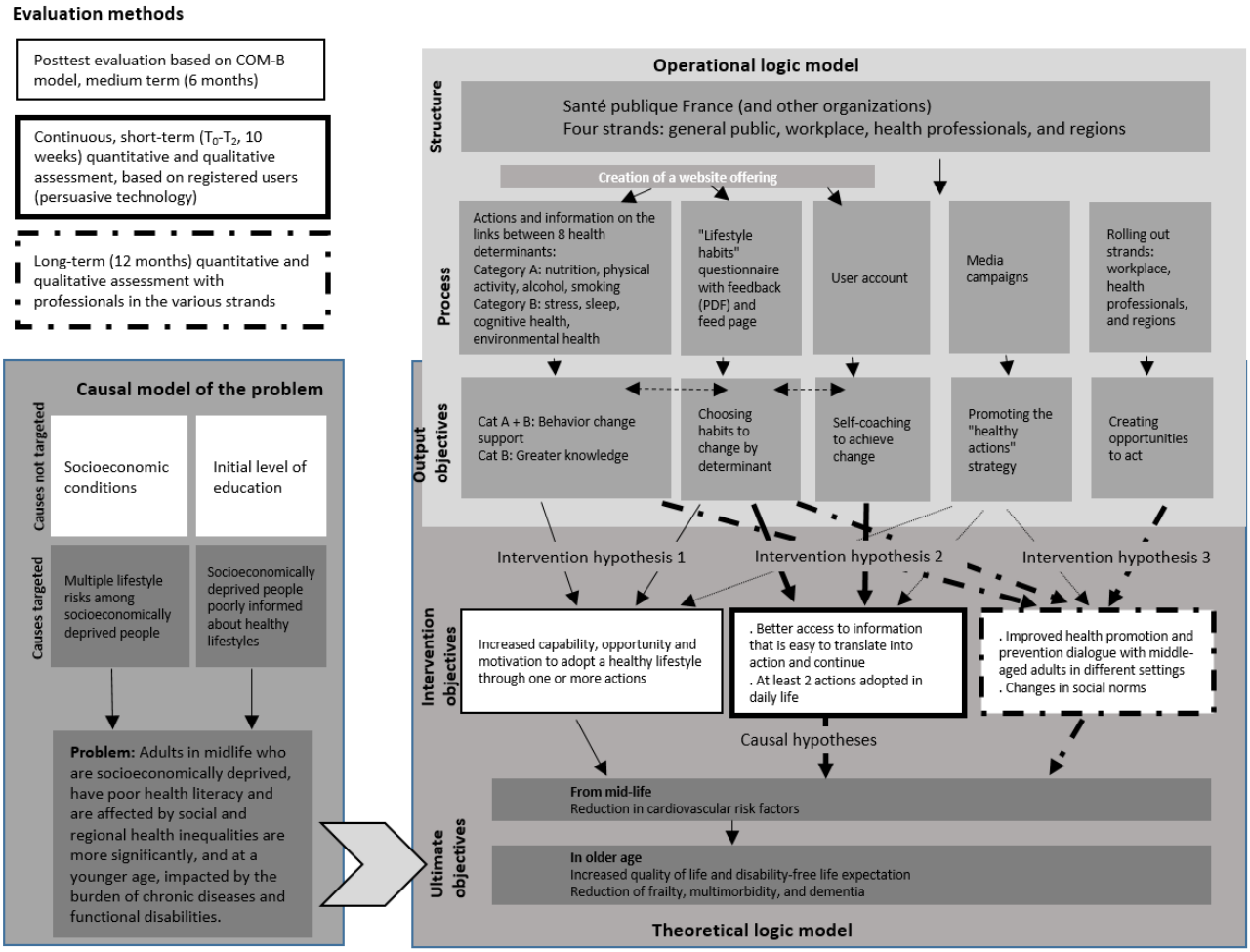
As no gold standard questionnaire on lifestyle habits is available, the present one is a concatenation of different examples taken from the literature and pretested with a target group of midlife adults during a qualitative study.

The personalized space for registered users was leveraged to form the basis of the assessment as the users' actions could be tracked via the content management system. The assessment could then be carried out continuously or in waves.

Conceptual Framework: Intervention Model

The first step was to identify the causes of the problem, shown in the "causal model of the problem" in Figure 1 [19], then to translate them into an objective in the "theoretical logic" part and finally to deduce the output and intervention objectives (operational logic model), leading to 3 evaluable working hypotheses.

Figure 1. Modeling the social marketing scheme to support the adoption of healthy lifestyles in midlife (adapted from Brousselle et al [19]). COM-B: capacities, opportunities, motivations-behavior.



The protocol aims to assess the impact of the website based on the small actions triggered among users to the different health determinants. Specifically, it is intended to evaluate the website's performance in terms of the following objectives: (1) engaging a specific population, (2) triggering behavior change, (3) raising awareness about a multifactorial approach to health, and (4) encouraging user interaction with the website's resources. The paper describes the methods and their relevant limits when constructing an assessment protocol for digital interventions. It questions the value of digital self-assessment and the time frame necessary to evaluate the adoption of healthy lifestyles, as no expert consensus is available on this topic. Finally, the article explores how behavior change models can strengthen the effect measurement of an assessment protocol.

Methods

Objectives of the Digital Intervention

The effect of the intervention on protective behaviors in midlife is communicated through 8 health determinants: diet, physical activity, smoking, alcohol, stress, sleep, cognitive health, and environmental health. The digital intervention is intended to help people aged 40-55 years, and in particular, socioeconomically disadvantaged people to (1) adopt multifactorial preventive actions in their daily lives; (2) increase their knowledge about lesser known determinants (stress, sleep, cognitive health, and environmental health); (3) support dialogue with health care professionals; and (4) develop psychosocial skills, especially the ability to resist social pressure.

Theory of Assessment of a Digital Intervention

The 3-pronged approach of "perceive, prepare, act," resulting from existing digital behavior change interventions [8,20], correlates with the functionalities of the website—questionnaire, actions, personalized space—designed using the behavior change techniques of capacities, opportunities, motivations-behavior (COM-B) [21].

Table 2 shows the indicators that can be used to answer the assessment questions.

- The mechanisms and factors that influence the choice of one or more actions and contribute to whether they are adopted are shown in "1. goals and planning—perceive, prepare, and act" as well as in the column "prepare" when a user likes one or more actions.
- The influence of personalized space on the adoption of actions (preferably multifactorial) and on the self-assessment of lifestyle habits can be understood on the basis of the items listed in the "act" column.
- The factors likely to influence target users' perception of their chosen health-promoting action are reflected in the fact that the questionnaire is repeated (2.4) and that behaviors are practiced, repeated, and changed (from 8.1 to 8.4).

Table 2. Transposing the BCT[a] of COM-B[b] onto the digital behavior change intervention context: perceive, prepare, and act.

COM-B	Digital behavior change intervention [8]		
	Perceive (website + questionnaire)	Prepare (actions)	Act (personalized space)
1. Goals and planning	1.6. Discrepancy between current behavior and goal (questionnaire)	1.1. Goal setting (behavior) 1.4. Planning behavior	1.5. Review behavior goals (increase practice) 1.6. Discrepancy between current behavior and goal (doing the action) 1.7. Review outcome goal(s) 1.9. Commitment (to be done, etc.)
2. Feedback and monitoring	2.2. Feedback on behavior (questionnaire)	—[c]	2.3. Self-monitoring of behavior 2.4. Monitoring of behavior outcomes (redo the questionnaire)
3. Social support	3.1. Social support (unspecified; internet resources) 3.2. Social support (practical) 3.3. Social support (emotional)	—	—
4. Shaping knowledge	4.2. Information about antecedents	4.1. Instruction on how to accomplish a behavior	—
5. Natural consequences	5.1. Information about health consequences 5.2. Salience of consequences 5.5. Anticipated regret	—	—
6. Comparison of behavior	6.2. Social comparison	6.1. Demonstration of the behavior	—
7. Associations	7.8. Associative learning (favorable environment and multifactorial approach)	—	7.1. Prompts or cues
8. Repetition and substitution	—	8.3. Habit formation	8.1. Behavioral practice or rehearsal 8.2. Behavior substitution 8.3. Habit formation 8.4. Habit reversal
9. Comparison of outcomes	9.1. Credible sources 9.3. Comparative imagining of future outcomes	—	—
10. Reward and threat		—	10.4. Social reward
11. Regulation	11.3. Conserving mental resources	—	—
13. Identity	13.1. Identification of self as role model	—	—
15. Self-belief		—	15.3. Focus on past success

[a]BCT: behavior change technique.

[b]COM-B: capacities, opportunities, motivations-behavior.

[c]Not applicable.

The typology of a target user, as described earlier in the objectives, can be combined with the indicators of the perception, preparation, and action stages to complete an assessment in advance.

Mixed Assessment Protocol

Three evaluative questions emerge concerning the personalized account and, by extension, the website.

- What mechanisms and factors influence the choice of one or more actions and contribute to the user adopting them?
- What influence does personalized space have on the adoption of actions that are preferably multifactorial and on the self-assessment of lifestyle habits?
- What factors are likely to influence target users' perception of their chosen health-promoting action?

Our protocol combining quantitative and qualitative assessment is based on data collected from the personalized space, which was designed with the objective of "outsourced self-regulation" [17], supplemented by additional questionnaires and individual interviews. The mixed assessment evaluates behavior changes made at different time points in the data collection process rather than the increase in quality of life and disability-free life expectancy. As mentioned earlier, the evaluable result is the user's loyalty to the logic models used [13] and not the loyalty necessary for a program to be effective [15]. Kelders et al [22] described the typical components through an analysis of 83 digital interventions: modular, updated once a week, use of persuasive technologies, and potential to interact with the communicator and peers [23].

The features of an assessment protocol are as follows.

- Before the digital intervention is launched: it supports the design and modeling of digital intervention.
    - Once launched, (1) it checks whether the users of the personalized space are between the ages of 40 and 55 years, whether they are socioeconomically deprived, and whether they have a low level of literacy; (2) it creates typologies of registered users; (3) it measures the effects (ie, changes in the behavior of registered users) through evaluable criteria and indicators such as adopting and maintaining a new healthy behavior, increased knowledge, improved psychosocial skills, and improved health variables [6,24]; and (4) it continually improves the website and personalized space to support the desire to change behavior in midlife [18,25].

Recording unexpected effects [16] sheds light on the adjustments needed in order to continually improve the intervention. Several hypotheses for these have been formulated: (1) the questionnaire does not engage users or it is never repeated; (2) the initial request does not correspond to the determinant that the user is "coached" on in their personalized space; (3) a highly disparate choice of actions makes it difficult or even impossible to implement them (no actions are adopted); and (4) actions are liked without a time objective being set.

Assessment Objectives

As stated above, the intention was to split the individuals included in the assessment into 2 groups. The 7 measurement objectives presented below apply to both groups. A detailed description of the objectives is given in Multimedia Appendix 1.

- Objective 1: To assess whether the user's profile matches the purpose of the site, namely, to reach socioeconomically disadvantaged people with a low level of health literacy and aged between 40 and 55 years at T0.
- Objective 2: To record lifestyle habits that deviate to some extent from public health recommendations at T0, T1, and T2.
- Objective 3: To record liked actions and articles while distinguishing actions in category A (change in behavior: diet, physical activity, smoking, and alcohol—additional contribution compared to other Santé publique France social marketing schemes) from those in category B (greater knowledge: sleep, stress, cognitive health, and environmental health—initial contribution given the absence of other Santé publique France resources). The assumption made is that the user chooses actions for category A and study pages for category B. Data are collected at T0, T1, and T2.
- Objective 4: To assess willingness to change behavior at T0.
- Objective 5: To assess the evolution of the behavior change between T0 to T1 and T1 to T2; to assess the frequency and routine nature of actions at T1 and T2.
- Objective 6: To assess re-engagement at T2.
- Objective 7: To assess lapsed connection to the personalized space before T1 and before T2 [26].

Assessment Time Frame

A digital behavior change intervention consists of several stages with a total average duration of approximately 10 weeks [8], although there is no consensus between experts over the time frame. Engagement with the digital intervention involves registering to create an account with a personalized space and then signaling preparation for behavior change (phase 1), followed by the adoption of 1 or 2 actions (phase 2), and a phase of lapsed activity on the site (phase 3). Reengagement with the intervention (phase 4) is prompted by the need to solve a problem, renew motivation, identify a new action, and so on. [7]. Split into 3 evaluable phases—T0, T1, and T2 (respectively phases 1, 2, and 4 according to Yardley et al [7], in Table 3). The expected results and collection methods are presented in Table 3. It is based on the assessment work of the VERB™ campaign (in normal type) [27], the lessons learned on health information-seeking behaviors (in italics) [28], the theory of small actions (in bold) [29], and digital behavior change interventions (in bold and italics) [7].

Table 2 presents the interaction between perceiving, preparing, and acting, which can be repeated randomly at the 3 assessment intervals set out in Table 3.

Table 3. Timing of the assessment process, evaluable results, and assessment indicators: engagement with physical activity.

Action verbs	Actions	Outcomes	Assessment or indicators
Phase 1 (T0): use of the digital intervention			
To be aware of and to understand	Campaign	—[a]	Quantitative posttest evaluation of social media campaigns
To access	*Information*	—	—
To engage with	**Information**	**Site log-in and completion of the questionnaire**	**Log-in data (quantitative)**
To choose	***A small target behavior***	***Actions or liked content pages, account created in the subscriber space, and healthy lifestyles***	***Interaction with the site and subscriber space data (quantitative and qualitative)***
Phase 2 (T1): use of the digital intervention and engaging with behavioral change			
To change in	—	Subjective norms, beliefs, self-efficacy, and perceived behavioral control	Qualitative data: questionnaires, verbatim comments, and individual interview
To use	*Information*	—	—
To intend to do	Physical activity	—	—
To engage with	**Behavior changes**	**Site log-ins and actions in the subscriber space**	**Qualitative and quantitative data from the subscriber space**
To choose	***A small target behavior and a concatenation of smaller goals***	***Actions or liked content pages and healthy lifestyles***	***Interaction with the site and subscriber space data (quantitative and qualitative)***
Phase 3: engaging with behavioral change			
—	—	—	—
Phase 4 (T2): use of the digital intervention and engaging with behavioral change			
To commit to and to maintain	Physical activity	Health outcomes	Log-in data (quantitative); interaction with the site and subscriber space data (quantitative and qualitative); and qualitative data: questionnaires, verbatim comments, and individual interview
To make	*Physical activity*	*Empowerment/ locus of control, satisfaction, activities of daily living, and health outcomes*	—
To choose	**A new small target behavior**	**Liked, validated actions**	—
To re-engage with	***Information if needed***	***Site log-ins and actions in the subscriber space***	—

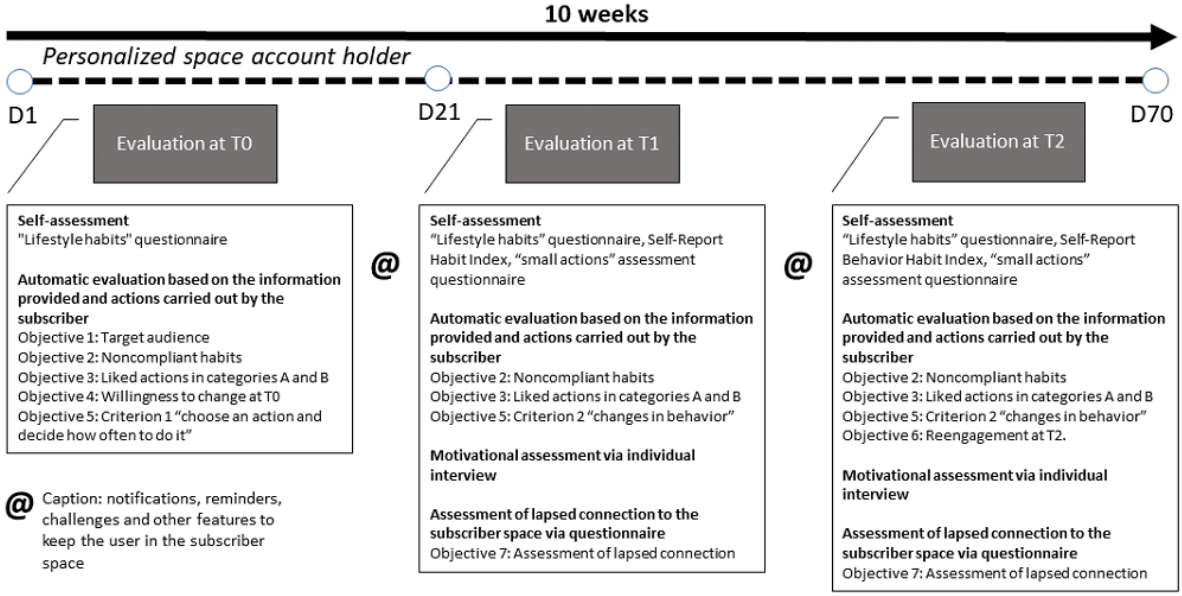
[a]Not applicable.

Furthermore, it is particularly important to determine (1) T1 (changes related to subjective norms, beliefs, self-efficacy, and perceived control of behavior), (2) T2 (level of empowerment, degree of satisfaction, activities of daily living, and self-reported health outcomes), and (3) between T0 and T1 and then between T1 and T2, there are 4 reasons for lapsing—forgetting, having a technical problem, permanently giving up on self-quantification, and suspending usage—but these do not necessarily mean that the adopted action has been abandoned [26].

Assessment Methods From T0 to T2

As detailed in Figure 2 [30], the assessment of the digital intervention at T0, T1, and T2 is intended to be explanatory, combining a quantitative and qualitative approach based on recording for both groups of users: (1) log-in data for the site and user account with personalized space, (2) data relating to specific and identifiable behavior changes by monitoring registered users from T0 to T2 via the content management system, (3) verbatim statements from users for classification into user profile; and (4) information about capabilities, opportunities and motivations via semistructured individual interviews with a sample of users.

Figure 2. Assessment methods from T0 to T2 (adapted from Trottier et al [30]).



Self-Assessment at T0, T1, and T2

The "lifestyle habits" questionnaire is the basis of the initial self-assessment at T0, then again at T1 to visualize the changes that have taken place and finally at T2 to identify developments (Table 4). Other suggested tools at T1 are the Self-Report Habit Index [31] to assess the power of the "frequency" factor for the action performed most often and the "small actions" assessment questionnaire. At T2, the Self-Report Behavior Habit Index is intended to show whether the behavior has become routine, supplemented by the "small actions" assessment questionnaire.

Table 4. Expected outcomes and measurement tools of the assessment protocol [32].

Objective	Domains	Measures	Source	Time frame	Measuring or recording tools
First results					
2. Lifestyle habits	Lifestyle habits more or less comply with public health recommendations	Results of lifestyle habits questionnaire	Server log files	T0, T1, and T2	"Lifestyle habits" questionnaire
3. Liked actions and articles	Adopting categories A and B actions related to one or more health determinants	Classification of actions by the user (including verbatim comments)	Server log files	T1, T2	Classification of actions
3. Liked actions and articles: multiple health factors	Understanding that health depends on multiple factors	Classification of actions by the user (including verbatim comments)	Server log files	T1, T2	Classification of actions
4. Willingness to change behavior	Statement of wanting to change a behavior	Classification of actions by the user (including verbatim comments)	Server log files	T0	"Lifestyle habits" questionnaire and Lapsing assessment questionnaire
5. Evolution of behavior change	Change in one or more lifestyle habits	Lifestyle habits questionnaire is repeated with one or more lifestyle habits changing	Server log files	T1, T2	"Lifestyle habits" questionnaire and classification of actions
5. SRHI[a]	Frequency of performing action	Self-assessment by SRHI	Server log files	T1	SRHI
5. SRBHI[b]	Extent to which action has become routine	Self-assessment using SRBHI	Server log files	T2	SRBHI
6. Re-engagement	Assess re-engagement	Classification of actions by the user (including verbatim comments); self-assessment by SRBHI	Server log files	T2	Classification of actions
7. Lapsed connection	Assess lapsed connection to the personalized space	Results of the assessment questionnaire on lapsed connection	By email	Before T1 and before T2	Lapsing assessment questionnaire
Mediators					
Effectiveness of mediator	Self-efficacy	Sense of personal efficacy [33]	Individual interview by group 1 and group 2 profile type	T1	Sense of personal efficacy scale
Effectiveness of mediator	Motivation	Situational motivation [34]	Individual interview by group 1 and group 2 profile type	T2	Situational motivation scale
Effectiveness of mediator	Capability, opportunity, and motivation	Information provided by the user through the individual interview	Individual interview by group 1 and group 2 profile type	T1, T2	Interview guide
Effectiveness of mediator	Frequency of personalized space log-in	Quantitative analysis of the user journey	Server log files	Continuous	Number of log-ins, liked actions and articles, incorporated or abandoned actions; time spent logged in; and interconnection between the determinants
Other results					
1. User profile	Biographical data	Categorized into group 1 or group 2: age, profession, level of health literacy, and absence of chronic disease	Results of lifestyle habits questionnaire and results of the "small actions" assessment questionnaire	T0	"Lifestyle habits" questionnaire and "Small actions" assessment questionnaire

Objective	Domains	Measures	Source	Time frame	Measuring or recording tools
1. User profile	Relationship between initial contribution (category B) and additional contribution (category A)	Personalized space: liked actions and studies	Server log files	T0-T2	Number of liked actions and articles by category
1. User profile	Any difference in behaviors between group 1 and group 2	Processing quantitative and qualitative data provided by registered users	Server log files	T1, T2	"Lifestyle habits" questionnaire, "Small actions" assessment questionnaire, and individual interview
1. User profile	Rate of lapsed activity in the personalized space	Lack of log-ins to the personalized space	Server log files	T0–T2	Number of log-ins between T0 and T2 and Lapsing assessment questionnaire

[a]SRHI: Self-Report Habit Index.

[b]SRBHI: Self-Report Behavior Habit Index.

To further support the objectives mentioned earlier, an automatic assessment at T0, T1, and T2 retrieves the information provided and actions carried out by the user.

The aim of the semistructured individual interview at T1 and T2 by groups 1 and 2 profile type and sampling is to reveal the impact of the capabilities, opportunities, and motivations on behavior change by combining the methodology of the COM-B, the theoretical domains framework [35] and the tiny habits theory. Taking a human-machine interaction perspective, it is very difficult to determine whether the choice of an action is based on conscious or unconscious motivation [8].

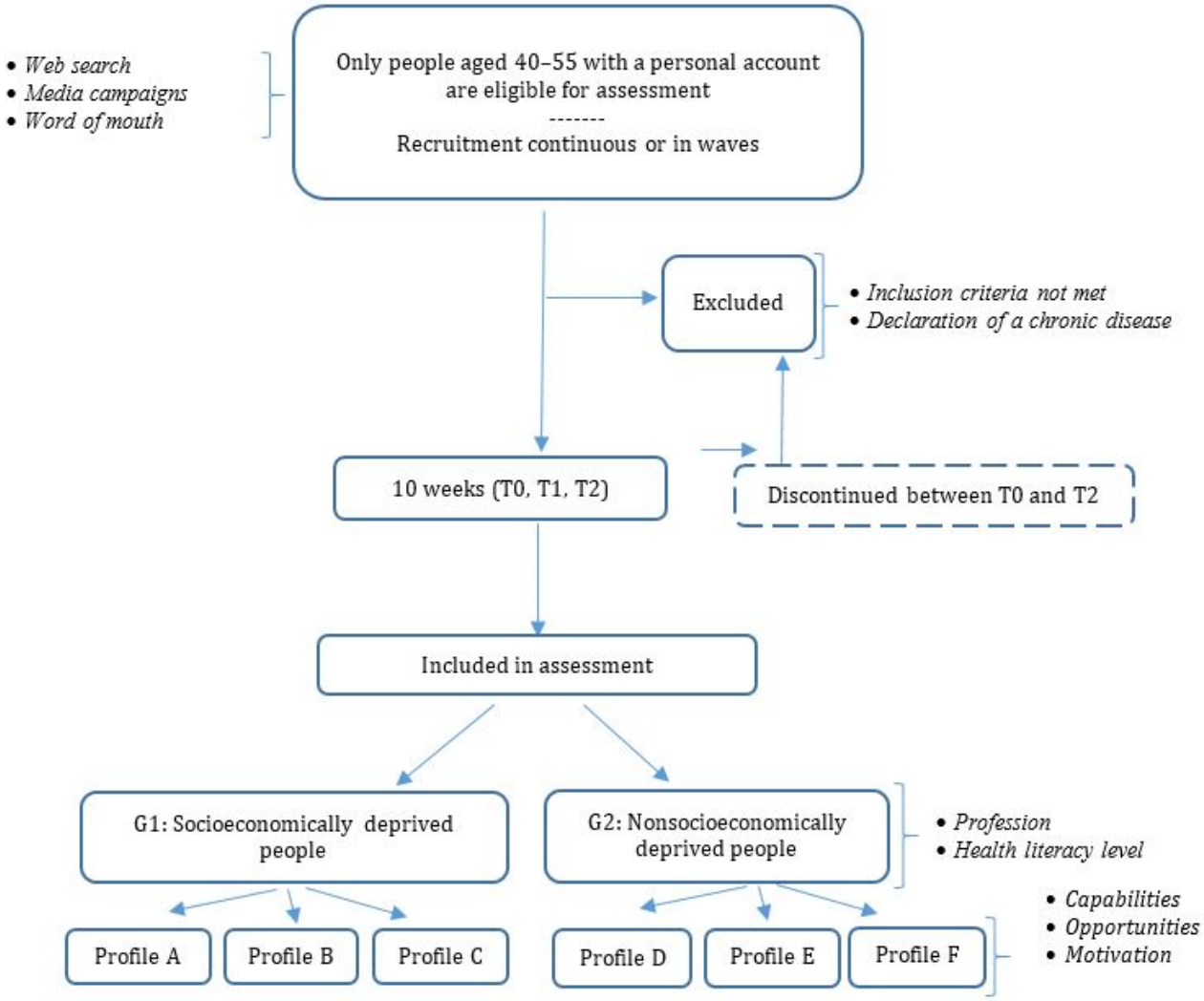
The assessment of lapsed connection to the personalized space before T1 and before T2 will be carried out via a questionnaire sent by email to the concerned users. The objective is to identify the reasons for the lack of use (with the aim of continually developing the personalized space) and the number of actions maintained without logging in.

Objectives 2, 4, and 5 make it possible to assess any unexpected effects: (1) the questionnaire is not the draw for the user or is never repeated (meaning that the user cannot view their progress in the personalized space; objective 2); (2) actions are liked, but no goal is set (objective 4); (3) a highly disparate choice of actions makes it difficult or even impossible to implement them (no actions are adopted; objective 5, criterion 1); and (4) the initial request differs from the action that the user is "coached" on in the personalized space (objective 5, criterion 2).

Assessment Population

The internet users, included in the assessment will be between the ages of 40 and 55 years, have registered to create an account on the website with a personalized space, and have carried out actions in their space during the 3 assessment stages: T0 (date of personal account creation), T1 (3 weeks after creation), and T2 (10 weeks after creation) (see Figure 3). Users will be divided into 2 groups. Group 1 will include socioeconomically deprived people and group 2 all other users. Each group will then be subdivided based on the "motivations," "capabilities," and "opportunities" expressed. By characterizing users into these 2 socioeconomic groups, the diversity of behaviors can be questioned, and corrections can be made to support group 1. Classification into group 1 will be based on 2 conditions: belonging to the lower socioprofessional categories and having a level of health literacy below 3.39 on domain 8 of the French Health Literacy Questionnaire [36].

Figure 3. Assessment diagram.



When people create their personal account, in accordance with the General Data Protection Regulation in force in Europe, registered users will need to consent to the use of their quantitative and qualitative data for study purposes and agree to be contacted as part of the assessment. No sensitive medical data will be recorded, and the data from the content management system will be separated from the information collected through the personalized space. The digital security officer at Santé publique France verified the compliance of this data management approach with French data protection regulations (Commission nationale de l'informatique et des libertés).

The protocol currently allows testing in a given context and on a regional scale, for example.

Results

This first version of the protocol responds to the objective to create a multidimensional assessment of a digital intervention based on the statement that during a given timeline, interactions with users aged 40-55 years can reveal their capabilities, opportunities, and motivations to adopt healthy lifestyles.

The assessment protocol based on the interactions with users in their personalized space of the digital behavior change intervention includes the evaluation of the following.

- Increased capability, opportunity, and motivation to adopt a healthy lifestyle through one or more actions.
- Improved access to information that is easy to translate into actions and to continue.
- At least 2 actions adopted in everyday life.

However, the protocol cannot evaluate improved health promotion and disease prevention dialogue with adults in midlife in different settings or assess changes in social norms.

As the construction of the website is currently delayed, no recruitment or effects analysis of the protocol could take place. The creation of a steering committee was abandoned.

Discussion

Expected Findings

As mentioned above, the protocol assesses the impact of the website based on the small behavior changes that it triggers among users in relation to different health determinants. The protocol has four aims: (1) engaging a specific population, (2)

triggering behavior change, (3) raising awareness about a multifactorial approach to health, and (4) encouraging user interaction with the website's resources. The research takes an interest in challenging the time frame necessary to evaluate the adoption of healthy lifestyles. It focuses on how the usage of behavior change models (COM-B) combined with the techniques of digital behavior change interventions [8] can strengthen the effect measurement of an assessment protocol. The assessment protocol is based on typical digital functionalities such as a user account, self-evaluation of healthy lifestyles (questionnaire), and feedback to engage people with behavior change. It fosters a continuous short-term evaluation of digital behavior change interventions.

Main Results

This appears to be the first assessment protocol for digital health promotion interventions. It documents the potential of the digital intervention in various respects, supporting it on the basis of the chosen models that led to the design of the personalized space and contributing to its continued development both in terms of its technical features and written content. The mixed assessment method delivers a granular analysis that sheds light on the effectiveness and even the efficiency of the website through its personalized space. To our knowledge, our assessment protocol for a digital personalized space, designed with the aim of changing health promotion and disease prevention behaviors, is the first of its kind in the sense that it goes beyond the measurement of the implementation and expressly targets the measuring effect. According to literature reviews, the effects in question will be behavioral change, greater knowledge, improved psychosocial skills, development of a support network, and improved health variables [6]. The protocol cannot be likened to assessments in investigational designs such as randomized controlled trials, which have been dismissed by some experts as unsuitable by some experts due to the complexity of health promotion interventions. The open design is considered effective "for the institutions that set it up and its flexibility matches the characteristics of health promotion interventions" [6].

Limitations

The breadth of the mixed assessment may make the process of interpreting the lessons learned more complex if the power of each item of "collectible" information proves to be insufficient. The absence of an expert consensus on the duration necessary for behavior change to occur throws into question the time frame of 70 days. The weakness of the protocol relates to the lack of real application given that the launch of the website is delayed.

Conclusions

Drafting an assessment protocol is a significant aid in the design of a digital intervention. This makes it possible to consolidate the choice of hypotheses for constructing the logical models used and the objectives targeted. A protocol helps to steer the digital intervention toward the action and regularly checks that it meets the needs of its target audience. The assessment protocol meets the SMART (specific, measurable, achievable, relevant, and time-bound) criteria.

The research presented here will impact digital interventions in health promotion and disease prevention. As the protocol demonstrates, both the implementation and effects can be assessed. Health promotion and disease prevention stakeholders may prefer an assessment of the program, but this is rarely carried out. Without assessments, a digital intervention can claim to be "evidence-inspired," although, with assessments, it is closer to "evidence-based."

Conflicts of Interest

None declared.

Multimedia Appendix 1
Detailed presentation of the 7 objectives of the assessment.
[DOCX File , 26 KB - resprot_v14i1e60559_app1.docx]

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Abbreviations

COM-B: capacities, opportunities, motivations-behaviors
SMART: specific, measurable, achievable, relevant, time-bound

Edited by A Schwartz; submitted 28.05.24; peer-reviewed by S Thongchoomsin; comments to author 16.09.24; revised version received 06.11.24; accepted 14.11.24; published 07.02.25.

Please cite as:
Soleymani D, Pougheon-Bertrand D, Gagnayre R
A Digital Behavior Change Intervention for Health Promotion for Adults in Midlife: Protocol for a Multidimensional Assessment Study
JMIR Res Protoc 2025;14:e60559
URL: https://www.researchprotocols.org/2025/1/e60559
doi:10.2196/60559
PMID:

Protocol

Developing and Evaluating an Interactive, Case-Based, Web-Based Active Learning Tool for Primary Care Physicians (Community Fracture Capture Learning Hub): Protocol for an Acceptability and Engagement Study

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Abstract

Background: The lack of osteoporosis treatment initiation after fragility fractures is a significant gap, especially in primary care. It is unclear whether barriers for primary care physicians (PCPs) arise from uncertainty about investigations, treatment initiation, or medication side effects. Key questions remain about whether active learning platforms improve treatment initiation rates better than passive methods and how PCP demographics affect learning outcomes. With PCPs increasingly using web-based platforms for continuing professional development due to time constraints and heavy workloads, an interactive community fracture capture (CFC) tool may serve as an effective alternative to in-person learning. Our CFC pilot study tested this new program's design and content, showing promising potential.

Objective: We aim to evaluate the interactive, case-based, web-based CFC Learning Hub, examining user acceptance and engagement with the platform, focusing on participants' interactions, satisfaction levels, and overall experience.

Methods: Participating PCPs are recruited through Praxhub, a web-based medical education platform, and provide electronic consent for data use after deidentification. They have been allocated into small groups (12-20 members) and join the CFC Learning Hub, a secure web-based community. This hub includes a web-based discussion forum with participant-contributed case studies and a knowledge repository. Over the 6-week program, participants will receive weekly modules with instructions, resources, discussion threads, and quizzes, along with interactive discussions moderated by experienced PCPs and physicians. The platform also hosts web-based surveys that, in combination with platform analytics, allow assessment of baseline knowledge gaps, level of activity or engagement, and improvements following the course completion. This study protocol demonstrates the creation and proposed evaluation of the CFC Learning Hub, featuring an interactive, case-based, small-group web-based learning platform equipped with flexibly scheduled, tailored modules to address the fracture treatment gap within the community. Both qualitative (via thematic analysis) and quantitative (by using 2-tailed paired *t* tests, Wilcoxon signed rank tests, and multivariable regression

analysis) analyses will be used to assess levels of engagement and acceptance and changes in PCPs' knowledge and confidence after engagement with the CFC Learning Hub.

Results: Recruitment of participants started in May 2022. Data collection, analysis, and reporting will be completed following the completion of four 6-week cycles of the program.

Conclusions: The study described in this protocol will provide important insights into the function and effectiveness of the CFC Learning Hub. This information will guide the expansion of the program. This initiative offers a simple digital solution for promoting current bone health practices tailored to PCPs' needs and thereafter to expand the rollout of the e-learning hub and implementation of fracture liaison models at a primary care level in Australia and elsewhere. Future applications may extend to other clinical areas and professions.

International Registered Report Identifier (IRRID): DERR1-10.2196/57511

(JMIR Res Protoc 2025;14:e57511) doi:10.2196/57511

KEYWORDS

community-based fracture capture bone hub; osteoporosis; virtual communities of practice; continuing professional development; primary care physicians; web-based learning platform; case-based education

Introduction

Osteoporosis: A Growing Global and National Concern and the Unmet Challenges in Fracture Prevention and Management

Osteoporosis affects around 200 million people globally, resulting in more than 8.9 million fractures each year, equivalent to 1 fracture every 3 seconds worldwide [1]. Furthermore, this disease burden is projected to increase dramatically in the coming decades as the global population is aging [2]. By the year 2050, the global occurrence of hip fractures is estimated to rise by 310% for men and 240% for women, compared with 1990 rates [3]. In Australia, osteoporosis incurred a societal cost of Aus $2.6 billion (~US $1.638 billion) in 2022 [2]. Despite the alarming increase in the prevalence of osteoporosis and the morbidity, mortality, and economic costs associated with low-trauma fractures in the aging population [4-6], there remains a substantial deficit in the implementation of effective interventions to prevent fragility fractures [7-9]. Despite the presence of effective diagnostic tools (eg, dual-energy x-ray absorptiometry [DXA]), fracture risk assessment tools (eg, FRAX) [10], and medications known to mitigate fracture risk, a substantial treatment gap exists in osteoporosis care, with only about 20% to 30% of individuals who sustain fragility fractures receiving guidelines-based care [2,11]. International and Australian data have unequivocally demonstrated the cost-effectiveness of hospital-based fracture liaison services (FLS) in secondary fracture prevention to address this treatment gap among patients presenting with low-trauma fractures, including in our own institution [12,13]. However, many patients with low-trauma fractures that may not require tertiary care (eg, vertebra, radius, and others) are investigated and managed purely at the primary care level and therefore may escape hospital-based services [14]. Furthermore, a recent survey of the International Osteoporosis Foundation Capture the Fracture program also noted a relative paucity of FLS centers in Australia [2]. The probability of initiation of osteoporosis medication following hip fracture within 12 months after discharge has been falling, despite these patients having the highest risk for imminent refracture [15,16]. The same investigation gap exists in primary fracture prevention among primary care physicians (PCPs); since 2016, there has been a plateau in subsidized bone density requests for Australians older than 70 years, despite the rapidly aging population [9,12,14,17].

Adapting Fracture Prevention Models: The Urgent Need for Improved Primary Care Strategies

A rational approach to improving fracture prevention outcomes in the community setting would be to adapt the hospital-based model of care at the primary care level. However, unlike the hospital-based FLS that depends on the coordinator to facilitate investigations and clinic appointments, community-based fracture capture relies solely on PCPs to detect, investigate, and treat osteoporosis [18]. Despite compelling evidence for efficacious treatments to manage osteoporosis in primary care, and in particular the initiation of therapies to minimize the likelihood of refracture, the application of evidence and guidelines into clinical practice, particularly by PCPs, remains unacceptably low in Australia and many other countries such as the United States, Malaysia, Singapore, Germany, France, and Canada [9,19-24]. Consequently, many Australians are not receiving optimal, timely care in the community. For example, despite being eligible for osteoporosis-related investigations (eg, DXA) and antiresorptive therapies (eg, denosumab and bisphosphonates), a large proportion of Australians are neglected in this respect. While the hospital FLS model focuses on secondary fracture prevention with the motto of "Stopping at One Fracture," the additional focus among PCPs should be primary fracture prevention with the aim of "Stopping the First Fracture" [25].

Empowering PCPs: A Novel Approach to Bridging the Osteoporosis Treatment Gap Through Live, Interactive Learning Hubs

PCPs are faced with enormous challenges in daily practice to deal with multiple chronic health conditions, their sequelae, and comorbidities within a limited consultation time. Despite this, PCPs are required to continuously extend their knowledge to ensure that evidence-based practice is applied to their patients [26,27]. PCPs are increasingly seeking information on the web for their continuing professional development (CPD) [28-31], which is a viable alternative to face-to-face learning that

potentially can be managed in their own time [32]. Hence, incorporating social media technologies for CPD has become a commonplace mechanism encouraging PCP learning in web-based group settings [29,33,34]. Including our Community Fracture Capture (CFC) Learning Hub pilot study, only a few recent studies have investigated the ability of web-based learning activities to mitigate the crisis in osteoporosis care by providing education, leveraging the scarce resources of the health care system, and enabling practitioners to offer better and more accessible skeletal health care locally and at a lower cost [35,36]. Our investigation of challenges PCPs face in using virtual communities of practice (VCoPs) for continuing medical education emphasizes the importance of trust building, efficient time management, and collaborative learning among health care professionals in building efficacious VCoPs [37]. We therefore aim to address the community osteoporosis treatment gap using a novel, live, and interactive CFC Learning Hub that provides a health VCoP to facilitate knowledge transfer to overcome barriers to osteoporosis recognition and management.

Although this program incorporates some elements typical of conventional courses, its distinctive combination of features and the unparalleled extent of flexible engagement opportunities set it apart. This uniqueness underscores our rationale for the study and the importance of conducting a formal research evaluation to fully assess its operational features, effectiveness, and potential impact on participants. Building on the feasibility study results, we aimed to create a more advanced version of the CFC Learning Hub with enhanced features. Therefore, this study aims to develop the CFC Learning Hub, an interactive web-based platform with case-based modules to improve fracture treatment among Australian PCPs and assess the impact of the CFC training model, while also examining the relationship between PCP demographics, clinical experiences, and knowledge gaps in treatment.

Methods

Study Context

The general design, development, and content planning for the interactive, patient-focused CFC Learning Hub have already been piloted to a small group of PCPs with favorable feedback and demonstrating excellent metric properties [35]. The CFC Learning Hub will be built from lessons learned from this feasibility study with the aim of enhancing PCPs' awareness and competence in caring for patients with osteoporosis. The hub was conceived, designed, and developed by an interdisciplinary team of experts, comprising specialist physicians with expertise in osteoporosis and bone health, experienced PCPs, information technology and data science experts, and a project manager. It took time and resources for specialists to discuss and agree on major decisions for the program. Therefore, the timing and resource for such projects require appropriate support because of the need to understand terms, expectations, deliverables, and measurables across disciplines. The project team, situated in Melbourne, Australia, drew on its learning, teaching, and clinical experience to define the following important design criteria for PCP participants and elements in the project:

1. Practicing PCPs registered for the training have been provided with case studies and asked to provide their own case study with anonymized patients to encourage engagement.
2. There is interactive engagement between all parties involved.
3. Experienced PCP peers lead the group as facilitators, with guidance where needed by specialist "advisors," promoting case discussions and guiding discussion of content according to its relevance and importance.
4. There is a minimum time commitment required for the award of CPD credits for participation.

Importantly, the CFC Learning Hub format is flexible in terms of the timing of participants' input. Comments can be posted and discussions can be viewed at any time of the day, in order to accommodate participants' workload and personal commitments. This learning platform provides an alternative to attending an on-site lecture or a webinar wherein a specific time slot needs to be set aside for attendance including discussion. The CFC Learning Hub will be driven by three principles: (1) sound learning pedagogy that is aimed at changing attitudes and behavior, supported by clear assessment structures; (2) learning analytics at the back end of the CFC Learning Hub to understand the development of the participants through studying their web-based participation in the discussion forum; and (3) usable and accessible features of the hub to ensure maximization of uptake of the system.

Education Platform

Education has been delivered via Praxhub [38], an Australian-based web-based platform for health care professionals to access CPD resources from leading health care organizations. At the time of publishing this paper, Praxhub is used by thousands of health care professionals from more than 150 countries and aggregate education from more than 50 health care organizations. The CFC Learning Hub represents a departure from the main model of webinars and web-based learning modules for PCPs on a wider scale by including a range of increased opportunities for engagement and interactions with the participants.

The Praxhub platform allows for "groups" to be set up, in which participants can join and each week's education modules can be hosted and made available to the participants. Before starting the CFC cycles, an early decision was made to make each of the groups "private"—meaning that only those participants invited into that group would have access to the modules and visibility of that group's activity (ie, conversations within the discussion thread). It was considered important to quarantine the activity within the group from the remainder of Praxhub's membership to create a more supportive and encouraging environment for individual participation. By extension, it was considered that a public group, in which conversations could be viewed by the broader Praxhub membership of health care professionals, may have the propensity to limit conversations (ie, active engagement) due to concern about criticism or professional judgement, as well as to avoid redundant discussions.

After assignment of participants to a designated private group, they attended an approximately 1-hour orientation session, conducted via a Zoom (Zoom Video Communications, Inc) meeting, to familiarize them with navigating the group and accessing the modules. Participants were informed by email (with a link in the email) of the availability of a new module each week. Within each module, participants were provided video or written instructions of the activities to be completed in that week, additional resources or materials to download and read, and a facilitated discussion thread in which to post questions to the specialists or PCP coordinator. The composition of each module is shown in Table 1. A weekly quiz was also made available for participants to probe their understanding of the week's materials.

An additional consideration in selecting Praxhub as the system to deliver the CFC Learning Hub program was its robust data collection. While Praxhub strictly uses these data to enhance the user experience and report completions of CPD activities on the platform, in accordance with its privacy policy, participant consent was provided to Praxhub for the limited disclosure of their deidentified data for the purposes of this study (see the *Data Collection* and *Ethical Considerations* sections).

The research measured various user-system interaction points to allow us to quantify the participants' engagement with the education program. These included dates and times (particularly time of day) when participants engaged with the education modules, whether videos were viewed or materials were downloaded, their engagement with other participants and the PCP coordinator and specialists via the discussion thread, and the responses to weekly quizzes.

These data were reviewed each week during the program to monitor participant-level engagement and at the end of each 6-week cycle to construct and understand how the participants engaged with the education and determine the performance in the program against the overall objectives.

Table 1. A summary of Community Fracture Capture Bone Hub 6-week content design.

Characteristic	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6
Cases	Live webinar + 1× case	1× case	2× case	2× case	2× case	Live webinar + 1× case
Hot topics	Osteoporosis introduction and investigation	Assessment of risk factors	Osteoporosis effects	Treatment and side effects	Treatment failure	Difficult osteoporosis cases
Surveys	Premodule survey	N/A[a]	N/A	N/A	N/A	Postmodule survey
Quizzes	N/A	1×	1×	1×	1×	N/A

[a]N/A: not applicable.

Education Program

The CFC Learning Hub is a web-based resource center for case studies, related resources to support PCP learning, and a web-based community discussion forum. Once enrolled, participants are required to watch a mandatory familiarization program to learn the function and capability of the hub and to submit 1 or 2 patient cases for discussion. Facilitators and specialist advisers will filter and select case studies that enable coverage of a syllabus of topics predetermined by members of the project team for this CPD course. Facilitators ensure that the posted case studies are anonymized and contain suitable, high-quality content for discussion. Each CFC Learning Hub cycle is scheduled for 6 weeks and comprises three main learning pillars: (1) osteoporosis investigation and treatment initiation, (2) treatment maintenance and monitoring, and (3) troubleshooting treatment side effects and treatment failure. In some cycles, a short video presentation will be delivered by a bone specialist to introduce the theme of that week. Participants will be exposed to a range of case studies over these modules and have access to resources to facilitate learning and novel paradigms of thinking about osteoporosis to address the treatment gap. In addition, there will be opportunities for peer-to-peer interactions and learning; the experience is enhanced and personalized by discussing difficulties that registrants encounter in their very own deidentified submitted cases. The CFC Learning Hub platform has two resources for PCP interactions: (1) a web-based knowledge repository (the "Knowledge Hub") containing prepopulated evidence-based research papers, guidelines, position statements, and other resources relevant to that week's topic curated by our team's subject matter experts, and (2) a web-based social network forum (the "discussion forum") where PCPs can freely post web-based comments including questions for discussion posted by facilitators; case studies as a way to encourage PCPs to learn and share their knowledge based on shared experiences and relevance to their immediate clinical practice; and topical discussions as either hot topics deemed relevant for PCPs, posted by our osteoporosis specialists, or other topics that were open for a wider discussion (ie, introductions (facilitators and PCPs introduce themselves) and burning questions (PCPs and facilitators post inquiries on osteoporosis; these will focus on significant issues arising during a group's participation). The platform's topical discussions section includes (1) diabetes and bone health, (2) atypical femoral fracture, (3) when to consider changing an osteoporosis therapy, (4) how to get the most from your patients' bone density testing, (5) an "Introduction" topic for all users to introduce themselves, and (6) a facility for PCP participants to post inquiries based on seeking specific information about osteoporosis. Facilitators can also raise questions to promote discussion. These inquiries are organized under the term, "Burning Questions." The Knowledge Hub will act as an accessible knowledge repository for all users at any time. It will be a dynamic source of information, being expanded

and adapted in response to participants' learning needs. Participating PCPs will complete 4 knowledge quizzes (1 quiz in each of weeks 2-5) and a questionnaire regarding osteoporosis caseload and demographics, confidence in case finding, investigations and treatment initiation, and barriers to osteoporosis case finding, investigations, and treatment initiation. The knowledge assessed will be in accordance with The Royal Australian College of General Practitioners (RACGP) and the Healthy Bones Australia (formerly Osteoporosis Australia) Osteoporosis Management and Fracture Prevention Guideline 2024 [39], a position statement developed by national experts to provide PCPs with clear guidance concerning the identification, investigation, and treatment of persons at risk for fragility fractures. In addition, pre- and postparticipation multiple-choice questions will be used for testing to assess knowledge transfer, change in confidence, and behavior (Table 1). The forum will be highly interactive (active learning) and case based and is supported by the RACGP and the Australian College of Rural and Remote Medicine approving the award of CPD points or hours to their fellows for active participation in the CFC Learning Hub (RACGP: 40 CPD points [2020-2022 triennium] and 12 activity hours [2023-2025 triennium], and Australian College of Rural and Remote Medicine: 8 Professional Development Program hours [February 23, 2020 framework] and 12 activity hours [2023-2025 framework]).

Description of the Platform, Setting, Recruitment, and Participants

Platform

Praxhub has developed a web-based community (web and mobile apps) to support the delivery and distribution of medical education. It is free of charge for doctors to register and their credentials are validated against the government-held register of doctors. Praxhub already has a preexisting large network of registered PCPs in Australia and has been recruiting participants through their web page and internal member communication system.

The invitation to participate in the CFC Learning Hub will be distributed via PCPs professional bodies and using the existing pool of PCPs registered with Praxhub. Interested PCPs will contact the project manager, after which they will be screened for eligibility to participate in the program and subsequently enrolled if they satisfy the selection criteria and consent to participate in the project, approving to take part in the 6-week web-based educational program, answer pre- and postparticipation surveys, and allow the CFC Learning Hub to use their data for auditing and research purposes.

Once registered, all participants will be allocated to a private group, through which they can access the topical presentations, cases, and discussion forums. Participants and facilitators will have a profile, which shows their professional qualifications, experience, practice location, awards, and achievements, in accordance with the information that is required for the program, in addition to a profile picture (avatar) for personalization and easy identification. Participants will be able to engage in case studies and discussion topics and access and post comments, text, images, links to videos, and documents at their convenience.

The aim is to enroll 12-16 PCPs to participate per CFC Learning Hub cycle, and participants can drop in and out based on their interest in the content and their availability.

PCPs will be eligible to participate in the program if they (1) are a medical practitioner currently active in general practice in Australia, (2) submit at least 1 (preferably 2) suitable case studies with discussion or learning points from their own clinical experience that include patients at risk or those with prevalent osteoporosis, and (3) have web access.

PCPs will be excluded if they are unable to commit at least 6 hours to the anticipated time required to meet appropriate CPD guidelines.

Measures

Data related to sessions and activities of participants in the CFC Learning Hub will be collected for all cycles. Our primary focus, at this stage of the project, is detecting participation patterns to characterize the interactions of participating PCPs with the platform and specifically with respect to osteoporosis investigation and treatment initiation, learning, and knowledge-sharing behaviors related to participation and engagement in the CFC Learning Hub.

We will define the following terms from Praxhub analytics:

1. A session includes all user-related activities from initial logging in to logging out of the CFC Learning Hub. All activities made between the logging in and out activities will be grouped within a session.
2. An activity includes downloading of content, viewing posts and content, and posting comments.

Measuring sessions and activities will discover participants' full active and passive engagement with the web-based system, which can be used to help measure the success of the platform (eg, high-session count means PCPs are frequently logging in, undertaking 1 or more activities, and then logging out). PCPs can actively engage through posting in a case study or topical discussion, while they can also engage passively via browsing and watching a brief video presentation in a case study or topical discussion. Initially, in the Knowledge Hub, we anticipate that PCP participation is likely mainly to be passive as PCPs browse the Knowledge Hub database. In addition, PCPs can actively engage with the Knowledge Hub by posting comments or queries. In measuring discussion forum use, the usage behavior for each case study and topical discussion will be assessed. For each case study and topical discussion, usage is measured from the creation date (on a Monday of each cycle's week) until the end of the cycle).

Interactive Learning Hub

Once the 6-week program commences, the weekly content for 1 or more topics, along with a short video presentation on some topics (cycles 3 and 4), delivered by senior PCP and bone specialists to introduce the theme of that week, will be released by the moderators at a predefined scheduled time. This is communicated to participants via customized electronic

correspondence allowing them to access and discuss. The content of these weekly modules is based on and selected from the following topics:

1. What is osteoporosis and why is it important?
2. Prevention strategies for osteoporosis and secondary fracture.
3. Who is at risk? Tools for assessing fracture risk.
4. Application in primary care.
5. The roles of allied health professionals—practice nurse, physiotherapist, and dietitian.
6. Physical activity and exercise: benefits and risks, beliefs about exercise.
7. Osteoporosis diagnosis and further evaluation. Appropriate initial workup.
8. DXA: Applications. What are its strengths and limitations?
9. Treatment: Approach to the choice of treatment and initiation of specific osteoporosis therapy.
10. Engaging patients in shared decision-making.
11. Calcium and vitamin D: Primary therapy and adjunctive therapy.
12. Monitoring for safety and effectiveness of therapy.
13. Recognizing and managing treatment "failure."
14. Issues with long-term therapy and "treatment holidays"?
15. Osteonecrosis of the jaw and atypical fractures associated with treatment.
16. Why are patients being missed?

The hub will direct participants to resources and organizational websites in line with the week's topic and case study. Along with the release of the educational resources, a relevant case study will be presented for discussion. Interactive and flexible discussion throughout the week will take place on predefined discussion boards within the CFC Learning Hub and will be moderated by PCP facilitators and experienced physicians.

Moderators and Data Gathering

Moderators will access the discussion boards during each topic discussion to monitor and participate in discussion at least once daily during each cycle. The time and way in which participants engage with the site will be quantitatively monitored throughout the duration of participation in the Learning Hub. Specifically, data that will be collected include (1) total number of discussion posts by each participant; (2) individual response time for each new discussion board opened on the web-based forum; (3) number of users who have actively participated in individual discussion board on the web-based forum; (4) the average time to reach a final resolution in each discussion on the web-based forum; (5) the accrued time that each participant spends logged onto the learning hub; (6) the total time that each participant spends on the web-based forum and individual pages on the learning hub, (7) the number of times internal and external websites are visited by each participant from the learning hub links; and (8) the overall popularity of web-based forums, as measured by number of page views, downloads, comments, rating, and followers of individual posts.

Data Collection

Sample Size and Justification

The aim is to enroll 12-16 PCPs to participate per CFC Learning Hub cycle. A relatively small number of participants in a VCoP (ie, 12-20) who are learning and seeking knowledge is desirable as participants are likely more incentivized to be an active rather than passive user [40-44]. For example, the study by Barnett et al [41] reported that PCPs felt less isolated and more motivated to exchange knowledge after joining a small VCoP for their family physician training.

Qualitative Analysis

The qualitative analysis will aim to (1) identify common themes related to barriers and facilitators of web-based learning, PCP perceptions, and attitudes toward the program, and (2) examine barriers to effective detection and management of osteoporosis in general practices in Australia (ie, PCPs using a virtual space for their specific learning needs rather than physical seminars).

To achieve this, the relational content analysis will be undertaken [45,46]. More specifically, 2 researchers within the team will inductively identify codes independently in the first instance. In this initial step, researchers will use both semantic (capturing explicit and obvious meanings of the text) and latent (capturing tone, intention, and underlying assumptions) coding approaches to explore a wider range of codes. Subsequently, in the second phase, the 2 researchers will discuss and debate on the codes to assess for patterns that coalesce around key themes. The codes are then presented as subthemes of the themes that are identified. Finally, all data will then be counted against the list of subthemes to explore how strongly each subtheme is represented in the dataset by a single researcher and a random sample will be validated by a senior researcher.

Due to the innovative nature of the e-learning hub, themes will be created from participants' transcriptions and validated through rigorously evaluating past and current initiatives made in this area (if any) in the literature. As the program progresses, we will seek to make necessary adjustments to the design and content of the e-learning hub.

The results of thematic analysis will be reported using a top to bottom approach with main (high level) themes reported first, following the subthemes emerged. All results will be supported by exemplary or representative quotes provided by participants.

We will also try to understand the differences in aforementioned areas based on PCPs' years of experience and level of web-based activity (subject to diverse participation and data availability). Overall, feedback by participants will be used to reevaluate and redesign the e-learning hub in terms of navigating and searching for relevant content for PCPs learning needs. The qualitative analysis will aim to identify common themes related to barriers and facilitators of web-based learning, PCP perceptions, and attitudes toward the program. We will also try to understand the differences in aforementioned areas based on PCPs' years of experience and level of web-based activity (subject to diverse participation and data availability). Due to the innovative nature of the e-learning hub, themes will be created from participants' transcriptions and validated through rigorously evaluating past

and current initiatives made in this area (if any) in the literature. As the program progresses, we will seek to make necessary adjustments to the design and content of the e-learning hub. Overall, feedback by participants will be used to reevaluate and redesign the e-learning hub in terms of navigating and searching for relevant content for PCPs' learning needs.

Quantitative Analysis

The data from all cycles will be analyzed separately and combined. The between-cycle differences in participants demographic data (ie, years in practice) and level of activity, including time spent on the platform, number of various resources accessed during the training, and number of modules or education activities they have participated in, will be assessed using Kruskal-Wallis test. Changes in participants' level of knowledge, measured using the proportion of correct responses provided to pre- and posteducation quizzes, will be assessed using either 2-tailed paired *t* tests or Wilcoxon signed rank tests, whereas multivariable regression analysis will be used to examine factors associated with levels of change in knowledge and confidence, while controlling for PCPs' experience, level of participation in the program, and baseline level of knowledge or confidence. Other potential confounders will be considered, subject to the data availability and sufficient power. The level of significance for the quantitative analysis is set at $\alpha < .05$.

Ethical Considerations

The Melbourne Health Human Research ethics committee approved this project (site reference 2016.24), adhering to institutional ethical review processes for research involving human participants. Electronic consent from PCP participants who joined the CFC Learning Hub was obtained to use their deidentified data for research and auditing purposes. The electronic consent process included a waiver of consent for case study patients, whose anonymized information was also used in the project. The data collection and management of electronic consent were carried out using Praxhub tools, ensuring appropriate safeguards for privacy and confidentiality. The data used in this study were fully anonymized to protect participant identities. No compensation was provided to participants in this program.

Results

Recruitment of participants started in May 2022 through initial contacts with PCP members on the Praxhub platform. The recruitment continued until August 2023. The expected quantitative and qualitative data on outcomes are currently being collected and their analysis will be available in early 2025.

Discussion

Overview

We hypothesize that (1) the CFC Learning Hub can provide a novel, peer-to-peer learning experience, offering up-to-date knowledge of primary and secondary fracture prevention strategies among a diverse range of PCPs, and (2) the improved confidence and motivation to investigate and treat osteoporosis, gained via interactive live web-based discussion among PCP peers and bone expert facilitators, can be quantified using predefined analytics tools.

International and Australian studies clearly establish the cost-effectiveness of hospital-based FLS for secondary fracture prevention, aiming to bridge the treatment gap for patients with low-trauma fractures [12,47]. Nevertheless, a considerable number of patients with low-trauma fractures receive investigation and management solely or predominantly from PCPs, potentially bypassing hospital-based services, or alternatively, they receive their ongoing care from their regular PCPs once acute fracture care is provided by hospital services [48]. Therefore, it is imperative for PCPs to maintain currency with fracture prevention protocols and primary care service delivery models. The translation and application of evidence and guidelines for osteoporosis management in primary care, particularly by PCPs, are unacceptably low internationally including in Australia, leading to underdiagnosis, underinvestigation, and undertreatment of osteoporosis in many countries [12,47,49-52]. Furthermore, a significant number of Australians are not receiving timely and appropriate management in primary care, as evidenced by the lack of access to osteoporosis-related investigations and therapies despite eligibility for such interventions [27,48,53]. An Australian review of 88,000 postmenopausal women attending PCPs found that 29% (20,248/69,358) of the targeted cohort had sustained at least 1 osteoporotic fracture, yet less than one-third of these women with fractures were receiving specific treatment for osteoporosis and 7% (3825/57,088) of these women were taking calcium alone [14]. Another Australian study reported that 76% (87/109) of men who had sustained an incident fracture remained untreated for osteoporosis 12 months after sustaining the fracture, despite being eligible for osteoporosis treatment [27]. These studies indicate that PCPs in Australia need additional resources to support primary care management of fragility fractures. Our education modules target the knowledge gaps specifically to address the issues of osteoporosis underdiagnosis and undertreatment and the need for timely and appropriate osteoporosis management.

Regarding the sufficiency of medical resources to cope with osteoporosis-related health issues, a recent paper presenting system dynamics modeling of the potential impact on fracture care of increasing hospital-based FLS demonstrated the probable inadequacy of these services to cope with the predicted fracture burden in years to come [54]. These observations underline the critical need to upgrade such care in the community, which inevitably will require high levels of PCP involvement. These analyses add emphasis to the need for effective education programs in this field.

Comparison With Prior Work

PCPs encounter substantial daily challenges in providing optimal care for patients with various chronic health conditions, necessitating the application of evidence-based treatment approaches to enable the best outcomes [35,37]. Therefore, VCoPs for CPD may represent suitable alternatives for PCPs, being primary health care providers, to overcome barriers they encounter such as time constraints to accessing educational activities and a preference for face-to-face learning. Our

collaborative group explored the challenges faced by PCPs in using VCoPs for their CPD, identifying seven themes crucial for designing and sustaining effective VCoPs: (1) low trust and risk perception, (2) patient information sharing, (3) timely responses, (4) relevant website access, (5) individual learning styles, (6) communication gaps between PCPs and specialists, and (7) the need for diversity and interactivity [37]. Following that exploratory study, few studies aimed to design virtual, interactive, and PCP-targeted bone health programs. In the United States, the Bone Health Tele Extension for Community Health Care Outcomes (TeleECHO) program [55] was proposed as one strategy that aimed at improving PCPs' knowledge related to treatment gaps in osteoporosis care, using real-time videoconferencing to mentor health care professionals in rural and underserved communities [36]. In that study, 263 health care professionals from various countries participated over 21 months, showing substantial improvement in self-confidence across 20 domains of osteoporosis care with the TeleECHO intervention and addressing the osteoporosis treatment gap through enhanced education and knowledge-sharing among health care professionals. Quantitative and qualitative assessments were made of participating PCPs' experience in our pilot program, which was developed because PCPs from different demographics might differ in their knowledge gap. Evidently, this CFC Learning Hub provided an innovative and interactive educational web-based tool to assist with increasing PCPs' knowledge of osteoporosis management models and in turn the application of these guidelines to improve patient care [35]. The pilot program revealed the hot topics (eg, about osteoporosis, risk assessment of osteoporosis, and treatment and prevention strategies) that triggered the most discussion, indicating lack of confidence or knowledge gaps in these areas that are addressed in our current learning modules to ensure more widespread distribution of this knowledge. In our published pilot program of the CFC platform, PCPs were engaged in practice-based, web-based learning where they discussed their own cases with peer facilitators and specialist advisors [35]. In that program, our prototype CFC Learning Hub recruited 7 PCPs, as a convenience sample of PCPs interested in bone health topics, and it included 2 key components: a web-based discussion forum and a knowledge repository (the Knowledge Hub). The discussion forum contained anonymized case studies (contributed by PCP participants) and topical discussions (topics that were not case studies). Using 2 complementary tools (Google Analytics and Igloo Statistical Tool), we characterized individual participating PCPs' engagement with the hub. The discussion included questions from participants directly to the facilitators regarding management dilemmas: this is a more practical tool to deliver knowledge than traditional questionnaires and quizzes. We measured the PCP participants' behavior by quantifying the number of web-based sessions attended by the participants, activities undertaken within these web-based sessions, written posts made per learning topic, and their time spent per topic. We calculated time spent in both active and passive engagement for each topic. The baseline questionnaire highlighted the knowledge gaps and the facilitators, specifically directed discussion to address these gaps during the hot topic discussions. This project draws on findings from the pilot study and insights gained from implementing assessment tools to expand the CFC Learning Hub.

Strengths and Limitations of the Program

Our educational program is positioned to deliver distinct outcomes compared with traditional face-to-face lectures and stand-alone, web-based webinars, offering PCPs time flexibility and leveraging the advantages of peer-to-peer and PCP-to-specialist interactions through web-based posts. It anticipates a departure from the traditional unidirectional nature of lectures by placing a strong emphasis on cultivating an interactive learning environment characterized by introspection and peer-to-peer discourse. This approach is designed to encourage participants to engage in more profound cognitive processing of the material, thereby fostering a nuanced comprehension. The integration of peer-to-peer discussions is a pivotal departure from conventional methods, establishing a collaborative and nonjudgmental forum for the exchange of insights, diverse perspectives, and shared learning experiences. This departure from traditional modes of education is anticipated to enhance the program's efficacy, providing a more profound and enriching educational encounter for participants due to its multifaceted nature. Osteoporosis presents diverse challenges across age groups and between sexes, requiring tailored approaches in primary and secondary fracture prevention. The absence of a universal solution adds complexity, necessitating nuanced insights for specific cohorts, such as those undergoing oncological treatment, relying on glucocorticoids, or in the posttransplant phase. With various modalities such as pharmaceutical interventions, over-the-counter supplements, and exercise-based strategies, the program's interactive and case-based nature is anticipated to align aptly with the intricate landscape of osteoporosis management, fostering a deeper understanding of this complex medical domain. For instance, our successful pilot study showcased the effectiveness of the program's innovative approaches in tracing the path from engagement to practice change as recognized by obtaining CPD accreditation for the activity, thereby affirming the rationale for informing a larger study with a specific focus on creating and facilitating more practice-based topics for PCP participants [35].

The limitations of this study include transferability of this work beyond Australia since there is a shift toward community-based rather than hospital-based fracture prevention programs, and PCPs are encouraged to develop subspecialty interests in chronic condition such as osteoporosis. This in-depth subspecialty education might be beyond the scope of PCPs elsewhere in the world. The success of this approach is dependent on PCPs' motivation to incorporate osteoporosis care into their workflow when it might be easier to refer to specialists. Personalized peer-to-peer discussion is more expensive to deliver per participant than traditional webinars and lectures and therefore might not be sustainable.

Principal Findings

The main contribution of this protocol paper is a detailed description of how to conduct and analyze co-design, interactive, peer-to-peer PCP learning activities to develop a digital collaborative environment that promotes up-to-date bone health practice among PCPs. The program platform has capacity and

agility to improve and adjust in real time based on participants number and needs.

The CFC Learning Hub will provide insights into the barriers to community-based osteoporosis identification and treatment initiation from the PCP perspective, as well as the effectiveness of a VCoP facilitated through an innovative web-based platform, along with methods for evaluating participation. The barriers identified might differ depending on region of practice and the experience level of the PCP. The pre- and postparticipation surveys permit quantification of knowledge and confidence gained. If successful, the CFC Learning Hub can be expanded to specifically target rural areas where interactive knowledge transfer and delivery can be logistically challenging.

Conclusions

There is an urgent need to address the treatment gap in osteoporosis care, particularly within primary care settings where PCPs play a central role. The identified challenges, such as low trust of web-based content, patient information sharing, timely responses, and communication gaps, underscore the importance of tailored educational interventions such as the CFC Learning Hub. The pilot program's success in engaging PCPs and addressing knowledge gaps suggests the potential of the CFC Learning Hub program and its innovative, web-based tools in improving osteoporosis management and patient care within primary care settings.

Acknowledgments

The study is funded by Amgen Australia Pty Ltd and Theramex. The funding bodies were not involved in the study design, content development, study conduct or data collection, analysis, and interpretation.

The authors thank The Royal Australian College of General Practitioners and the Australian College of Rural and Remote Medicine for approving the Community Fracture Capture (CFC) Learning Hub as an accredited professional learning activity, and The University of Melbourne Department of Medicine at The Royal Melbourne Hospital and the Faculty of Engineering and Information Technology of The University of Melbourne for supporting the research team and providing required resources.

Data Availability

The datasets generated during and analyzed during this study are available from the corresponding author on reasonable request, once the relevant findings have been published.

Authors' Contributions

AMF, CC, RA, SC, and JDW contributed to study conceptualization, writing of the original draft, and project administration; AMF, CC, RA, SC, SS, CJY, RB, SP, LC, and JDW contributed to the methodology and investigation; JDW, CC, RA, RB, CYJ, SC, and LC contributed to conducting the learning sessions; SS contributed to providing regular liaison with Praxhub; AG, AMF, CC, RA, SC, and JDW contributed to the data curation; and JDW, CC, and SC contributed to study supervision. All authors have read, provided feedback, and agreed to the final version of the manuscript for publication.

Conflicts of Interest

None declared.

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Abbreviations

ACRRM: The Australian College of Rural and Remote Medicine
CFC: community fracture capture
CPD: continuing professional development
DXA: dual-energy x-ray absorptiometry
FLS: fracture liaison services
PCP: primary care physician
RACGP: The Royal Australian College of General Practitioners
TeleECHO: Tele Extension for Community Health Care Outcomes
VCoP: virtual community of practice

Edited by A Schwartz; submitted 20.02.24; peer-reviewed by CH Chan; comments to author 16.09.24; revised version received 01.11.24; accepted 15.01.25; published 25.02.25.

Please cite as:
Fathalla AM, Chiang C, Audehm R, Gorelik A, Chang S, Yates CJ, Snow S, Barmanray R, Price S, Collins L, Wark JD
Developing and Evaluating an Interactive, Case-Based, Web-Based Active Learning Tool for Primary Care Physicians (Community Fracture Capture Learning Hub): Protocol for an Acceptability and Engagement Study
JMIR Res Protoc 2025;14:e57511
URL: https://www.researchprotocols.org/2025/1/e57511
doi:10.2196/57511
PMID:

Protocol

Identifying, Engaging, and Supporting Care Partners in Clinical Settings: Protocol for a Patient Portal–Based Intervention

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Abstract

Background: In the United States, the landscape of unpaid care delivery is both challenging and complex, with millions of individuals undertaking the vital role of helping families (broadly defined) manage their health care and well-being. This includes 48 million caregivers of adults, 42 million of whom are caregivers of adults aged 50 years or older. These family care partners provide critical and often daily support for tasks such as dressing and bathing, as well as managing medications, medical equipment, appointments, and follow-up care plans.

Objective: This study aimed to implement a novel patient portal–based intervention to identify, engage, and support care partners in clinical settings.

Methods: The project team collaborated with 3 health care organizations (6 primary care practices in total) to design and implement a patient portal–based intervention. Three days in advance of a visit, patients were invited to log on to their patient portal account and answer a brief questionnaire as part of the routine electronic check-in process asking them to (1) identify themselves as the patient or someone answering for the patient, (2) report major life changes, (3) set the agenda for the upcoming visit, and (4) report on care partner responsibilities. Respondents' answers to this brief questionnaire were available to providers ahead of the visit. Patients with care partner responsibilities, as well as care partners answering the questionnaire on behalf of patients, were provided a link to the ARCHANGELS Caregiver Intensity Index to measure the intensity of their caregiving role and motivate care partners to connect with suggested state and local resources.

Results: The intervention was launched in September 2022 at Organization A. Organization B launched in May 2023 in one clinic and June 2023 in the other. In focus groups, staff and clinicians reported that the intervention was easy to implement and did not cause workflow disruption. At 6 months post implementation, across both organizations, a total of 22,152 patients had received questionnaires and 13,825 (62.4%) had submitted completed questionnaires. Full data will be reported at the completion of the intervention period.

Conclusions: Early results suggest that the intervention could be an easily scalable and adaptable method of identifying and supporting care partners in clinical settings.

International Registered Report Identifier (IRRID): DERR1-10.2196/66708

(JMIR Res Protoc 2025;14:e66708) doi:10.2196/66708

KEYWORDS

patient portal; previsit questionnaire; caregivers; care partners; questionnaires; support; engagement

Introduction

Caregiving in the United States

In the United States, the landscape of unpaid care delivery is both challenging and complex. Millions of individuals undertake the vital role of helping someone else manage their health care and well-being. This includes 48 million caregivers of adults, 42 million of whom are caregivers of adults aged 50 years or older [1]. Family (broadly defined) care partners provide critical and often daily support for tasks such as dressing and bathing, as well as managing medications, medical equipment, appointments, and follow-up care plans [2-4]. The role of a care partner can be fulfilling as well as challenging. Many care partners report a sense of purpose and fulfillment related to the care they provide, and some research suggests that caregiving has a protective health effect [5-8]. Other studies suggest that having caregiving responsibilities can also be correlated with poorer mental and physical health, finding substantial rates of chronic illness and poorer mental health over time [9-13].

Surveys of care partners taken during the COVID-19 pandemic noted particularly high levels of stress and adverse mental health symptoms, including anxiety, depression, and suicidality [10-12], possibly due to the reduced availability of services related to social distancing and closures by home care services and caregiver respite services [13]. A survey of more than 10,000 US adults conducted between late 2020 and early 2021 revealed significant mental health issues. A total of 70% of all care partners reported experiencing at least one adverse mental health symptom such as anxiety, depression, or suicidal thoughts, in comparison to 32% of respondents with no care partner responsibilities [10]. While the pandemic represented an extraordinary challenge to care partners, surveys conducted before the pandemic also found significantly higher rates of adverse mental health conditions among this population [14,15].

Providing care partners with psychosocial support has been shown to help both care partners and their care recipients [16,17]. However, identifying care partners and linking them to services remains challenging [18]. While care partners frequently interact with the health care system on behalf of patients, they often lack a way to access support for themselves [19,20]. A visit to a care recipient's health care provider rarely includes a discussion of care partner stress. As well, adding time to discuss caregiving responsibilities and available resources to an already busy clinical visit is often not feasible [21]. Identifying care partners (both patients who are care partners and care partners of patients) before or during clinical visits and connecting them to resources, without adding to clinical work, could be beneficial to patients, care partners, and clinicians.

Use of Patient Portals

Electronic health records (EHRs) and secure patient portals offer a ready opportunity to identify care partners in need of services. Most health care providers use EHRs and have online patient portals through which their patients can access their medical information, message their clinicians, renew prescriptions, schedule appointments, and more [22]. Previsit questionnaires, administered through the patient portal in preparation for a visit, have become more commonplace [23]. These questionnaires can provide an opportunity for clinicians to learn more about patient needs and concerns before a visit [24]. In addition to previsit data collection, portals offer the opportunity for interventions and the provision of resources outside of the clinic visit [25]. Studies suggest that portal-based interventions can lead to improvements in psycho-behavioral outcomes, such as health knowledge, self-efficacy, and decision-making [25,26]. While these benefits are typically focused on patients' reported health care needs, they can also be extended to other aspects of patients' lives, including their caregiving responsibilities.

Here we report on a multisite intervention designed to implement a method of identifying, engaging, and supporting care partners in office-based clinical settings using the patient portal. Specifically, we sought to create a model of care that identified care partners through a previsit questionnaire ahead of their own health care appointments, engaged them through the incorporation of their self-reported visit concerns and priorities into the questionnaire data, and activated them to understand their caregiver intensity and connect with resources without requiring additional action from the care team. We report here on the intervention design and interim feasibility data. The intervention took place for 1 year and the interim data were gathered at 6 months.

Methods

Intervention Components

Caregiver Intensity Index

The ARCHANGELS Caregiver Intensity Index (CII) [27] is designed as a self-assessment instrument of caregiver intensity across multiple dimensions. Individuals who complete the CII are provided with a numeric score between 0 and 100, a color (clear: low intensity; yellow: moderate intensity; and red: high intensity), and the top two drivers and top two buffers of their caregiver intensity. Those completing the CII are then directed to a microsite with resources specific to their needs and the community in which the patient receives care. The project team collaborated with each implementing site to ensure that the resource page was comprehensive.

In-Clinic Materials

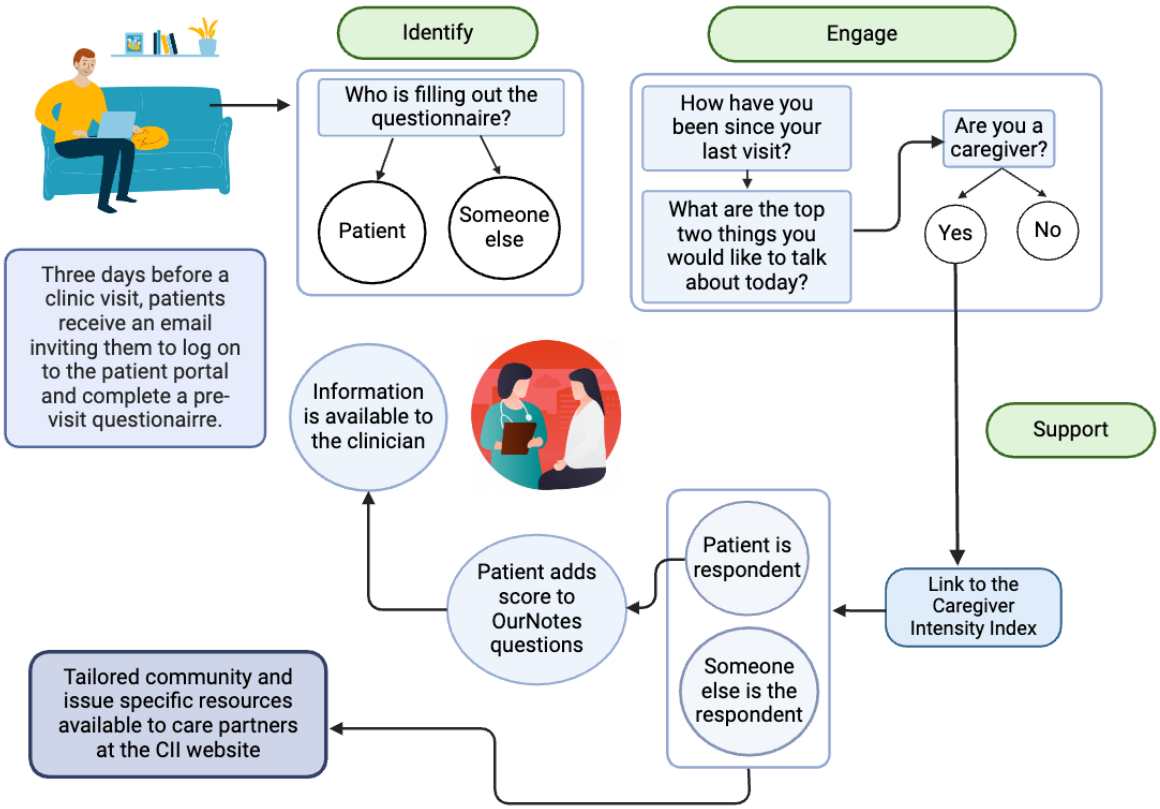
Each participating site was provided with in-clinic posters, wallet-sized handouts (referred to as "Care Cards"), and tip sheets for clinicians and staff. The posters and Care Cards included scannable QR codes that linked patients to the CII. These QR codes were specific to each site and modality, which allowed tracking of how resources were accessed (whether via poster, Care Card, after-visit summary, or previsit questionnaire). The tip sheets for clinicians and staff contained information on how to talk with patients about caregiving responsibilities and how to find patients' completed questionnaires in the EHR.

Previsit Questionnaire

The team at Organization A convened regularly with the project team to draft and refine the previsit questionnaire, adapting a previously tested questionnaire [24] with input from clinic staff and clinicians as well as feedback from patient and family advisors in the organization's Patient and Family Advisory Council. The final previsit questionnaire was also tested at Organizations B and C.

The final previsit questionnaire, to be sent to all patients aged 18+ years with an upcoming visit (except those whose upcoming visits were Medicare annual wellness visits, annual physicals, or telehealth visits), comprised the following items (see Multimedia Appendix 1 for complete survey branching logic and the exact wording of the questions): (1) Identification: respondents were prompted to specify if they were the patient or were completing the previsit questionnaire on the patient's behalf (either as a designated portal proxy or by logging in as the patient; note: if someone other than the patient is filling out the questionnaire, they are answering the questions for the patient, not for themselves). (2) Life changes notification: respondents were asked to communicate significant life changes since their last clinic visit. (3) Visit agenda-setting: respondents were asked to identify the one or two most important things they wished to discuss at the upcoming visit. (4) Care partner responsibilities: respondents were asked if they had caregiving duties and to share for whom they provided care. (5) Receipt of care partner support: respondents were prompted to indicate if they received help managing their health and health care from another person. (6) Caregiver intensity index: respondents reporting caregiving responsibilities were given a link to the CII and provided with an opportunity to report their color and score in the previsit questionnaire. Those who answered the previsit questionnaire on behalf of the patient were given the CII link but were not given the option of sharing their score (Figure 1).

Figure 1. Previsit questionnaire flowchart.



We integrated previsit questions into the EHR for testing, assessing both the patient-facing interface within the patient portal and the corresponding view for clinic staff and clinicians upon submission of responses.

EHR Macros

Two macros were developed: 1 for clinicians to incorporate information about the CII in the patient visit summary and another enabling clinicians to integrate questionnaire responses into their notes.

Education for Clinicians and Staff

Before implementation, the project team conducted sessions with staff and clinicians from participating practices to demonstrate how to access the previsit questionnaire within the EHR, identify workflow adjustments, and provide an overview of the in-clinic materials. The project was approved by the institutional review boards at all project sites.

Stakeholder Input

The project team met with staff and clinicians at each participating site at 3 and 6 months, both in person and virtually. These meetings were held to identify and address implementation issues, provide ongoing education and support to clinic staff and clinicians, and surface feedback and concerns about the initiative.

Plans for Statistical Analysis

Upon the intervention period's completion at all sites, we will summarize the study participants' demographics, their usage of the CII, and the Caregiver Intensity scores. To compare the characteristics between groups, we will use the chi-square test or Fisher exact test for categorical variables and the Student *t* test for continuous variables. Multivariable regression models will be used to explore the associations between the Caregiver Intensity score and patient demographic factors. We will also use qualitative analytic methods to identify key themes and subthemes in the free-text responses. All statistical analyses will be performed using SAS software (version 9.4; SAS Institute Inc).

Ethical Considerations

The protocol was approved and deemed exempt from full review by the institutional review boards at Beth Israel Deaconess Medical Center (IRB protocol # 2021P000928) and the University of Michigan (IRB protocol # HUM00225451). Per the exempt status of the intervention, informed consent was not required. Patients were informed about their right to opt out of the intervention in the invitation email. All data will be deidentified in the analytic data file. No personally identifying information will be included in the analytic file. Participants were not compensated.

Results

We engaged 3 health care organizations to collaborate on the design and implementation of the intervention (Figure 1). The first site (Organization A) is a prominent academic medical center network in the Northeast. Within this network, we partnered with three clinics situated in suburban areas outside

a major metropolitan hub. Our second partner (Organization B) is a large academic medical center based in the Midwest. Within this center, we collaborated with two primary care clinics: a general internal medicine practice and a combined general internal medicine and pediatrics practice. Our third partner organization (Organization C) is a nonprofit health care entity serving primarily urban communities in the Northeast. The clinic associated with this organization predominantly serves low-income and racially diverse populations.

Two of these organizations are situated within regions commonly supported by the Ralph C Wilson Jr Foundation (the project funder), namely western New York and southeastern Michigan. The selection of the third site was based on existing strong professional relationships between project team members and the organization's leadership, coupled with the organization's keen interest in participating. Characteristics of participating health care organizations are shown in Table 1.

Table 1. Site characteristics.

Characteristics	Organization A	Organization B	Organization C
Total number of clinicians	• Clinic 1: n=2 • Clinic 2: n=6 • Clinic 3: n=5	• Clinic 1: n=22 • Clinic 2: n=20	2
Total number of clinic staff	• Clinic 1: n=17 • Clinic 2: n=13 • Clinic 3: n=15	—[a]	11
Clinic location	• Clinic 1: suburban • Clinic 2: suburban • Clinic 3: suburban	• Clinic 1: mixed • Clinic 2: mixed	Urban
Organizational payer mix, %			
Medicaid	14	28	57
Medicare	10	30	21
Private commercial insurance	72	40	20
Uninsured	2	2	1
Other unknown	3	—	—

[a]Not applicable.

Each organization established a dedicated work group that convened regularly with the research team (Table 2). These groups consisted of clinical champions, clinic leadership, project managers, and information technology staff. All partner organizations use the same electronic health record system.

Table 2. Organizational workgroups.

Collaborators	Organization A	Organization B	Organization C
Clinical champion	✓	✓	
Project manager		✓	
EHR[a] medical director	✓		
EHR team member	✓	✓	✓
Director of grants and program management			✓
Chief innovation officer	✓		
Social worker			✓
Practice administrator			✓

[a]EHR: electronic health record.

Organization A launched the intervention on September 30, 2022, and Organization B launched on May 17, 2023, in one clinic and June 1, 2023, in the other. Organization C was not successful in implementing the previsit questionnaire in their EHR and withdrew from the initiative. This was due to a mix of factors, including the lack of a clinical champion, the low usage of the patient portal among its patients combined with a higher reliance on paper documents by staff, and varied methods across clinics and staff as to if and how questionnaires submitted from the portal are identified and reviewed ahead of visits.

Adult patients at least 18 years of age were eligible to participate in the initiative. As shown in Figure 1, patients with a patient portal account and with an upcoming clinic visit were sent an invitation through the patient portal, 3 days ahead of a visit, to complete the previsit questionnaire. All visit types were included in the initiative with the exception of Medicare annual wellness visits, annual physicals, and telehealth visits. Annual wellness visits and physicals were excluded by request at participating sites because patients were already asked to complete a substantial number of questionnaires before those visits. Telehealth visits were excluded due to clinician concern that asking patients to fill out the previsit questionnaire would serve as a barrier to the telehealth login process and cause a delay in care. As shown in Figure 1, all the information provided by patients, or by others on patients' behalf, through the previsit questionnaire was available to clinicians in the EHR. Patients and care partners who did not complete the previsit questionnaire could access the CII through QR codes on the in-clinic materials (eg, care cards, posters, or the after-visit summary).

At the 3- and 6-month check-ins, clinic staff and clinicians reported few challenges with implementing the intervention. The primary challenge was learning to access patients' previsit questionnaire responses in the clinician and staff EHR view. Clinic staff and clinicians reported that some patients expressed appreciation for the opportunity to share and discuss their caregiving responsibilities. Further, they reported that few patients complained about being asked to fill out the previsit questionnaire. Clinic staff and providers said they felt better prepared to discuss care partner responsibilities with patients because they had resources to offer. Based on clinician and staff concerns with lengthy patient responses to the life changes and agenda-setting questions, the project team made minor wording changes to those questions and instituted character limits on the free text responses (see final questionnaire in Appendix). Finally, staff reported minimal disruption to workflows after adjustments to reduce the character limits of agenda-setting questions.

At 6 months post implementation, 25,611 surveys were assigned to 13,299 patients at Organization A and 16,265 questionnaires to 8853 patients at Organization B. At Organization A, 7076 questionnaires were received from 5350 patients. At Organization B, 6749 questionnaires were received from 4982 patients. Because the previsit questionnaire was tied to clinical visits, patients with multiple visits during the observation period received more than one invitation to complete a previsit questionnaire (Table 3).

Data for the full intervention period will be published in a future paper.

Table 3. Questionnaires assigned and submitted.

Disposition of questionnaires	Organization A	Organization B
Number of questionnaires assigned to patients, n	25,611	16,265
Number of questionnaires submitted by patients, n/n (%)	7076/25,611 (27.6)	6749/16,265 (41.5)
Number of patients assigned at least one questionnaire, n	13,299	8853
Number of patients submitted at least one questionnaire, n/n (%)	5350/13,299 (40.2)	4982/8853 (56.3)

Discussion

Principal Findings

We report on the rationale, development, and early uptake from the first 6 months of implementing a practice-based intervention aimed at identifying, engaging, and supporting care partners in office-based clinical settings using the patient portal. Early results from this work suggest that the intervention is acceptable to clinicians and staff and simple to implement. While we did not directly ask patients and care partners about their willingness to complete the previsit questionnaire, our robust response rate suggests that the intervention is feasible for patients and that it is possible to identify care partners before or during a clinical visit and connect them to resources.

To our knowledge, our intervention represents the first systematic attempt to identify, engage, and support care partners in clinical settings through a previsit questionnaire. Previous work focused on identifying patients' visit priorities using a similar methodology and found much lower rates of patient uptake than our preliminary findings suggest [24]. Understanding the extent to which the local clinical environments and patient populations affected implementation will be a critical area of focus for the final evaluation [28]. Our preliminary findings suggest that patients were generally receptive to completing the previsit questionnaire through the patient portal. The usage of previsit questionnaires is becoming more prevalent for assessing Social Determinants of Health and identifying resources or referrals that may benefit patients [29]. Incorporating caregiver-related responsibilities within Social Determinants of Health assessment efforts could also merit attention as a strategy for raising awareness of caregiver needs and integrating care partner identification and support within care delivery if our findings hold in the final evaluation.

While the role of a care partner can be fulfilling, it can also be fraught with numerous challenges, leading to elevated rates of mental and physical health issues among care partners [28]. Identifying care partners is a first step in understanding their capacity and needs, and in facilitating access to appropriate resources. Doing so within care delivery enables clinicians to become aware of caregiving responsibilities; however, busy clinical practices may struggle to address these needs. By providing resources outside of the clinical visit, our intervention could help to support caregivers, clinicians, and staff. Staff reported minimal burdens and disruptions to their workflow and the intervention was relatively simple to implement.

Our protocol has several limitations that should be noted. First, while the protocol includes in-office materials for patients and clinicians, patients must have access to the internet in order to

take the CII and explore the resources offered. This requirement may exclude a subset of patients with lower digital literacy. Future efforts could explore the possibility of, for example, text-based options using mobile devices. Second, our protocol is implemented in 5 primary care practices associated with academic medical centers. These centers may have resources for implementation that are not available in community-based practices. Finally, our protocol was designed for and implemented in health care organizations with the same commercially available EHR system. Implementing in other EHR systems may require adjustments to the protocol.

In the final 6 months of the project, we will monitor whether staff continue to report minimal workflow disruptions, whether patient feedback remains predominantly positive or neutral, or if there is an increase in complaints. If current results hold, and we find that patients with caregiving responsibilities are using the CII, this portal-based intervention could be a scalable and adaptable method of identifying, engaging, and supporting patients and their care partners in clinical settings. Should that be the case, we will widely disseminate our findings through the peer-reviewed and gray literature, as well as develop and disseminate "how-to" toolkits for primary care practices. Further studies focused on implementation in a larger number of diverse settings, by patient population, electronic medical record vendor, types of care delivery organizations, and geographic regions, will also be important as we seek to engage and support care partners through the health care system.

Conclusion

Millions of adults help another person with their health and care, and their needs are often unidentified and unmet. Despite the impact of caregiving responsibilities on physical and mental health, often their own health care providers do not know about their responsibilities. The early assessment of this unique pilot seeking to identify care partners through previsit questionnaires and in-office materials indicates that this low-burden effort may be an effective tool for identifying and supporting care partners. Future analyses of data from the full one-year pilot will give a more complete picture of the results and the possibility of adapting and scaling this intervention beyond the individual clinics involved in the study.

Acknowledgments

The authors would like to thank the Ralph C. Wilson, Jr. Foundation for its support of this work. We would also like to express our gratitude for the work of our clinical partner sites and the thousands of patients and care partners who completed the questionnaire. The research presented in this study was funded by the Ralph C. Wilson, Jr. Foundation.

Data Availability

The datasets generated during and analyzed during this study are not publicly available per the requirements of the participating organizations to maintain strict confidentiality and disclosure standards for patent data obtained during the course of routine care. For this reason, the data are also not available from the corresponding author.

Authors' Contributions

CMD contributed to conceptualization, methodology, investigation, formal analysis, writing-original draft, and writing-review and editing. DW contributed to methodology, investigation, formal analysis, writing-original draft, and writing-review and editing. ZD assisted with formal analysis, writing-original draft, and writing-review and editing. AD contributed to conceptualization, writing-original draft, and writing-review and editing. IH handled investigation, writing-original draft, and writing-review and editing. JA contributed to methodology, investigation, writing-original draft, and writing-review and editing. AC assisted with methodology, investigation, formal analysis, writing-original draft, and writing-review and editing. NC contributed to methodology, investigation, writing-original draft, and writing-review and editing. JM assisted with methodology, investigation, writing-original draft, and writing-review and editing. JN handled methodology, investigation, writing-original draft, and writing-review and editing. KO'D assisted with methodology, writing-original draft, and writing-review and editing. CW contributed to methodology, investigation, writing-review and editing. SSW assisted with methodology, investigation, formal analysis, writing-original draft, and writing-review and editing. JY contributed to investigation, formal analysis, and writing-review and editing. JLW assisted with methodology, writing-review and editing. The sponsor recruited Organization C.

Conflicts of Interest

AD and SSW are the cofounders of ARCHANGELS. ARCHANGELS sells services designed to support care partners, including the use of the CII. AC is employed by ARCHANGELS. AD is a member of the BIDMC trustee advisory board.

Multimedia Appendix 1
Previsit questionnaire.
[DOCX File , 16 KB - resprot_v14i1e66708_app1.docx]

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Abbreviations

CII: Caregiver Intensity Index
EHR: electronic health record

Edited by T Leung; submitted 20.09.24; peer-reviewed by M Tomita, M Avdagovska; comments to author 27.11.24; revised version received 18.12.24; accepted 06.01.25; published 04.03.25.

Please cite as:
DesRoches CM, Wachenheim D, Ameling J, Cibildak A, Cibotti N, Dong Z, Drane A, Hurwitz I, Meddings J, Naimark J, O'Donnell K, Winger C, Winnay SS, Young J, Wolff JL
Identifying, Engaging, and Supporting Care Partners in Clinical Settings: Protocol for a Patient Portal–Based Intervention
JMIR Res Protoc 2025;14:e66708
URL: https://www.researchprotocols.org/2025/1/e66708
doi:10.2196/66708
PMID:40053789

Protocol

Using the Community Resilience Model and Project ECHO to Build Resiliency in Direct Support Professionals: Protocol for a Longitudinal Survey

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Abstract

Background: Individuals with intellectual disabilities or autism spectrum disorder (ID/A) sometimes require supportive services from direct support professionals (DSPs). The supportive care provided to individuals with ID/A by DSPs can vary from assistance with daily living activities to navigating society. The COVID-19 pandemic not only exacerbated poor outcomes for individuals with ID/A but also for DSPs, who report experiencing burnout in the aftermath of the pandemic. DSPs are critical to providing much-needed support to individuals with ID/A.

Objective: The goal of this study is to evaluate the impact of the community resilience model on DSP burnout and neurodivergent client outcomes using the Project ECHO (Extension for Community Healthcare Outcomes) telementoring platform as a dissemination tool.

Methods: This protocol leverages community resilience theory and telementoring through the Project ECHO model to foster resilience in DSPs and their neurodiverse client population. ECHO participants' resilience behaviors will be evaluated via surveys including the Connor Davison Resilience Scale and the WHO-5 Well-Being Index. These surveys will be administered preprogram, at the end of the 8-week ECHO program, and 90 days after the ECHO program's completion. Pre-post relationships will be assessed using generalized estimating equations. The main outcomes will be self-reported changes in knowledge, self-efficacy, and resilience.

Results: All ECHO program cohorts and follow-up data collection have concluded, with 131 survey participants. The project team is currently analyzing and interpreting the data. We anticipate having all data analyzed and interpreted by February 2025.

Conclusions: DSPs provide critical services to individuals with ID/A. By providing skills in resiliency via the ECHO model, participants will be able to apply resiliency to their own professional lives while fostering resilience within their neurodiverse client base, leading to increased positive outcomes for both groups.

International Registered Report Identifier (IRRID): DERR1-10.2196/59913

(JMIR Res Protoc 2025;14:e59913) doi:10.2196/59913

KEYWORDS

neurodiversity; community resilience model; Project ECHO; direct support professionals; autism; telementoring; methods and feasibility; resiliency; intellectual disabilities; ASD; autism spectrum disorder; DSP; supportive care; community resilience; burnout; resilience; neurodivergent client; neurodevelopmental disorders; evidence-based knowledge

Introduction

Intellectual disabilities and autism spectrum disorder (ID/A) are lifelong, complex neurodevelopmental disorders characterized by social, cognitive, and adaptive skill deficits [1,2]. These skill deficits vary in levels of severity for each individual with ID/A and may require supportive care [2]. Direct support professionals (DSPs) provide supportive care to individuals with ID/A in the form of community integration, including employment navigation, assistance with daily living activities, and advocacy [3].

Individuals with ID/A are especially vulnerable to trauma and may struggle more to identify and implement successful coping strategies. Pairing this with undereducation in recognizing and responding to trauma among the service provider community creates a significant gap in services available to individuals with ID/A. Stress responses in individuals, including those with ID/A, can be moderated by factors that increase resilience. Resilience is defined as a process of interactive adaptation that facilitates coping in the face of adversity linked with a person's neurological and psychological makeup and socioecological contexts [4]. Fostering resilience for both service providers and individuals with ID/A can enhance their adaptive stress responses across all domains of functioning. Currently, there are limited resources in the community that can adequately address building resiliency, specifically in this population.

Prior to the COVID-19 pandemic, DSPs were already in the midst of a workforce crisis long characterized by low wages, training challenges, and high turnover rates [5]. However, DSPs working with those in the ID/A community reported experiencing lower quality of life and even higher percentages of burnout during the COVID-19 pandemic [6,7]. Evidence suggests that the COVID-19 pandemic exacerbated already-existing support system weaknesses, resulting in the displacement of DSPs that strained an already short-staffed workforce, increased hours worked by those not displaced, and worsened work-life quality [6,8]. These issues, compounded by the complexity of providing supportive care for this population during a global public health crisis, presented the need for resilience training and improved support for DSPs. Resiliency is associated with the achievement of life satisfaction, positive well-being, competent functioning, and improved quality of life after experiencing stressors or adversity [9]. Therefore, fostering resilient behaviors in DSPs as well as their neurodivergent clients is critical to strengthening and empowering neurodivergent individuals and creating more inclusive neurodiverse communities.

To better support individuals with ID/A, DSPs require new and advanced knowledge and skills to provide best-practice care. Providing training and resources in resiliency-building skills would allow DSPs to assist these often-overlooked populations while also providing DSPs with the tools needed to navigate post–COVID-19 working conditions. Further, it is well-known that individuals with ID/A who receive services and support from DSPs experience better personal outcomes, especially when the same DSP is engaged over time [10]. Identifying training and supportive opportunities for DSPs that improve DSP resilience, improve the health and resilience among the ID/A community, and improve the well-being and retention of the DSPs could significantly improve care for adults with ID/A. Unfortunately, current resources and supports that address building resiliency for DSPs are limited. In response to this service gap and the COVID-19 pandemic, Project ECHO (Extension for Community Healthcare Outcomes) at Penn State College of Medicine developed the "Fostering Resilience for Neurodiverse Communities ECHO" program for professionals serving neurodivergent individuals. The goal of this program is to share strategies to build resilience and better support those in their care to address trauma and stress needs as they reintegrate following the COVID-19 pandemic. These strategies were intentionally designed to have wide application so that service professionals could also benefit. The intent was to create resources and strategies that the neurodivergent clients and their service providers could use together in an embrace of more inclusive neurodiverse community building. This protocol aims to detail the Fostering Resilience for Neurodiverse Communities ECHO program conduction, curriculum, data collection, and planned outcomes analysis to facilitate further use of the ECHO model with other audiences, including those supporting neurodiverse populations. Our program's intended outcome is to invoke positive change in the knowledge, confidence, and resiliency of DSPs after participation in the ECHO program.

Methods

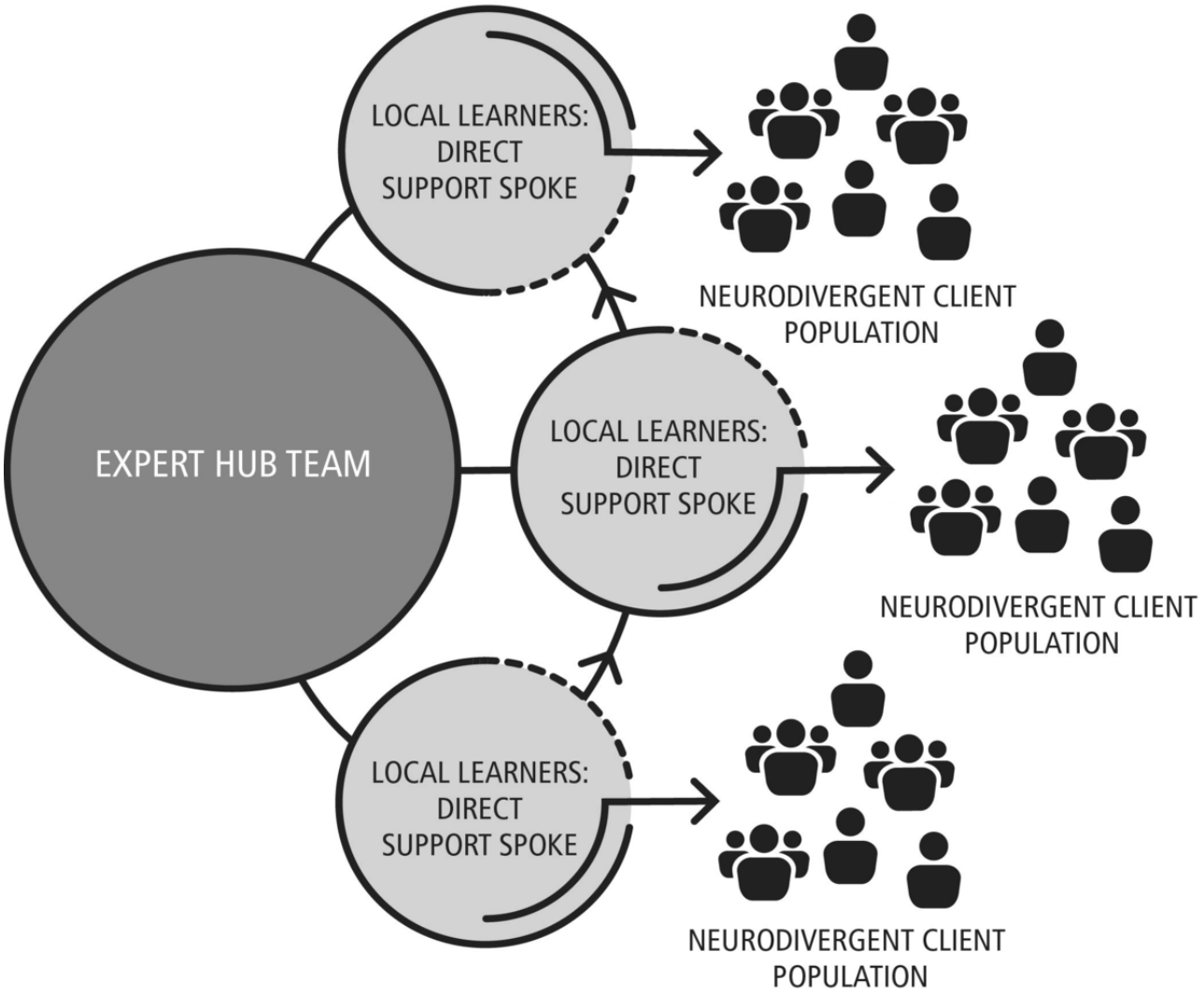
Project ECHO

The Fostering Resilience for Neurodiverse Communities ECHO program used the ECHO platform to provide DSPs with evidence-based knowledge and skills to best support their neurodiverse clients in building resiliency following the COVID-19 pandemic. Project ECHO is an evidence-based educational model with the power to rapidly transfer knowledge and exponentially increase capacity to deliver best-practice care to underserved populations [11-18]. The ECHO model's "all teach, all learn" approach is the infrastructure for knowledge-sharing in underserved communities around the world. The heart of the ECHO model is its hub-and-spoke knowledge-sharing networks, led by expert specialist teams (hub), mentoring multiple DSPs (spokes) via teleconferencing (Figure 1). The ECHO model is not "telemedicine" where specialists assume the care of the client; rather it is a guided model aimed at practice improvement, in which DSPs retain responsibility for clients, and operate with increasing independence as skills, confidence, and self-efficacy grow. Unlike traditional learning, Project ECHO facilitates rapid dissemination of knowledge and increased capacity to deliver

best-practice care by utilizing case-based, collaborative learning to support the discussion of learners' challenges and barriers to guideline implementation.

The ECHO model has 4 core principles: (1) use technology to leverage scarce resources; (2) share best practices to reduce disparities; (3) use case-based learning to master complexity; and (4) monitor outcomes to ensure benefit. DSPs and other professionals (spokes) who serve neurodiverse populations participated in weekly web-based ECHO sessions with a multidisciplinary specialty team at Penn State College of Medicine (hub) with behavioral health, psychiatry, and community resource expertise. Project ECHO used Zoom, a user-friendly, Health Insurance Portability and Accountability Act–compliant, cloud-based software application for video conferencing.

Figure 1. The ECHO (Extension for Community Healthcare Outcomes) hub-and-spoke learning model.



ECHO sessions featured presentations of deidentified client cases by DSPs and team members and brief lectures by specialists. The ECHO specialists and DSPs collaborated to discuss the case and develop recommendations for the DSP and the client. The hub team provided technical assistance and training on resilience building and facilitated the discussion of cases provided by spokes. Together, hub experts collaborated with spoke participants to share knowledge, expertise, best practices, and experiences while discussing deidentified cases and developing recommendations. Over time, spoke participants developed expertise while also engaging in a wider community of learners. Spoke participants were empowered to address the difficulties faced by their clients in their communities. As a result, ID/A clients gained access to best practices and resources through DSP participation in the ECHO sessions.

The Fostering Resilience for Neurodiverse Communities ECHO hub team consisted of multidisciplinary experts who provide care to neurodiverse patients. This team included the Clinical Director and Associate Clinical Director of the Division of Autism Services at Penn State Health Milton S. Hershey Medical Center, a psychologist with experience in behavioral health, a board-certified psychiatric nurse practitioner, a licensed clinical social worker, and a board-certified behavior analyst. Additionally, the expert specialist team also consisted of a neurodivergent self-advocate to provide a client perspective and expertise to case discussions. The project team included a project manager, education specialist, and program director from Project ECHO at Penn State College of Medicine who support the day-to-day operations of the ECHO model.

Proposed Approach: Community Resilience Model

This protocol details the use of the community resilience model (CRM) to train DSPs to foster resilience in themselves as well as their neurodiverse clients, including individuals with ID/A, through the Project ECHO platform [19]. The overarching objective of the Fostering Resilience for Neurodiverse Communities ECHO series was to teach the skills of the CRM to professionals who serve neurodiverse clients to promote psychological flexibility in themselves and their clients.

The CRM is a community-based approach for coping with acute and chronic stress states [19]. It is a sensory-focused approach aimed at increasing mental well-being and greater resilience, which has been successfully used in diverse populations and settings, including front-line health workers at the height of the COVID-19 pandemic [20,21]. Its neurobiological basis is aimed at down-regulating stress responses in the body through a skills-based approach that has wide applicability. CRM is a community-based approach where community members not only help themselves but also support others within their social networks. CRM aims to create "resiliency-focused communities," an approach well suited for the intended outcomes of this project [19].

Using CRM, the hub team developed a curriculum addressing trauma, stress, anxiety, improving resilience, and more. A portion of the Fostering Resilience for Neurodiverse Communities ECHO curriculum promoted using the iChill App to teach the CRM through a set of self-help skills [22]. Participants registered for one cohort of the Fostering Resilience for Neurodiverse Communities ECHO program. Each ECHO cohort consisted of 8 weekly 75-minute ECHO sessions. A comprehensive list of topics can be found in Table 1. Goals aligned with the approach are found in Textbox 1.

Table 1. Fostering resilience for neurodiverse communities ECHO[a] series topics.

Session	Didactic topic
1	What is trauma? Traumatic stress, expressions of trauma, and trauma responses
2	Anxiety: Intolerance of uncertainty
3	What is resilience? Introduction to CRM[b]: why is it important? Resilience zone and widening the zone
4	Resilience skills I: Tracking, resourcing, and grounding
5	Resilience skills II: Gesturing, shift and stay, help now!
6	Crisis risk reduction and safety considerations
7	Adapting skills for those with brain differences
8	Fostering community reengagement

[a]ECHO: Extension for Community Healthcare Outcomes.

[b]CRM: community resilience model.

Textbox 1. Intended programmatic goals.

1. Increased awareness and better recognition of trauma issues related directly to the COVID-19 pandemic and past trauma issues that have been exacerbated by it
2. Better understanding of the community resilience model and the importance of developing greater resiliency for both providers and neurodivergent clients
3. Ability to guide direct support professionals and other team members into effective use of available resources to better meet the needs of the individuals they are supporting

Participants and Recruitment

Participants for this program were DSPs and those supervising DSPs who participated in Fostering Resilience in Neurodiverse Communities ECHO sessions. Within Pennsylvania, DSPs directly supporting neurodivergent individuals, as well as direct supervisors of DSPs, were recruited through targeted email listservs. An informative recruitment flyer was disseminated directly to DSPs through the Pennsylvania Department of Human Services' Office of Developmental Programs. The project team also leveraged social media platforms through the autism services, resources, education, and training network to promote the ECHO program.

The initial recruitment survey was distributed via flyer with a public-facing survey link. However, participants were screened after entering basic demographic or contact information, at which point study staff would invite eligible participants to complete questionnaires. Screening criteria included those employed currently as a DSP or as a direct supervisor of DSPs. Once approved by study staff, participants received surveys via email with personalized links, ensuring that all surveys except for the initial recruitment survey were not publicly available. After completion of all preprogram surveys, participants were invited to participate in ECHO sessions.

Survey Administration

All surveys were hosted electronically and, aside from the public recruitment survey, were only accessible via email. Project data were collected and managed using REDCap (Research Electronic Data Capture), developed by Vanderbilt University

and hosted at Penn State Health Milton S. Hershey Medical Center and Penn State College of Medicine, which was supported by Penn State Clinical and Translational Science Institute. REDCap is a secure, web-based application designed to support data capture for research studies [23].

Survey responses were collected across multiple cohorts from August 2022 to August 2024. Initial survey completion was mandatory for participation in the ECHO series, but completion of session evaluations, final program surveys, and follow-up surveys was voluntary.

Survey questions were not randomized and were displayed on a single page per survey. Adaptive questioning was utilized in every survey to minimize survey fatigue. Participants did have the ability to review and change answers before submitting each survey.

Participants answered several demographics (eg, geographic location) and professional questions (eg, credentials, job title, provider type). Participants were also asked about their experience in providing care to neurodiverse populations and how the acuity of care provided to their neurodivergent clients has changed throughout the COVID-19 pandemic. Participants completed several educational evaluations at baseline and postprogram to measure programmatic impact.

The recruitment survey contained 36 questions. The preseries assessment, which was only administered to participants who were screened as eligible for participation by study staff, contained 59 questions. The session evaluations were completed after every ECHO session and contained 14 questions. The final program evaluation contained 83 questions. The 90-day follow-up survey contained 35 questions.

Response Rates

Survey view rates were not available for this study. Study staff closely monitored response rates. The public recruitment survey was closed once at least 40 eligible participants were enrolled. Study staff screened for eligibility as participants completed the surveys. Additionally, study staff monitored the completion of preprogram questionnaires to ensure that only those who completed the preprogram questionnaires were invited to join the ECHO sessions. Session evaluations, final program evaluations (n=66), and follow-up evaluations (n=51) were also closely monitored by study staff to ensure completion and data integrity.

Questionnaire Development

Upon registering for a Fostering Resilience for Neurodiverse Communities ECHO cohort, participants answered several demographics (eg, geographic location) and professional questions (eg, credentials, job title, provider type). Participants were asked about their experience in providing care to neurodiverse populations and how the acuity of care provided to their neurodivergent clients has changed through the COVID-19 pandemic.

Participant self-efficacy was measured at baseline and postprogram using adapted versions of measures identified in the literature [22,24]. Respondents completed each item with their respective level of confidence on several items on a 5-point Likert scale ranging from “not confident” to “highly confident.” Next, participants rated their respective level of confidence on a 6-point Likert scale, ranging from “no confidence” to “highly confident” [21,23]. In postprogram evaluation, participants self-reported changes in clinical knowledge and the application and dissemination of knowledge learned from the Fostering Resilience for Neurodiverse Communities ECHO series. This was measured using a series of questions using a 5-point Likert scale, ranging from “strongly disagree” to “strongly agree,” and included “I applied or shared knowledge learned in ECHO sessions to the neurodiverse clients who have ID/A support,” “I applied or shared knowledge learned in ECHO sessions to the direct support professional I supervise,” “I applied or shared knowledge learned in ECHO sessions with my colleagues in similar roles as mine,” “I applied or shared knowledge learned in ECHO sessions with my supervisors and/or agency management team,” and more.

The Connor-Davison Resilience Scale [25] and the WHO-5 Well-Being Index [26] were used to determine the impact on participant resiliency. Participants were asked to report the use of CRM skills. Additionally, participants’ use of the iChill app [22] that is promoted through the ECHO series is explored through a sequence of questions including, “do you use the iChill app on your phone or tablet,” “if yes, how often do you use it,” and “how helpful is the app?” Participants also responded to several questions related to their experience and satisfaction with the Fostering Resilience for Neurodiverse Communities ECHO series.

Planned Data Analysis

All variables will be summarized using descriptive statistics to assess their distributions and missing data. Pre versus post, pre versus 90-day follow-up, and post versus 90-day follow-up comparisons will be made for all outcome variables. For binary and ordinal (5-category Likert scale) categorical outcomes, we will use binomial or ordinal generalized estimating equation models, which account for the correlation between multiple observations made on each subject over time, to estimate odds ratios between the time points. The magnitude and direction of the odds ratios will allow us to assess the effect size of any significant changes over time. The *P* values for odds ratios that relate to the comparisons between time points, which generally will be all 3 possible comparisons, will be adjusted for multiple comparisons using the Tukey method for each outcome variable. This will maintain a familywise error rate of 0.05. Using this approach will also allow us to include any significant covariates in the model for adjustment if necessary. A sensitivity analysis will be applied to the ordinal outcome variables using quantile regression of the median by using the difference between the outcome responses for each pair of time points as the outcome variable in the model. This will also allow us to adjust for any covariates and use the same Tukey method of adjustment for multiple comparisons. All analyses will be performed using SAS software (version 9.4; IBM Corp) developed by the SAS Institute.

Ethical Considerations

Approval for this project was obtained from the Penn State Institutional Review Board at the Penn State College of

Medicine in Hershey, Pennsylvania (STUDY00018204). Our program was given a not-human subjects research determination because it did not meet the definition of human subject research as defined in 45 CFR 46.102(e) and (l). This determination was made because the intention of this protocol is to assess and improve ECHO processes rather than contribute to generalizable knowledge. Because our program was determined to be a quality improvement activity, consent from ECHO participants was not required. The project data were only accessible to project staff. Participant data were deidentified and aggregated by ECHO staff before use in reporting and analysis.

Monetary incentives were provided for follow-up survey completion for September 2022, January 2023, and April 2023 cohorts only. Monetary incentives were based on the number of surveys completed: completion of at least 7 of 8 session evaluations: US $200; completion of only the 90-day follow-up survey: US $25; and completion of at least 7 of 8 session evaluations AND completion of the 90-day follow-up survey: US $225.

Reporting Guidelines

We used the Checklist for Reporting Results of Internet E-Surveys (CHERRIES) [24].

Results

The ECHO cohorts ran from September 2022 to May 2024, with final follow-up survey data collection occurring in August 2024. There were 131 unique participants who attended ECHO sessions across the 6 cohorts. Participants were DSPs or supervisors of DSPs located in Pennsylvania, although 2 participants indicated that they were from other states (New Jersey and Oregon). Participants were from rural (n=35) and urban (n=94) counties, while other participant rurality is unknown (n=2). Data analysis is planned to be concluded by January 2025.

Discussion

The COVID-19 pandemic has shed further light on the pressing need to provide neurodiverse populations with the skills and resources necessary to successfully navigate society and the ongoing workforce crisis impacting the DSPs serving these populations. In response to the need presented to equip DSPs with resilience-building tools for themselves and their neurodivergent clients, Project ECHO at Penn State College of Medicine launched the Fostering Resilience for Neurodiverse Communities ECHO series. This ECHO series trains DSPs in ways to foster resilience in their neurodivergent clients and themselves. We anticipate that DSPs participating in the ECHO program will report feeling more confident and resilient in their roles.

The CRM has been implemented in other audiences, including health care professionals such as nurses, and it was found that brief resiliency trainings using CRMs for nurses resulted in improved well-being and resiliency among participants [25]. Additionally, the Project ECHO model has been used in resiliency training for first responders, resulting in increased confidence in resiliency skills [26]. The application of the CRM paired with the Project ECHO model for DSPs outlined in this protocol is a novel approach to resiliency training. Other applications of the CRM occur over shorter periods, with one training session lasting 3 hours [21,25]. The application of the CRM in this protocol will give DSPs tools to apply CRM principles in 75-minute ECHO sessions, held once per week over 8 weeks, leveraging active learning, engagement, and community-building, which defines the Project ECHO model. While our study is innovative and comprehensive, it is not without limitations. We rely on self-reported measures of knowledge acquisition, self-efficacy, resiliency building, and satisfaction, potentially resulting in self-report bias of over or underreporting a change in the above-mentioned outcomes. Other less biased outcome measures include supervisor-reported questionnaires, usage data of the iChill application, and retention rates of DSPs, which can be incorporated into future studies.

The Fostering Resilience for Neurodiverse Communities ECHO program introduces a unique opportunity for the application of resilience-building strategies across a variety of contexts to individuals who can apply them directly to their work and in real time. Common themes already identified within the ongoing ECHO program indicate the need for more trauma-informed training among DSPs and other professionals who serve neurodiverse populations, particularly in underserved and marginalized communities. We anticipate this training will result in increased self-efficacy, improved well-being, and expanded application of resiliency skills for DSPs and their neurodiverse clients.

Acknowledgments

The authors would like to acknowledge Dr Gregory Cherpes for his support of this project. The authors would also like to acknowledge the Project ECHO team at Penn State, specifically Ellie Hogentogler, Jackie Sabol, and Caitlin Kline. We would also like to acknowledge the members of the Project ECHO expert hub team, including Nicholas DeMarco, Erin Edwards, Keely Hirsch, Mary Krupa, Andrea Layton, and Jesse Northridge. Additionally, we would like to acknowledge Kara Bowers and Emily Heilbrunn for their contributions to the first draft of this protocol. Last, we would like to thank all the community providers who attended and presented cases in the ECHO sessions. This project was funded by the Pennsylvania Department of Human Services through the Money Follows the Person program. The project described used REDCap, which was supported by the National Center for Advancing Translational Sciences, National Institutes of Health, through grant UL1 TR002014. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH.

Authors' Contributions

KPL contributed to supervision, investigation, and writing – review and editing; LLF contributed to writing – original draft, writing – reviewing and editing, project administration, and data curation; SC contributed to writing – reviewing and editing; JML contributed to project administration, conceptualization, resources, and writing – reviewing and editing; EL contributed to methodology and formal analysis; MM contributed to conceptualization, methodology, funding acquisition, supervision, and writing – reviewing and editing; and JLK contributed to supervision and writing – reviewing and editing.

Conflicts of Interest

None declared.

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Abbreviations

CRM: community resilience model
DSPs: direct support professionals
ECHO: Extension for Community Healthcare Outcomes
ID/A: intellectual disabilities and autism spectrum disorders
REDCap: Research Electronic Data Capture

Edited by A Schwartz; submitted 25.04.24; peer-reviewed by J(Thomas, B Bao; comments to author 22.10.24; revised version received 11.11.24; accepted 24.01.25; published 06.03.25.

Please cite as:
Lenker KP, Felix LL, Cichy S, Lehman E, Logan JM, Murray M, Kraschnewski JL
Using the Community Resilience Model and Project ECHO to Build Resiliency in Direct Support Professionals: Protocol for a Longitudinal Survey
JMIR Res Protoc 2025;14:e59913
URL: https://www.researchprotocols.org/2025/1/e59913
doi:10.2196/59913
PMID:40053792

Protocol

Integrating Ambient In-Home Sensor Data and Electronic Health Record Data for the Prediction of Outcomes in Amyotrophic Lateral Sclerosis: Protocol for an Exploratory Feasibility Study

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Abstract

Background: Amyotrophic lateral sclerosis (ALS) leads to rapid physiological and functional decline before causing untimely death. Current best-practice approaches to interdisciplinary care are unable to provide adequate monitoring of patients' health. Passive in-home sensor systems enable 24×7 health monitoring. Combining sensor data with outcomes extracted from the electronic health record (EHR) through a supervised machine learning algorithm may enable health care providers to predict and ultimately slow decline among people living with ALS.

Objective: This study aims to describe a federated approach to assimilating sensor and EHR data in a machine learning algorithm to predict decline among people living with ALS.

Methods: Sensor systems have been continuously deployed in the homes of 4 participants for up to 330 days. Sensors include bed, gait, and motion sensors. Sensor data are subjected to a multidimensional streaming clustering algorithm to detect changes in health status. Specific health outcomes are identified in the EHR and extracted via the REDCap (Research Electronic Data Capture; Vanderbilt University) Fast Healthcare Interoperability Resource directly into a secure database.

Results: As of this writing (fall 2024), machine learning algorithms are currently in development to predict those health outcomes from sensor-detected changes in health status. This methodology paper presents preliminary results from one participant as a proof of concept. The participant experienced several notable changes in activity, fluctuations in heart rate and respiration rate, and reductions in gait speed. Data collection will continue through 2025 with a growing sample.

Conclusions: The system described in this paper enables tracking the health status of people living with ALS at unprecedented levels of granularity. Combined with tightly integrated EHR data, we anticipate building predictive models that can identify opportunities for health care services before adverse events occur. We anticipate that this system will improve and extend the lives of people living with ALS.

International Registered Report Identifier (IRRID): DERR1-10.2196/60437

(JMIR Res Protoc 2025;14:e60437) doi:10.2196/60437

KEYWORDS

amyotrophic lateral sclerosis; machine learning; precision health; ALS; health monitoring; electronic health record; EHR; federated approach; in-home sensor data

Introduction

Amyotrophic lateral sclerosis (ALS) is a rapidly progressing neurodegenerative disorder that usually leads to death within 3 years of symptom onset and within 2 years from diagnosis [1]. The sequence and rate of ALS progression can vary widely depending on the phenotype, age at onset, and diagnostic delay [2,3]. Pharmacological developments (eg, Riluzole and Radicava) can slow disease progression, but the result is always premature death, typically due to respiratory failure, pneumonia, or heart failure [4,5].

Treatment in a specialized, multidisciplinary ALS clinic is among the strongest predictors of quality of life and prolonged survival among people with ALS [6]. In the United States, these clinics take the form of ALS Association Certified Treatment Centers of Excellence, which, by definition, must include a multidisciplinary team with treatment standards based on the American Academy of Neurology Practice Parameters [6,7]. Even in this best-case treatment setting, though, weeks or months may pass between clinic visits. Rapid physiological and functional declines between visits mean that a person with ALS can be hospitalized or deceased before the care team is aware of their change in status. The time between clinic visits represents a critical gap in the multidisciplinary care of people with ALS. A reliable, noninvasive system for passively detecting physiological and functional decline between visits would give the multidisciplinary team unprecedented ability to predict outcomes and, more importantly, make near–real-time treatment recommendations to counteract disease progression, prolong independence, and maintain quality of life. Rates of respiratory decline and lower extremity functional decline, in particular, are reliable prognostic indicators for ALS survival time [1]. In addition to pharmacological options, targeted nonpharmacologic interventions can reduce perceived fatigue, improve manual dexterity, prevent falls, promote myriad cognitive improvements, and preserve the overall quality of life among those living with ALS [8]. These interventions, enabled by early detection of decline, are most effective when delivered in the context of multidisciplinary programs, resulting in longer survival and higher quality of life [6,9].

To monitor the decline, members of the research team have developed a passive, in-home, sensor-based system for monitoring physiological biomarkers and functional status through a combination of hydraulic bed sensors, motion sensors, and privacy-preserving depth sensors [10]. The system can reliably capture pulse, respiration rate, bed restlessness, room activity, gait speed, stride length, and falls. It has been deployed in more than 300 senior housing units and private homes throughout the midwestern United States since 2005. The system was developed and tested in two phases with support from the National Institutes of Health (National Institute of Nursing Research 1R21NR011197-01, Rantz, principal investigator). The first phase was retrospective [11-13], reviewing 3 years of significant health events from previous study participants. Parameters deemed important for an aging-in-place population include increasing or decreasing bed restlessness, pulse, respiration, time in bed, increasing bathroom activity, and decreasing general activity and time away from home [10,14-16]. Previous iterations of the system have been described extensively elsewhere [17,18]. The current iteration is a closed-source implementation purchased from Foresite Healthcare and maintained by the research team.

Our previous work makes clear that it is possible to detect and track very early signs of health changes using passive in-home sensing. In some cases, the onset of clinical declines may be detected before patients are aware of changes [18-20]. The system captures a variety of important biomarkers and functional data, including the key variables for predicting decline among people with ALS. The purpose of this work is to adapt the existing sensor system to predict physiological and functional decline in people living with ALS. This approach relies on a myriad of multimodal data, including robust sensor signals and structured electronic health record (EHR) data from distinct platforms. Here, we describe a necessarily federated approach to combining these distinct data types into a single dataset for the generation of the prediction algorithm. We hypothesize that this approach is feasible.

Methods

Design

The goal of the parent study is to adapt the existing sensor-based alert system to facilitate early detection of physiological and functional declines among people living with ALS. To this end, the study considers three hypotheses: (1) the enhanced sensor system is feasible for collecting biometric data and health outcomes from people living with ALS; (2) enhanced sensor system data, processed through an unsupervised machine learning approach, may enable early detection of health status changes among people living with ALS; and (3) changes in health status detected by the multidimensional streaming clustering approach can predict adverse health outcomes, including pneumonia, hospitalization, and death among people living with ALS.

This paper specifically addresses the methodology for hypothesis 1, testing the feasibility of the federated collection, storage, and analysis of data from the sensor system and EHR. Data collection is scheduled to continue through December 2025, and interim findings are reported in the *Results* section below. Full results of this process will be reported elsewhere upon completion of the study.

Recruitment

Participants are recruited from the ALS Association Certified Treatment Center of Excellence at University of Missouri Health Care. Inclusion criteria are age 18 years or older, a clinical diagnosis of ALS by a qualified neurologist as documented in the EHR, home zip code within 100 miles of the clinic, and

either the presence of a live-in caregiver (eg, spouse or adult child) or a Montreal Cognitive Assessment (MoCA) score >22. Recruiting coordinators are allowed to omit scoring individual MoCA items if, in their clinical judgment, response difficulties are due to speech or motor deficits resulting from ALS, rather than cognitive impairment. ALS genotype and phenotype, enrollment in clinical trials, and any other treatments are not considered inclusion or exclusion criteria.

Sensor System

We use three types of in-home sensors: hydraulic bed mats, thermal depth sensors, and motion tags, to monitor participant health. The sensor systems function effectively regardless of lighting conditions, providing a noninvasive, passive way to monitor participant health. The bed sensor is installed beneath the participant's mattress, where signals are best captured during rest. It uses a hydraulic pressure transducer to gather composite ballistocardiogram signals, which are deconvolved into components of sleep restlessness, respiration rate, and pulse. Ballistocardiogram signals are a mechanical measure of blood flow produced by cardiac activity, analogous to electrocardiogram signal patterns. The composite signals are partitioned into their respective components using signal-filtering algorithms. The ballistocardiogram component is subjected to a sixth-order bandpass filter with a 0.7-10 Hz cutoff. The respiration component is subjected to a sixth-order low-pass filter with a 0.7 Hz cutoff. Instances of heightened bed restlessness appear in the signal data as periods marked by higher amplitude and increased noise.

A wall-mounted thermal depth sensor generates a series of depth images, where each pixel corresponds to a coordinate measurement within the scene [17]. The depth images contain 3D point-cloud coordinates of the participant during walks. Validated algorithms extract gait parameters from these depth images. Gait parameters for stride time, stride length, walking speed, and participant height are derived from the point cloud silhouettes. To overcome the limitations posed by the sensor's field of view, which can be potentially occluded by furniture or other objects, a centroid-based gait parameter estimation technique has been developed. This approach permits the collection of additional gait parameters, such as gait bounce, trunk sway, asymmetry, and entropy across all 3 axes (X, Y, and Z), as well as the XY diagonal with partial leg occlusion during stride. In addition to gait parameters, a standardized Timed Up and Go fall risk assessment score is computed from the average in-home walking speed, as captured by the depth sensor [17]. In the event of a detected fall, the depth sensor performs a dual function: sending an immediate alert to designated contacts and generating a short video clip of the fall event for subsequent investigation or diagnosis.

Passive infrared motion sensors are deployed using the ZigBee (Connectivity Standards Alliance) protocol, a high-level radio communication protocol designed for low-power wireless data transmission. The motion sensors are installed in key locations such as the bathroom, bedroom, living room, kitchen, and front door to capture room-level activity. Abnormal activity in these spaces, based on the time of day or night, may suggest potential health issues, such as a urinary tract infection or the onset of cognitive decline. As the motion sensors detect movement in infrared light, they are effective at identifying activity regardless of lighting conditions. In addition to motion counts, we calculate room activity density, represented as the number of motion events within a unit of time for a respective sensor, providing an overall level of activity for each room.

The system has been tested in a multiresidential environment and can handle the presence of visitors, distinguishing them from residents based on gait patterns [18]. In a commitment to maintain privacy and comply with HIPAA (Health Insurance Portability and Accountability Act) standards, all data collected from these sensors are anonymized and time stamped with a study-specific participant identifier, which is used to deterministically link with sensor data. The data are stored in a secure AWS instance.

EHR Data Integration

We leveraged the REDCap (Research Electronic Data Capture; Vanderbilt University) Fast Healthcare Interoperability Resource (FHIR) interface to extract participants' most recent clinical information directly from the backend Oracle Health EHRs Database system of University of Missouri Health [21-23]. The REDCap FHIR interface enables interoperability with EHR systems, allowing real-time data extraction. By leveraging the FHIR interface, we can extract relevant data elements, such as laboratory results, vital signs, and clinical assessments, to populate the registry with up-to-date information. To ensure data accuracy and completeness, we map the extracted EHR data to the corresponding REDCap data fields using standardized terminologies, such as *ICD-9-CM* (*International Classification of Diseases, Ninth Revision, Clinical Modification*), *ICD-10* (*International Statistical Classification of Diseases and Related Health Problems 10th Revision*), LOINC (Logical Observation Identifiers Names and Codes), SNOMED CT (Systematized Medical Nomenclature for Medicine–Clinical Terminology), and RxNorm. This mapping process facilitates seamless data integration and enables efficient data retrieval for further analysis. Once the EHR data are extracted and mapped to REDCap data fields, the data are stored in the REDCap database. REDCap provides a secure and user-friendly platform for managing research data, allowing researchers to more easily access clinical information on people with ALS. However, the current FHIR interface does not support real-time extraction of unstructured notes, which were manually extracted and uploaded into the same REDCap project, along with an additional outcome ascertainment form for collecting monthly evaluations of the ALS Functional Rating Scale-Revised (ALSFRS-R). All EHR data collected into REDCap are anonymized and time stamped, with a study-specific participant identifier created to deterministically link with sensor data.

Data Management Plan

The extracted EHR data from REDCap and sensor data are loaded into a single study-designated cloud storage via Secure Shell File Transfer Protocol or Transport Layer Security 1.2 Protocol, hosted on a HIPAA-compliant, cloud-based data enclave. Data are integrated and analyzed via the self-service "Analytic Workbench," hosted within the same data enclave. Uninterrupted monitoring of accesses and activities occurs on

the study database following established best practices that have been implemented at the system level. Researchers' access details are required to be reviewed on an annual basis according to current data use protocols. Access to the study database is restricted to the study period, plus an additional 5 years after the end of the study period, to facilitate subsequent requests to validate and reuse the database for future analyses and retrospective projects [24].

Data Analysis

Sensor Feature Engineering

We will test the preliminary efficacy of the expanded sensor platform for detecting changes in health status among people living with ALS. The Center for Eldercare and Rehabilitation Technology has previously developed a multidimensional streaming clustering algorithm that can simultaneously monitor all of the inputs of the existing sensor platform and detect cumulative deviations from expected patterns. The multidimensional streaming clustering approach applies principal components analysis and t-distributed stochastic neighbor embedding to identify the "normal" relationships between multiple biometric variables. The change in each variable over time can be treated as a vector, and those vectors can effectively be summed to produce a single vector leading to a single point in feature space. The point represents the patient's cumulative health status for the day, and the vector indicates day-to-day changes in that overall health status. When tracked over time, these changes reveal a cluster of expected behavior. The cluster is defined not only by its central mean value but also by the degree of typicality of the values. Typicality is an indicator of the consistency within the cluster, comparable with SD. Importantly, those clusters remain relatively stable and identifiable within a given period. Potential alterations in function can then be identified by retrospectively tracing the daily point trajectory as it approaches or leaves the cluster boundary. This deviation from typicality is often a warning sign of health decline caused by injury or illness. Outliers indicate potential moments of acute health decline, triggering a warning to health care staff. This same approach will be leveraged using expanded sensor platform data (including input from the Garmin 245 wearable sensor) to generate and monitor clusters of baseline data for people with ALS.

To establish the preliminary efficacy of the system, we will follow the methods demonstrated by Wu et al [25]. We will retrospectively compare outlier points to any adverse health outcome indicators from the EHR to explore whether detected outliers occurred in the period immediately preceding adverse health outcomes. This process begins with an exploratory visual analysis conducted by the Center for Eldercare and Rehabilitation Technology and Clinical Teams. We can then bin outliers into true and false positives and bin adverse health events into caught and missed events, establishing the sensitivity and specificity of the outliers as alerts to health status change. These results will achieve two important goals. First, they will answer the preliminary efficacy question, providing our first indication of whether this system can potentially detect health status changes in people living with ALS. We will also investigate the associations between the outliers and ALSFRS-R score changes and irregularities.

Early Detection Modeling

We will develop multiple state-of-the-art machine learning models (including but not limited to regularized logistic regression, least absolute shrinkage and selection operator, support vector machine [26], random forest [27], gradient boosting, and deep neural networks [28]) to achieve optimal performance for predicting future ALSFRS-R scores. Machine learning approaches broadly involve three phases: training, validation, and testing. In the training phase of a supervised learning approach, investigators define the relevant predictors (eg, biometric sensor data and outlier warnings) and outcomes (eg, ALSFRS-R score change, EHR indicators of pneumonia, hospitalization, and death) of interest. The system feeds the predictors and outcomes into a recurrent neural network first to extract sequential features, and then each of the identified algorithms creates a predictive model that can subsequently predict outcomes in novel datasets. We will perform the training phase on the first 12 months of retrospective sensor and EHR data. When the training and validation phases involve continuous collection of data from a single or growing dataset, the holdout method suggests a 2:1 ratio of training to validation data. Therefore, we will complete the validation phase with the final 6 months of prospective data collection. In the validation phase, inputs (eg, biometric data, gait, and sleep) are fed into the model and predicted outputs (eg, adverse health outcomes) are compared to real-world outcomes (eg, EHR outcome indicators of pneumonia, hospitalization, and death) [29]. Validation tests are then conducted for both traditional sensitivity and specificity, as well as for overfitting of the model. The validation phase allows us to fine-tune the relative weights of each factor in the model, improving its predictive validity. The optimal predictive model will be selected based on testing accuracy.

Ethical Considerations

This study was approved by the University of Missouri Institutional Review Board (project number 2084262) and the U.S. Army Medical Research and Development Command (USMRDC) Office of Human Research Oversight (log number E03062.1a). All participants provided informed consent. Sensor data are deidentified on the device before transmission to the REDCap database. EHR data are deidentified in the REDCap FHIR process before transmission to the REDCap database. Participants are not compensated.

Results

User Statistics

A total of 4 participants have been recruited (Table 1). None of the 4 participants required accommodations to complete the MoCA. Preliminary data from participant 1 are summarized in the preliminary analysis below (Figures 1-4). Specific dates of diagnosis and enrollment are not provided, as they could be combined with general geographic information to effectively deidentify participants with a rare condition. Sensor feature engineering and early detection modeling, based on all 4 participants, will be analyzed and reported in 2025.

Examples of monitoring results are shown in Figures 1-4, all scaled to the identical period from September 11 to December 29, 2023.

Figure 1 depicts motion density in the home, with the most motion detected during a prolonged family visit in November and considerable time spent out of the home around the December holidays (black boxes).

Figure 2 illustrates the number of movements detected in different rooms of the home, featuring spikes in time spent in bed (tall yellow lines) and confirming several nights spent outside the home in December (absence of yellow and red lines).

Figure 3 displays in-bed respiration rate (bottom purple plot) and four techniques for estimating pulse rate: energy [30] in brown, Hilbert transform [31] in red, k-means clustering [32] in black, and windowed peak-to-peak deviation [33] in blue.

Figure 4 depicts, from top to bottom, average gait speed, stride length, and stride time. Notably, reductions in average gait speed are indicated by orange lines on December 3 and 10, 2023. These represent system-generated alerts. The December 3, 2023, alert reads:

> *Walking Speed Decrease: The average walking speed of 91.4 cm/s observed during the current 7-day period ending on 12/03/2023 is 3.4 cm/s (3.6%) lower than the average walking speed of 94.8 cm/s observed during the 7-day baseline period which ended on 11/26/2023.*

Table 1. Participant characteristics.

Characteristics	Participant			
	1	2	3	4
Age (years)	62	70	55	45
Sex	Male	Male	Male	Male
Race	White	White	White	White
Days since Dx[a] at enrollment, n	617	41	24	56
Initial ALSFRS-R[b] composite score	31	20	38	27
Deceased	No	Yes	No	No
Days of data collected, n	330	48	86	59

[a]Dx: diagnosis.

[b]ALSFRS-R: Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised.

Figure 1. Whole home movement data density by hour from September 11 to December 29, 2023.

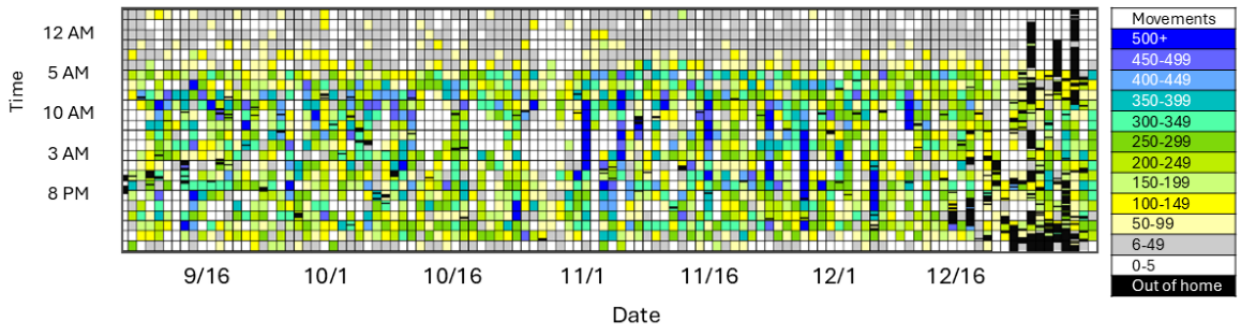


Figure 2. Per-room movement detections over 24-hour periods from September 11 to December 29, 2023. Red: bathroom; yellow: bedroom; green: front door; lavender: kitchen; purple: living room.

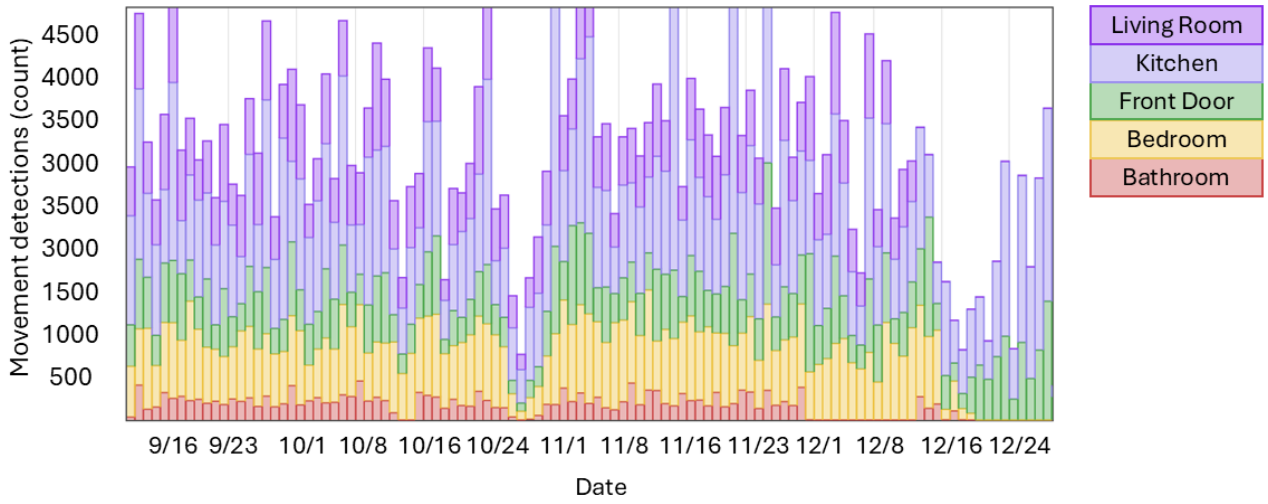


Figure 3. Heart rate and respiration rate by day from September 11 to December 29, 2023. Brown: energy; red: Hilbert transform; black: K-means clustering; blue: windowed peak-to-peak deviation; purple: respiration rate.

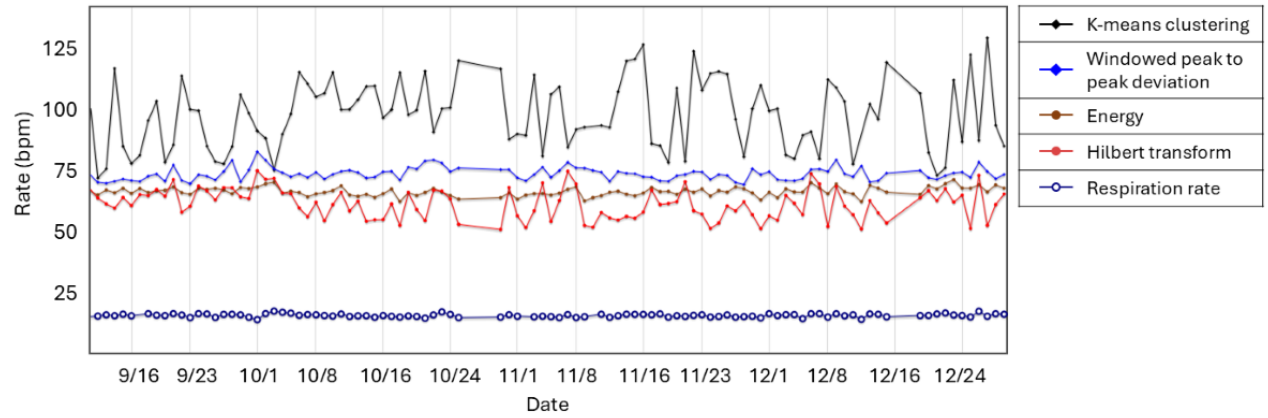
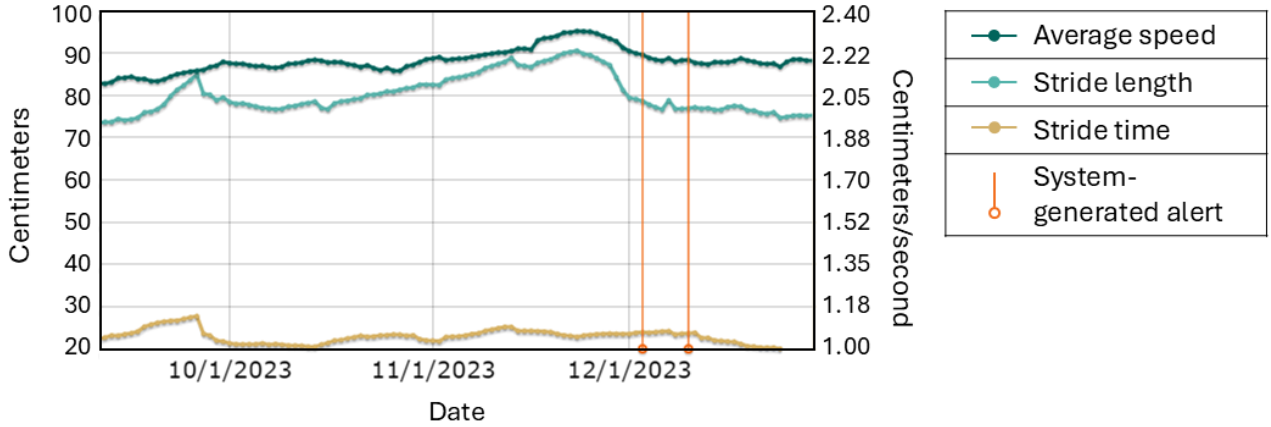


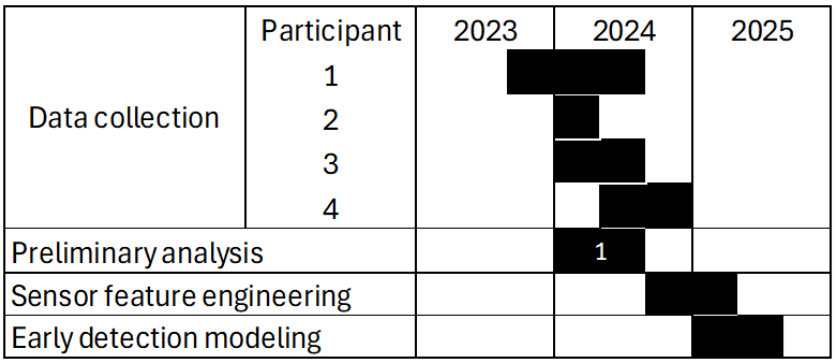
Figure 4. Gait data by date from September 11 to December 29, 2023. Light green: stride length (cm); dark green: average speed (cm/s); yellow: stride time (s); orange: system-generated gait alerts.



Evaluation Outcomes

As of this writing (fall 2024), sensor feature engineering is underway, and early detection modeling will be reported upon completion. The timeline of this work-in-progress is provided in Figure 5.

Figure 5. Timeline. "1" indicates the phase of work presented in this paper.



Discussion

Preliminary Results

This paper describes a federated approach to the collection of in-home sensor data and the extraction of EHR data to create predictive models of health status change in people living with ALS. This approach is feasible for collecting both biometric data and health outcomes from people living with ALS. The sensors are nonintrusive and privacy preserving by design, making them acceptable to participants. Similarly, the FHIR process is nonintrusive and ensures timely, secure extraction of records for machine learning purposes.

In the next phase of this work, we will process the data using both supervised and unsupervised machine learning approaches to detect health status changes and predict adverse health outcomes, including pneumonia, hospitalization, and death among people living with ALS. We anticipate that the results generated by this protocol will inform subsequent clinical trials for the prediction of ALS progression, providing guidance for interventions and their optimal timing.

Impact

This work represents a novel application of a remote sensor monitoring platform that has been previously validated in other settings and populations, such as stroke and independent living. This approach has tremendous potential in ALS, where progression is often rapid and, until now, unpredictable. It allows us to capture around-the-clock health state parameters, including during the critical late stages of decline. The system may provide important insight into physiological changes in late-stage ALS and suggest new intervention strategies to slow the rate of decline throughout the course of the disease.

Limitations

We anticipate several challenges during the course of this study. The sensor data are limited to physiological measures, gait parameters, and household-level motion activity, which may not adequately capture the full spectrum of deficits observed in ALS and are reported through clinical evaluations such as the ALSFRS-R. Recruitment has been lower than projected, which could reduce our ability to develop a reliable predictive model. Even if the sample size meets projections, there remains concern regarding whether the sample will be representative of the larger population of people living with ALS due to the geographic limitations of our single-site study. Our sampling frame results in a sample that is disproportionately White and non-Hispanic. This is an inherently criterion-referenced, single-subject approach, where each patient's biometric indicators are evaluated only in terms of deviation from their own established historical norms. In contrast, hypothesis 3 will involve creating a predictive model based on historical data. A model built from a homogeneous sample may overfit the characteristics of that sample. Overfitting occurs when relatively few outcome events are represented in the data, thus overweighting their contribution to the model. As a result, the model becomes tuned to detect cases that match the original training phase cases but cannot adapt to novel cases that differ from the training cases. As such, our initial model may not perform as well with people with ALS from non-White and Hispanic backgrounds, including Black people with ALS, who are known to receive later diagnoses and have faster rates of decline [34]. Our validation phase will recognize the limited diversity available in our sample. Importantly, we will design the initial model to evolve with additional data.

Future Work

The project described in this paper will conclude in 2025. The authors have secured additional funding from the ALS Association (24-AT-722) to develop models to predict ALSFRS-R scores from sensor data and develop sensor-derived clinical alerts. That multisite project will provide a more diverse sampling frame to improve representation in the model. Future plans include clinical trials to establish the efficacy and effectiveness of this approach for delaying adverse outcomes.

Conclusions

This study will provide important new insights into the progression of ALS at a previously impossible level of granularity. The federated system described in this paper will facilitate the development of predictive algorithms for illness, falls, hospitalization, and death. This approach has the potential to transform the clinical assessment workflow through the implementation of decision-support predictive analytics, enabling more proactive and personalized care strategies. By integrating sensor-informed care for clinicians and caregivers, we hope that this work may lay the foundation for clinical trials to intervene ahead of adverse outcomes with the goal of extending and improving the quality of life of people living with ALS.

Acknowledgments

This work was supported by the Department of Defense Office of the Congressionally Directed Medical Research Programs through the Amyotrophic Lateral Sclerosis Research Program Clinical Development Award under W81XWH-22-1-0491. Opinions, interpretations, conclusions, and recommendations are those of the authors and are not necessarily endorsed by the Department of Defense. The Department of Defense was not involved in the implementation of any stage of this work. Foresite Healthcare was not involved in the implementation of any stage of this work. No generative artificial intelligence was used at any stage of this work. The authors wish to acknowledge the invaluable contributions of Mr Zachary Selby, software support analyst.

Data Availability

The datasets generated and analyzed during this study are available from the corresponding author on reasonable request. This paper adheres to the Guidelines and Checklist for the Reporting on Digital Health Implementations (iCHECK-DH) checklist, a copy of which is available from the corresponding author upon reasonable request [35].

Authors' Contributions

WEJ contributed to the conceptualization, funding acquisition, investigation, methodology, project administration, resources, supervision, visualization, writing of the original draft, and review and editing. NM contributed to data curation, formal analysis, investigation, methodology, software, validation, visualization, writing of the original draft, and review and editing. XS contributed to data curation, formal analysis, funding acquisition, investigation, methodology, resources, supervision, validation, and writing of the original draft. MP contributed to the conceptualization, funding acquisition, methodology, supervision, and writing of the original draft. ASMM contributed to the conceptualization, funding acquisition, methodology, resources, supervision, and writing of the original draft. JHE contributed to data curation, investigation, and project administration. VJ contributed to funding acquisition, project administration, and resources. MS contributed to conceptualization, funding acquisition, methodology, resources, and supervision.

Conflicts of Interest

The University of Missouri and MS have minority ownership stakes in Foresite Healthcare, which produces the sensor platform. MS also serves on the Advisory Board of Foresite Healthcare. These conflicts are managed by the University of Missouri Conflict of Interest Committee to ensure objective research conduct.

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Abbreviations

ALS: amyotrophic lateral sclerosis
ALSFRS-R: Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised
EHR: electronic health record
FHIR: Fast Healthcare Interoperability Resource
HIPAA: Health Insurance Portability and Accountability Act
ICD-9-CM: *International Classification of Diseases, Ninth Revision, Clinical Modification*
ICD-10: *International Statistical Classification of Diseases and Related Health Problems, 10th Revision*
LOINC: Logical Observation Identifiers Names and Codes
MoCA: Montreal Cognitive Assessment
REDCap: Research Electronic Data Capture
SNOMED CT: Systematized Medical Nomenclature for Medicine–Clinical Terminology

Edited by A Schwartz, T Leung; submitted 10.05.24; peer-reviewed by CY Wu; comments to author 04.10.24; revised version received 27.11.24; accepted 30.01.25; published 12.03.25.

Please cite as:
Janes WE, Marchal N, Song X, Popescu M, Mosa ASM, Earwood JH, Jones V, Skubic M
Integrating Ambient In-Home Sensor Data and Electronic Health Record Data for the Prediction of Outcomes in Amyotrophic Lateral Sclerosis: Protocol for an Exploratory Feasibility Study
JMIR Res Protoc 2025;14:e60437
URL: https://www.researchprotocols.org/2025/1/e60437
doi:10.2196/60437
PMID:

Protocol

Contactless Sleep Monitoring for the Detection of Exacerbations in People With Chronic Obstructive Pulmonary Disease: Protocol for a Longitudinal Observational Study

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Abstract

Background: Exacerbations of chronic obstructive pulmonary disease (COPD) are one of the main causes of mortality, and early detection of exacerbations is thus essential. Telemedicine solutions have shown promising results for the detection of exacerbations in COPD and have increasingly been used. However, the effect of telemedicine is divergent. According to several studies, respiration rate (RR) increases before, during, and after an exacerbation and the change is measurable with several contactless devices. Despite this, RR is rarely measured, and telemedicine solutions only use wearable devices for measuring RR, even though wearable respiratory monitoring devices have been associated with certain drawbacks. Contactless devices are often used during sleep, as measurements conducted during sleep minimize the risk of disturbance from physical activities. However, the potential of measuring RR and heart rate (HR) during sleep for the detection of exacerbations in COPD remains unclear.

Objective: The aim of this observational study is to investigate whether contactless measurement of RR, HR, and sleep stages can be used to detect exacerbations in people with COPD.

Methods: An observational study including 50 participants with COPD will be conducted. The participants reside in Aalborg municipality, located in the North Denmark Region. Participants will use a contactless monitor (Sleepiz One+) near their bed during sleep for a period of 4 months. After data collection, descriptive statistics will be used to identify any extremes or variations in RR, HR, or sleep stages in the nights preceding an exacerbation. Correlation analysis will be performed to evaluate the relationship between the number of exacerbations and extremes or variations in RR, HR, or sleep stages. Finally, qualitative interviews will be conducted with 12 participants to explore their experiences of sleeping with the monitor nearby.

Results: Recruitment started at the end of April 2024. A total of 12 participants have been recruited, and the remaining participants are expected to be recruited during March and April 2025. Six out of 12 participants have completed the data collection and qualitative interview stages. Overall data collection is expected to be completed by September 2025. The results are expected to provide insight into the potential for identifying extremes or variations in RR, HR, or sleep stages in the days preceding an exacerbation. Additionally, the results are expected to assess the correlation between the number of exacerbations and extremes or variations in RR, HR, and sleep stages.

Conclusions: The findings from this study may clarify the possibility of using a contactless monitor to detect exacerbations in COPD. Furthermore, the results may have the potential to improve the ability to predict exacerbations in the future.

International Registered Report Identifier (IRRID): DERR1-10.2196/63230

(JMIR Res Protoc 2025;14:e63230) doi:10.2196/63230

KEYWORDS

disease exacerbation; chronic obstructive pulmonary disease; contactless measurements; sleep monitoring systems; heart rate measurement; respiration rate measurement; radar technology; health literacy; patient remote monitoring

Introduction

Chronic obstructive pulmonary disease (COPD) poses a global health challenge. In 2019, around 212 million people were diagnosed with COPD, and it was the third leading cause of death with approximately 3.3 million deaths [1,2]. COPD is associated with significant economic costs, which increase with the progression of the disease [1]. In the European Union, the direct expenses related to respiratory diseases are estimated to comprise approximately 6% of the total annual health care expenditures, with COPD accounting for 56% of respiratory disease expenditures [1].

Exacerbations in COPD are characterized by exacerbation of shortness of breath and/or coughing with increased sputum over a period of <14 days. These escalating symptoms may be accompanied by rapid breathing and/or rapid pulse [1,3]. Frequent exacerbations are associated with reduced quality of life (QoL), increased risk of rehospitalization, and higher mortality rates compared to fewer exacerbations [4]. Hence, it is essential to prevent exacerbations.

Timely treatment of exacerbation reduces the risk of hospitalization and increases QoL [5,6]. Identification of the first symptoms of exacerbations is therefore essential to initiate early treatment. For early detection of exacerbations, telemedicine solutions are increasingly used, which seem to have a positive effect on QoL and hospital admissions [7,8]. However, the effectiveness of telemedicine solutions in preventing exacerbations is not convincing, and the results are generally divergent, indicating the need for further research [7-11].

In telemedicine, monitoring of physiological parameters is widely used for early detection of exacerbations. Primarily, oxygen saturation and heart rate (HR) are measured and used for detection of exacerbations [11-14]. However, the telemedicine solutions are generally based on studies with a low methodological quality, highlighting the need for robust, well-designed clinical trials [14].

According to several studies, both respiration rate (RR) and HR increase before, during, and after an exacerbation [15-17]. Despite measurement of RR being more effective than HR for early detection of exacerbation, only a few telemedicine solutions include measurements of RR [11-14]. The lack of RR measurement may possibly be attributed to the general challenge of measuring RR over an extended time period at home [18]. Moreover, respiratory monitoring equipment has been associated with certain drawbacks such as discomfort and difficulty in use [19]. Overall, the usability of respiratory monitoring systems is sparsely investigated [18].

Various contactless devices are capable of measuring RR [20], including contactless radar-based monitors [21,22]. Existing telemedicine solutions only use wearable devices for RR measurements [19,23-25], even though it seems possible to measure a change in RR during exacerbation using contactless devices [26]. Contactless devices enable free movement and eliminate the discomfort associated with wearable devices. Discomfort can hinder measurement over an extended time period [22,27,28], and contactless devices are therefore increasingly used for measurements of physiological parameters [29]. However, contactless devices require the user to be near the device and are therefore often used for overnight measurements, where the user remains close to the device for an extended time period [20]. During sleep measurement, it is essential that the equipment is contactless to minimize the impact on sleep quality [30]. Sleep monitoring minimizes the risk of measurements being influenced by factors such as physical activity. Several contactless devices are capable of measuring both RR and HR [20-22]. To the best of our knowledge, no previous studies have conducted frequent contactless measurement of RR and HR during sleep for detecting exacerbations in people with COPD.

The overall objective of the study is to investigate whether physiological variables such as RR, HR, and sleep stages can be used to detect exacerbations in people with COPD. This study is based on the hypothesis that data from frequent measurement of RR and HR during sleep can be used to detect exacerbations in COPD. Ultimately, these data may improve the prediction of exacerbations in COPD.

Methods

Study Design

This study is a longitudinal observational study and is expected to run from April 2024 to September 2025 [31,32]. This study will recruit participants from the Danish telemedicine service, TeleCare Nord (TCN), which is part of routine care in the North Denmark Region [33]. The telemedicine service includes measurements of oxygen saturation, pulse, blood pressure, weight, and patient-reported outcomes once a week [34].

Eligibility Criteria

Inclusion Criteria

People aged ≥18 years with a diagnosis of COPD will be included in the study, and both men and women are qualified. Moreover, people residing in the Aalborg Municipality will be deemed eligible to participate.

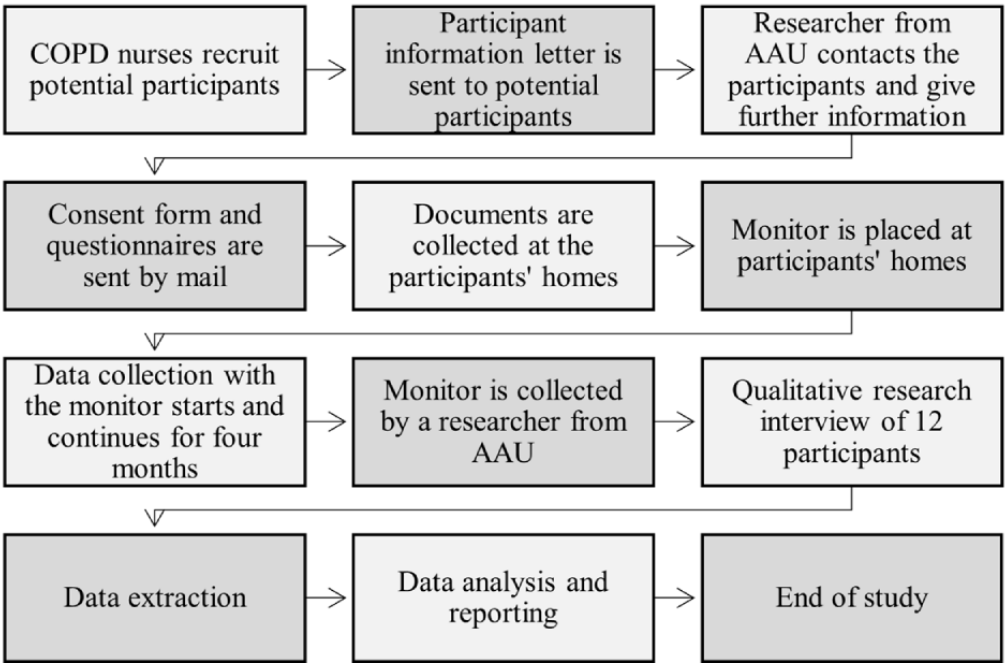
Exclusion Criteria

The exclusion criteria are the inability to complete questionnaires, pregnancy, nursing, electronic implants, and children or pets sleeping in the same bed as the participants, as it can disturb the measurements.

Recruitment

For the observational study, 50 participants will be recruited from Northern Jutland, Denmark. Initially, recruitment is conducted by specialized COPD community nurses (or a related clinician; Figure 1). The specialized COPD nurse gives a short introduction to the trial and in case of someone is interested in participating, a researcher from Aalborg University (AAU) will send a participant information letter by mail. Hereafter, the participants are contacted by a researcher from AAU who will provide further information about the study. If the individual is interested in participating, a consent form and questionnaires regarding baseline information will be sent by mail.

Figure 1. The study procedure from recruitment until the end of the study. AAU: Aalborg University; COPD: chronic obstructive pulmonary disease.



Study Setting

After the participants have received and completed the questionnaires and consent forms, a researcher from AAU will collect the documents at the participants' homes. Subsequently, a contactless radar-based monitor (Sleepiz One+) will be placed near the participants' bed. The monitor measures RR, HR, and sleep stages, including rapid-eye-movement sleep, light sleep, and deep sleep. The participants are asked to take measurements throughout the study period. The monitor measures changes in distance originating from breathing activity and heart contractions by using Doppler radar. These distance changes are analyzed using signal processing algorithms to extract RR and HR every fifth second.

The monitor is positioned on a stand 5-10 cm above mattress level, 40-50 cm from the participant pointing to the lower part of the chest. The monitor measures the participant during sleep and only measures the person who is positioned closest to the monitor. Therefore, the participants will be instructed to stay closest to the monitor during sleep, since it would disrupt the measurements if partners were sleeping closest to the monitor. Furthermore, participants will be instructed to turn on the monitor before going to sleep and turn it off upon waking throughout the entire study to ensure consistent data collection. This approach also prevents the monitor from recording data from partners who may go to bed earlier or stay in bed longer than the participants.

Neither the nurses nor the participants will have access to the data from the monitor during the study. Data from the monitor are solely used retrospectively to investigate whether it is possible to identify changes in RR, HR, or sleep stages preceding exacerbations. After the researcher from AAU had placed the monitor at the right position and ensured that the monitor works, data collection was carried out for 4 months.

The data will automatically be transmitted through Wi-Fi to a web application connected to the monitor, enabling data extraction. This web application allows users to view and analyze data collected by the contactless monitor. Participants will be registered as users in the web system by a researcher from AAU, who will also connect a monitor to each individual participant.

The questionnaires will be used to explore health status and health literacy. The health status involves baseline information (gender, age, civil status, educational level, deployment, years since COPD diagnosis, smoking status, and comorbidities), the COPD Assessment Test (CAT) [35], the Medical Research Council (MRC) dyspnea score [36], and The European Health Literacy Survey Questionnaire (HLS-EU-Q16) [37,38]. Additionally, the Danish Short Test of Functional Health Literacy in Adults (DS-TOFHLA) [39] questionnaire will be distributed to assess health literacy.

In cases of missing data for more than 2 consecutive nights, the participants will be contacted by a researcher from AAU by telephone to clarify the underlying reason and resolve that. Once data collection for 4 months (±10 nights) is completed, the monitor is collected by a researcher from AAU.

Data will be extracted from the web application connected to the monitor, TCN, and the National Patient Registry to determine the number and dates of exacerbations. Exacerbations are defined as hospitalizations caused by COPD or self-initiated treatment with antibiotics and/or steroids [40]. To obtain the exact dates of exacerbations, hospitalizations related to COPD will be extracted from the National Patient Registry. Similarly, to determine the dates of exacerbations related to self-initiated treatment, participants are already registering their use of antibiotics and steroids as part of TCN. If self-initiated treatment is registered, a researcher from AAU will contact the COPD nurse to obtain information about when the treatment began, thereby obtaining the exact date of the exacerbation.

User Experience

A total of 12 participants will be asked to participate in a qualitative research interview, focusing on the experience and acceptance of sleeping with the monitor nearby over an extended period. The number of informants for the qualitative research interviews is expected to be sufficient, as data saturation is typically achieved with 12 participants [41]. However, the final number of informants may vary slightly, depending on when data saturation is achieved. To explore the participants' perspectives on using the monitor, the qualitative research interview will be supplemented with the System Usability Scale (SUS) [42] to gather additional information regarding the usability of the system.

Interviews and surveys will be conducted after participants have used the monitor for at least 2 months, allowing them to gain a more realistic understanding of the long-term use.

Data collected during the interviews will be analyzed using the thematic analysis approach developed by Liamputtong [43] and Braun and Clarke [44]. The SUS score will be calculated in accordance with the guidelines presented by Lewis and Sauro [45]. The scores will be analyzed descriptively by using statistical tools in Excel (Microsoft 365 MSO; version 2406, build 16.0.17726.20222).

Statistical Analysis

Overall, the data analysis will include descriptive statistics and logistic regression. Descriptive statistics will be used to calculate mean, SD, and variance for RR, HR, and the time spent in different sleep stages. Logistic regression is particularly relevant when working with binary outcomes to calculate the probability of an event occurring based on one or more independent variables. Since this study investigates whether changes in physiological parameters occur in the nights preceding an exacerbation, logistic regression is an appropriate method for analysis. Logistic regression will be used to calculate the probability of developing an exacerbation based on the descriptives derived from RR, HR, and sleep stages as independent variables. Odds ratios based on logistic regression and the F statistic ($P<.05$) will determine whether each descriptive is independently associated with developing an exacerbation. Furthermore, correlations between the descriptives will be examined.

Sample Size

A sample size of 40 participants will provide 90% power to demonstrate a significant correlation coefficient of 0.5 between the number of exacerbations and extremes or variations in RR, HR, and sleep stages. Considering a presumed dropout rate of 25%, based on previous findings in a study among people affiliated with TCN (ClinicalTrials.gov NCT05218525), 50 participants need to be recruited in this study.

Ethical Considerations

The study has been approved by the Regional Ethical Committee for Medical Research in the North Denmark Region (N-20230072). The study will be performed in accordance with the tenets of Helsinki Declaration [31] and the principles of Good Clinical Practice. Written consent will be obtained from each participant after detailed verbal and written information about the study has been given and will be obtained before inclusion in the study [31]. Data will be anonymized and stored securely in compliance with the Danish Data Protection Rules [32]. The protocol will not be modified unless a new approval from the Regional Ethical Committee is obtained. The participants will not be provided with any compensation for their participation. There are no expected risks associated with participation in the trial. There is no increased risk of exacerbations, as the participants are not exposed to any interventions that could contribute to the development of exacerbations in COPD.

Results

The study received final approval from the Regional Ethical Committee for Medical Research in the North Denmark Region on April 10, 2024 (N-20230072). In April 2024, the first participant information letter was sent by mail to the initial potential participants. The first participant was recruited in May 2024. A total of 12 participants have been recruited so far. Six out of 12 participants have been completed. These participants have also participated in qualitative research interviews at the end. The delivery of the remaining monitors has been delayed and is expected to be underway in March and April 2025. The remaining participants will be recruited once the delayed monitors are received. Data collection will begin as participants are recruited. The first participant completed the data collection stage at the beginning of October 2024 and the last participant is expected to complete this stage by September 2025.

Discussion

Anticipated Findings

The main finding of this study is presumed to be a new way to detect COPD exacerbations using contactless sleep monitoring. The study aims to provide knowledge regarding the possibility of detecting COPD exacerbations through frequent measurements of RR, HR, and sleep stages collected by using a contactless monitor during sleep. If the study proves that exacerbations can be detected by contactless measurements, the results have the potential to improve the ability to predict exacerbations in the future. Predicting exacerbations enables the possibility of initiating early treatment, which is expected to reduce hospitalizations and increase the quality of life among people with COPD.

Additionally, the study is also expected to provide knowledge regarding the experience of using the monitor more permanently. This is considered valuable knowledge about the potential of the monitor, as users' experience and acceptance are important to consider when developing and implementing new technologies [46,47].

An expected strength of this study is the high frequency of measurements conducted over an extended time period. To our knowledge, no previous studies have monitored RR by a contactless monitor with a high frequency of measurements over an extended time period in people with COPD. However, continuous data collection can be crucial in this study because

missing data from the nights preceding an exacerbation can reduce the ability to detect exacerbations, as symptoms primarily change a few days prior to onset [48]. While the recommendation to turn the monitor on/off throughout the entire project period is expected to meet the participants' needs regarding privacy in the bedroom, this recommendation can also increase the risk of missing data. Therefore, it is important to be aware of missing data throughout the study period.

Another expected strength is that the measurements are conducted during sleep without physically touching the participants. This is expected to eliminate the discomfort associated with wearable equipment. Moreover, conducting measurements during sleep reduces the risk of data being influenced by factors like physical activity, which can be challenging to control when people perform the measurements at home during the day on their own. Øverst på formularen

This study may be limited by the risk of observing too few exacerbations during the project period. To address this, most participants will collect data during the winter, when exacerbations are more frequent. However, participants will also collect data at different times of the year, and thus across different seasons, which will help increase the generalizability of the results. Additionally, to mitigate this potential limitation, exacerbations of varying severities will be included to increase the likelihood of capturing exacerbations. This approach was also chosen because it is of interest to examine whether it is possible to detect changes or patterns in the days preceding different severities of exacerbations. The study has the potential to improve the ability to detect COPD exacerbations and thereby initiate early treatment to reduce hospitalization.

Dissemination Plans

The results are expected to be published in international scientific journals. All results will be reported anonymously. The results will be published irrespective of whether they are positive, negative, or inconclusive. The authorship will be admitted to persons who have participated to the design, interpretation, conduct, and reporting of the trial. The results will also be communicated to participants who have indicated that they wish to be informed.

Acknowledgments

We would like to express our thankfulness to the TeleCare Nord administration office and Telma for making it possible to carry out this observational study. We would also like to thank Sleepiz AG for providing monitors. Complete funding for the observational study, with a total budget of 42,000 DKK (US $6100.75), has been provided by Sleepiz AG. The budget will be used for salary of the clinicians, transport costs, submission to the Regional Ethical Committee in the North Denmark Region, meetings, and publication of results.

Data Availability

Data will not be made publicly available as the study participants have not consented and their data fall under General Data Protection Regulation regulations.

Authors' Contributions

Conceptualization and methodology: JE, TK, OH, and SH
Writing—original draft: JE
Writing—review, editing, and finalization:TK, OH, and SH

Conflicts of Interest

None declared.

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Abbreviations

AAU: Aalborg University

CAT: COPD Assessment Test
COPD: Chronic obstructive pulmonary disease
DS-TOFHLA: Danish Short Test of Functional Health Literacy in Adults
HLS-EU-Q16: The European Health Literacy Survey Questionnaire
HR: Heart rate
MRC: Medical Research Council dyspnea score
QoL: Quality of life
RR: Respiration rate
TCN: TeleCare Nord

Edited by A Schwartz; submitted 14.06.24; peer-reviewed by H Saner, F Dong; comments to author 06.09.24; revised version received 01.11.24; accepted 25.02.25; published 14.03.25.

Please cite as:
Egmose J, Kronborg T, Hejlesen O, Hangaard S
Contactless Sleep Monitoring for the Detection of Exacerbations in People With Chronic Obstructive Pulmonary Disease: Protocol for a Longitudinal Observational Study
JMIR Res Protoc 2025;14:e63230
URL: https://www.researchprotocols.org/2025/1/e63230
doi:10.2196/63230
PMID:

Protocol

A Multicomponent Strategy to Improve HIV Pre-Exposure Prophylaxis in a Southern US Jail: Protocol for a Type 3 Hybrid Implementation-Effectiveness Trial

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Abstract

Background: Pre-exposure prophylaxis (PrEP) is an effective approach for preventing HIV infection, but it is underutilized by populations who may benefit the most, including people living in the Southern United States and those involved in the criminal legal (CL) system. Improving the access and use of PrEP for these groups could decrease HIV-related health disparities. Beyond individual outcomes, HIV prevention for CL-involved people can have a significant public health impact on HIV incidence due to a high turnover between jails and the community.

Objective: We will develop, implement, and evaluate a multicomponent PrEP implementation strategy for the Dallas County Jail (DCJ) to increase the initiation of this HIV-preventive intervention for CL-involved individuals.

Methods: This is a type 3 hybrid implementation-effectiveness study that takes a combined approach by assessing the implementation of a strategy to identify candidates for PrEP at the DCJ and linking them to PrEP providers upon community re-entry while also gathering information about clinical outcomes. The approach is guided by the EPIS (exploration, preparation, implementation, sustainment) framework. Initial formative work (exploration) involves qualitative interviews of diverse key stakeholders to identify factors that may influence linkage to PrEP after jail release. These findings will undergo rapid qualitative analysis (preparation) to inform the adaptation of a multicomponent jail PrEP implementation strategy protocol. This approach, which will include an electronic health record (EHR) prediction model and integration of a PrEP patient navigator into the jail health team, will allow medical providers and the navigator at the DCJ to engage individuals most likely to benefit in shared decision-making about PrEP and navigate them to community PrEP care (implementation) in a process that begins before release from jail and ends with successful care linkage. Regular quantitative and qualitative evaluations of this approach will allow for ongoing stakeholder input, refinement of the implementation strategy, and maintenance of the program (sustainment).

Results: Findings from 26 qualitative interviews (9 formerly incarcerated individuals, 9 county jail staff, and 8 employees of community organizations) have been obtained, analyzed, and mapped to an implementation strategy formalized in a jail PrEP protocol. An HIV risk prediction model based on EHR data to identify individuals most likely to benefit from PrEP has been

developed and internally validated and is ready to be deployed. We anticipate the availability of preliminary study findings in 2026.

Conclusions: This study will provide key insights into the feasibility and effectiveness of a PrEP implementation strategy among people at increased risk of HIV acquisition in an urban jail in Southern United States. This practical and scalable strategy can be used as a model for other urban jails to address HIV-related inequities.

International Registered Report Identifier (IRRID): DERR1-10.2196/64813

(JMIR Res Protoc 2025;14:e64813) doi:10.2196/64813

KEYWORDS

pre-exposure prophylaxis; PrEP; HIV; HIV prevention; jail; incarceration; health disparity; electronic health records; EHR; southern United States

Introduction

It was estimated that there were 31,200 new HIV infections across the United States in 2021 [1], with a disproportionately high percentage of new diagnoses occurring in the South [2]. New HIV infections disproportionately affect men who have sex with men (MSM) and Black and Hispanic populations [3]. HIV prevention with pre-exposure prophylaxis (PrEP) can reduce the risk of HIV acquisition by 99% [4,5], but its public health impact depends on connecting populations at risk of HIV to PrEP care and continuing care over time [6-9]. Uptake of PrEP is increasing among White MSM on the east and west coasts but remains limited in minority groups in the South [10-12] where HIV incidence is the highest [13]. The PrEP-to-need ratio, defined as the number of PrEP users divided by new HIV diagnoses [14], is lower in the South than in any other region, particularly among racial and ethnic minorities, further highlighting inequitable access [15].

To decrease HIV incidence, there is a need to improve PrEP use in populations most heavily impacted by HIV. Launched in 2019, the federal *Ending the HIV Epidemic* (EHE) initiative provides an evidence-based framework for decreasing HIV incidence in the United States by 90% by 2030 [16]. The EHE initiative identifies that a critical component of epidemic control is to focus prevention efforts on geographic hotspots, including the 48 counties with the highest incidence, which are disproportionately in the Southern United States, and 7 states with major rural HIV epidemics. Active multisector partnerships among local public health departments, health care facilities, academic institutions, and community organizations are pivotal to achieving the EHE initiative's goal [8,17].

Dallas County in Texas is one of the largest HIV hotspots in the South, with high rates of new HIV infections and major racial and ethnic disparities in HIV incidence and access to preventive services. In 2021, Dallas County had one of the highest rates of persons newly diagnosed with HIV at 38 per 100,000 population, compared to the national incidence of 11.5 per 100,000 population [18]. The rate of new HIV diagnoses was even higher for Black individuals in the county, at 72 per 100,000 population [19]. Despite the dense HIV epidemic in Dallas County, only 25% of the estimated number of people with indications for PrEP were prescribed it in 2023 [3]. Barriers include high rates of uninsurance and poverty [20,21], medical mistrust and stigma [22,23], low HIV risk perception [15], and high rates of incarceration [24].

About 1 in 7 people with HIV pass through US jails and prisons each year, making the justice system a potentially high-impact setting for HIV testing and prevention [25]. In Texas, the Department of Justice estimated in 2021 that 1.4% of the prison population is living with HIV, which is 4 to 5 times greater than the prevalence in the general US population [26]. Individuals in the criminal legal (CL) system, including those who are in jail, in prison, or under community supervision (ie, probation and parole), also remain at disproportionate risk for HIV infection due to higher rates of sexually transmitted infections (STIs) [27], condomless sex [28,29], transactional sex [30], shared injection drug use equipment [31], dissolution of primary intimate partnerships [32], and broader socioeconomic barriers to medical care (eg, unemployment and homelessness) [33]. Opt-out HIV testing in jails is feasible and can identify many new infections while avoiding the burden of requesting a test among patients [34]. Testing uptake when offered in a nonjudgmental opt-out manner is 80% to 95% [35-37] and should be followed by linking incarcerated individuals to appropriate HIV treatment or preventive care [38-42]. Yet, despite recommendations for the practice of opt-out HIV testing by the Centers for Disease Control and Prevention (CDC), only about a third of US jails offer opt-out HIV testing [43].

Given that most individuals spend less than a month in jail and often cycle multiple times between incarceration and the community [44], there is a high potential public health impact of HIV prevention strategies in jails. Barriers to PrEP implementation in jails exist at several ecological levels and include limited knowledge of PrEP among those likely to benefit and their providers [45,46], lower perceived than actual risk of HIV [47,48], and distrust of institutions [49]. The timing of HIV prevention interventions is also significant, with the transition to living in the community being a particularly pivotal period when HIV transmission–risk behavior is increased and other personal needs take priority during community re-entry [50,51]. For these reasons, effective PrEP implementation strategies in jails may require multiple components to be successful [52-54]. For example, interventions at the individual level have included supporting HIV prevention after incarceration through a mobile app with customized wellness goals and incentives [55]. Building on evidence from CL-involved people with HIV transitioning to the community, peer education and patient navigation are being explored as

approaches to improving HIV prevention [56-59]. At the dyadic level, patient-provider shared decision-making around PrEP, which has been used in the community, is also being applied in correctional settings [60-63]. The objective of our study is to assess specific needs and recommended strategies and use these findings to develop, implement, and evaluate a multicomponent PrEP implementation strategy for the Dallas County Jail (DCJ), which is the 8th largest jail in the nation and located in an HIV hotspot [64].

Methods

Study Setting

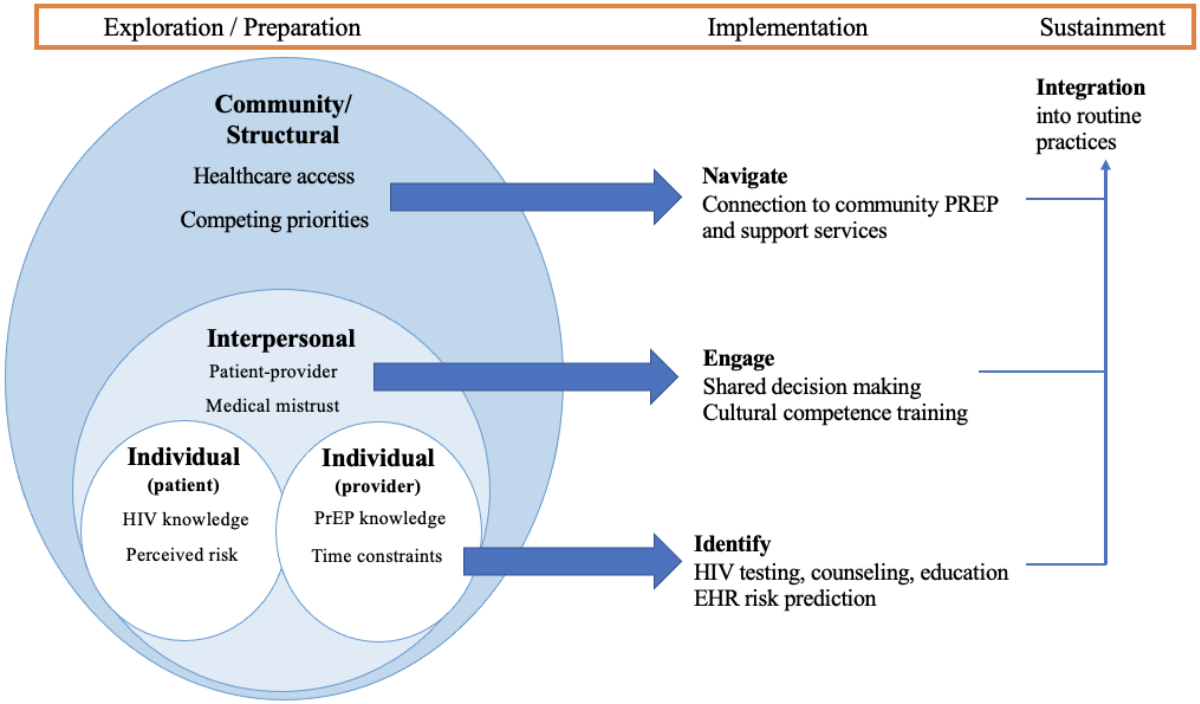
The DCJ is the main jail facility for Dallas County, with 51,000 incarcerated individuals per year (86% men, 48% Black, and 30% Hispanic) and approximately 275 individuals entering and leaving the jail daily. The mean length of stay is 45 days, and 11% of people transfer to prison [65]. Parkland Health, a teaching hospital for UT Southwestern Medical Center, provides health care services at the jail for approximately 6200 patients monthly. Health care for individuals experiencing incarceration is paid for by Dallas County.

Of over 12,000 HIV/STI tests performed each year at the DCJ, there are approximately 50 to 100 new HIV diagnoses (personal communication by Dr Barry-Lewis Harris, April 2024) and high STI positivity (5% syphilis, 5% gonorrhea, and 11% chlamydia) [35,66], which is a recommended indication for PrEP use. The approach to HIV testing at the DCJ is a combination of opt-in and opt-out. All persons entering the jail complete a nursing intake questionnaire to review medical history, receive the option for HIV/STI testing (opt-in), and, for men, indicate if they want to be in separate housing for MSM as a safety precaution. All individuals who undergo blood draws are offered opt-out HIV testing. Individuals with negative HIV test results are not routinely counseled about the results, and few, if any, receive information about PrEP. Currently, new initiation of PrEP is not permitted at the DCJ, and thus, the study will focus on linkage to PrEP after release.

Study Design

This is a type 3 hybrid implementation-effectiveness study, which takes a combined approach in assessing implementation while also gathering information about clinical outcomes associated with implementation [67]. We will track established implementation outcomes (eg, feasibility, acceptability, and penetration), effectiveness (eg, attending PrEP visits and new HIV/STI diagnoses), and sustainability, including integration into routine processes at collaborating agencies and duration of any positive effects in care processes and outcomes. We will use the EPIS (exploration, preparation, implementation, sustainment) framework [53,54] to guide our efforts to identify and address performance gaps in DCJ PrEP care. Although originally developed for public service sectors, the EPIS framework has since been widely applied in health care, including in jails [54]. As shown across the top portion of Figure 1, our key study concepts and activities reflect EPIS framework components.

Figure 1. Conceptual socioecological model of pre-exposure prophylaxis (PrEP) implementation for criminal legal–involved people. EHR: electronic health record.



Study Aims

Aim 1: Exploration

Using the socioecological model as a conceptual model [68], we will identify and describe specific individual, interpersonal, and community/structural factors that influence PrEP implementation through qualitative interviews and focus groups with key stakeholders in the jail and Dallas community (Figure 1).

Participant Characteristics and Recruitment

Participants will be individuals aged 18 years or older who are medical providers or administrators in the DCJ or in the surrounding community, people formerly incarcerated in the DCJ, representatives of community-based organizations serving those affected by HIV or with criminal justice involvement, and members of the public health department. Of note, due to restrictions on recording individuals at the DCJ and due to the benefit of addressing the postincarceration transition, the individuals we recruit will be formerly incarcerated rather than currently incarcerated. Formerly incarcerated individuals will be referred by their health care providers in community clinics or can self-refer in response to Institutional Review Board (IRB)-approved flyers posted in community-based service organizations. Health care professionals will be recruited at routine staff meetings and via email invitations. Administrators will be contacted about participation via email or personal contact from members of the study team.

Data Collection

We will conduct 20 to 30 semistructured interviews, which, based on our previous work, should be sufficient to reach saturation (ie, the point at which no new information is being uncovered through additional interviews). Individual interviews are preferred for formerly incarcerated individuals, jail staff, and members of community organizations due to the sensitive nature of questions and the convenience of scheduling.

Separately, we will also conduct a focus group with 10 to 12 members of the HIV/AIDS Re-Entry Coalition (HARC) in Dallas County during one of their quarterly teleconferenced meetings. The HARC is a group comprised of individuals from diverse community organizations who regularly collaborate to enhance the delivery of health and supportive services to individuals who have been recently released from incarceration. Feedback is especially valuable from these group discussions given the breadth and length of experience of the members. Lastly, we will conduct 2 focus groups during a summit event in which we will invite PrEP-providing organizations to compare their experiences and challenges in providing PrEP and related services amid the dynamic funding landscape and to assess opportunities for collaboration.

Semistructured interview and focus group guides will be tailored to each target group, and topics will reflect the range of factors relevant to PrEP implementation across different socioecological levels, as shown in Figure 1. All participants will also be asked to provide feedback on how to adapt and optimize the components of our implementation strategy for local populations, settings, resources, and norms. All interviews and focus groups will be audio recorded and conducted by research staff experienced in qualitative methods.

Data Analysis

We will conduct both a rapid qualitative analysis during data collection and a systematic thematic analysis when all data have been collected. The purpose of the rapid analysis is to promote consistent data capture, facilitate communication among the members of the research team about findings, and monitor progress toward saturation [69]. The thematic analysis will systematically categorize patterns in findings across interviews within a group (eg, patients) and across groups (eg, patients, jail providers, and health care leaders), using iterative thematic analysis in accordance with best practice techniques [70,71]. All data will be managed in NVivo 12.0 (QSR International). The study's principal investigators in conjunction with a study co-investigator who is an established qualitative methodologist will jointly develop a thematic codebook based on a review of the rapid analysis data and 20% of the interview fieldnotes, with codes mapped to the socioecological model presented as part of Figure 1. Trained research staff will double-code all interview transcripts, resolving discrepancies through discussion and conferring with the qualitative co-investigator as needed. A synthesis of the major findings will be presented to stakeholder groups to confirm appropriateness [72].

Aim 2: Preparation

In aim 2, our qualitative findings from aim 1 will inform the refinement of a multicomponent PrEP implementation strategy for CL-involved individuals. We will adapt and hone approaches to identify incarcerated people at increased risk for HIV using electronic health record (EHR) clinical decision support tools and patient-reported data to prompt providers to conduct HIV/STI tests and discuss PrEP with those most likely to benefit; engage CL-involved individuals in shared decision-making about PrEP using adaptations of previously developed patient decision aids; and navigate these individuals to existing PrEP services in the Dallas area after release.

Datasets to Identify Individuals at Increased Risk for HIV

The Parkland Center for Clinical Innovation (PCCI) has developed and validated an automated matching algorithm to extract data from the DCJ EHR (PEARL) and match it to data from Parkland's EHR (Epic) from 2010 to the present. Records will be matched based on multiple variables, including patient name, preferred name, date of birth, gender, sex assigned at birth, race or ethnicity, and social security number as available. We will exclude any individuals younger than 18 years. Individuals may have multiple encounters in both the jail and Parkland EHRs due to repeat jail incarcerations or medical visits, and these data will be incorporated as summary variables (eg, number of prior episodes of gonorrhea) with statistical adjustments for repeated measures in an individual. This combined dataset will provide rich data for identifying PrEP candidates and allow us to develop an HIV prediction model. This component of the study will involve the collection of existing data and the development of tools and protocols, and therefore, a waiver of consent will be obtained. Furthermore, matching of records using the identifiers above will be performed behind the firewall of the PCCI, and all datasets will

be deidentified prior to sharing with the rest of the research team.

Validation of the HIV Risk Prediction Model

We will use our prior models for predicting incident HIV [73,74] to identify candidate variables for our HIV prediction model. Subsequently, the use of temporal validation will assess how well our model will perform prospectively, dividing our dataset into a derivation dataset (2015-2021) and a validation dataset (2022-present). We will train our model to predict incident HIV diagnoses, defined as positive HIV screening and confirmatory tests or new HIV diagnosis codes without prior evidence of HIV in the EHR [73-75]. We will have ample data on new HIV diagnoses to train our models, as Parkland has a robust HIV testing program and diagnoses more new cases of HIV than any other entity in Dallas [76]. Jail EHR data may be more limited in scope because the jail generally provides short-term episodic care. However, given high recidivism rates [77], many incarcerated individuals will have multiple data points in the jail EHR to inform HIV risk prediction, including data on prior HIV/STI testing and substance use.

We will compare the performance of parsimonious versus full models in the validation dataset based on their ability to discriminate between patients with and those without incident HIV using the C-statistic or area under the receiver operator characteristic curve and the Hosmer-Lemeshow goodness of fit test. Additionally, we will use multiple complementary approaches for estimating HIV risk to capture the greatest number of individuals with indications for PrEP. This will include anyone who identifies as transgender, requests MSM housing, has had a recent STI, or opts-in for HIV/STI testing, in addition to those flagged by our EHR model. We will compare EHR models against these criteria to measure the added value of each approach (eg, number of individuals identified by our model as likely to benefit from PrEP who are missed by patient-reported data and vice versa).

Protocol Development

In conjunction with our risk prediction model, the findings from our aim 1 stakeholder interviews will directly inform our protocol for identifying persons who are at increased risk for HIV and likely to benefit from PrEP. This will include elements, such as which practitioners receive EHR alerts about potential PrEP candidates and the content of staff trainings for collecting and acting on patient-reported data and EHR alerts. We will select a final process for identifying candidates for PrEP discussions based on sensitivity (ie, missing as few persons at increased risk as possible), feasibility, and efficiency, while taking into account priorities identified by stakeholders in aim 1.

A key consideration for sexual health discussions in the jail setting is privacy. Feedback in aim 1 will inform how and where these discussions will take place. Providers may also desire additional training in assessing sexual risk, as knowledge of PrEP among correctional nursing staff and clinical providers is vital for successful implementation [78]. Furthermore, the approach to incarcerated individuals about sensitive topics, such as sexual health and substance use, will be informed by best practices, including having these screenings conducted one-on-one by medical staff and partnering with community-based organizations [79]. Any paper materials given to patients will be adapted to the American Medical Association's recommended 6th grade reading level and worded to avoid disclosing the health status.

Navigation for Individuals Likely to Benefit From PrEP

Individuals who are identified as being at increased risk for HIV and who test negative for HIV will be considered PrEP candidates. We will develop a PrEP decision-support tool to be used with the diverse populations present in the jail, informed by stakeholders' preferences from aim 1. This will include presenting information on sexual health and HIV prevention for multiple populations (eg, transgender people and cisgender women), local details on HIV epidemiology, and ways to afford and access PrEP. Individuals identified as PrEP candidates will meet with medical providers or navigators (depending on stakeholders' preferences) to review HIV prevention options and our patient decision-support tool. Patients will be informed that they will not be charged for these visits, as for all care related to communicable diseases in the DCJ. At this visit, the provider or navigator will assess the patient's knowledge of and interest in PrEP. Together with the patient, they will work through the decision-support tool. If the patient plans to pursue PrEP care after incarceration, the navigator will initiate the navigation protocol.

PrEP Care Navigation and Linkage Following Release

Those interested in PrEP will receive intensive navigation that includes both in-person and electronic referrals. Similar to existing navigation protocols (eg, for hepatitis C [80]), the navigator will initiate this process while the individual is still in jail. The navigator will obtain detailed patient contact information, identify and address the patient's health priorities and potential barriers to care, and create a personalized step-by-step process for accessing PrEP services after release. Patients will also be able to contact the navigator after jail release directly by phone or SMS text messaging.

Multiple PrEP providers in the Dallas community employ peer outreach workers who accompany patients to their PrEP visits. We will work with these providers to develop a protocol for seamless hand-off from the jail-based navigator to the community-based peer. For electronic referrals, we will integrate stakeholders' preferences for details regarding the transfer of information to community PrEP sites, including what information to communicate, how to communicate, and the timing of communication. Findings from our aim 1 qualitative data will help us pinpoint solutions to barriers or competing priorities to PrEP that patients identify. In some cases, we anticipate that multiple referrals will be necessary for patients to successfully access PrEP.

Aim 3: Implementation and Sustainment

In aim 3, we will deploy our multicomponent strategy at the DCJ and assess its impact on implementation and clinical outcomes for PrEP, as specified in Table 1.

Table 1. Quantitative implementation outcomes, metrics, timing, and data source.

Hybrid type 3 domain and outcome	Metrics (among patients with high risk)	Timing (month range)	Data source[a]
Implementation			
Feasibility	HIV/STI[b] testing offered	1-24	EHR[c], navigator
Feasibility	PrEP[d] discussions offered	1-24	EHR, navigator
Feasibility	Shared decision-making tool offered	1-24	EHR, navigator
Feasibility	PrEP navigation visits offered	1-24	EHR, navigator
Feasibility	PrEP referrals offered	1-24	Navigator
Penetration	Providers discuss/refer for PrEP	1-24	EHR, navigator
Acceptability	HIV/STI testing completed	1-24	EHR
Acceptability	PrEP discussions completed	1-24	EHR, navigator
Acceptability	Shared decision-making tool used	1-24	EHR, navigator
Acceptability	PrEP navigation visits completed	1-24	EHR, navigator
Acceptability	PrEP referral completed	1-24	Navigator
Effectiveness			
PrEP	PrEP visits in the community	1-24	Navigator
PrEP	PrEP prescription	1-24	Navigator
PrEP	PrEP use at 3 months	1-24	Navigator
HIV/STI	New HIV/STI diagnoses	1-24	EHR
Sustainment			
All	Reassess all study outcomes	25-30	All

[a]Qualitative assessments (3 times per year) complement quantitative metrics for all outcomes.

[b]STI: sexually transmitted infection.

[c]EHR: electronic health record.

[d]PrEP: pre-exposure prophylaxis.

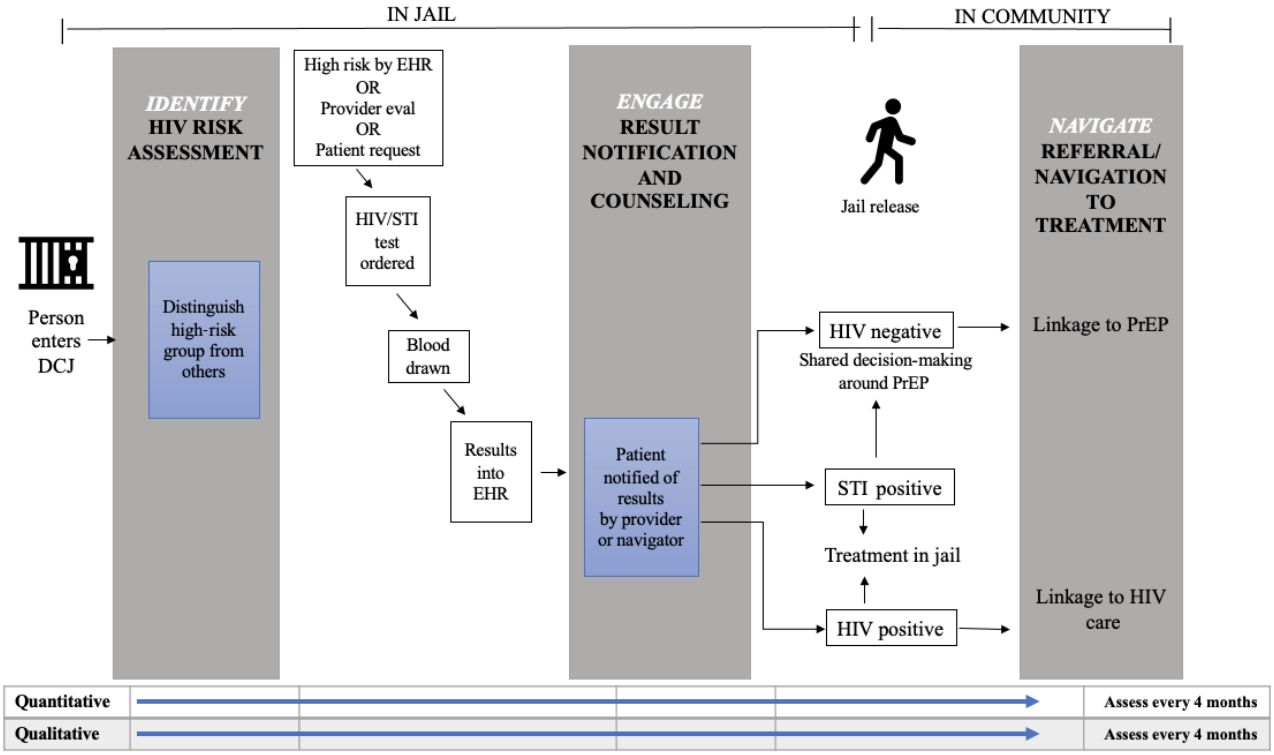
Training of DCJ Staff

The project principal investigators will conduct a 2-session interactive group training for frontline DCJ practitioners to introduce our PrEP implementation strategy. Session 1 will be adapted from trainings on culturally competent sexual health care, HIV, and PrEP [81], including clinical indications for PrEP and barriers and facilitators to its adoption in the jail and local community. Session 2 will introduce the rationale and practical aspects of using patient-reported and EHR data to identify PrEP candidates, as our prior qualitative work suggests that providers are more likely to trust, adopt, and use HIV risk assessment tools if they understand how they work [82]. The session will also review how providers and navigators can engage patients in the shared decision-making process and will include demos of PrEP decision-support tools. Lastly, session 2 will cover PrEP navigation processes, including PrEP resources in Dallas County, and navigation protocols. Postsession evaluations will be conducted for rating quality and usefulness.

Steps for Strategy Implementation

Our strategy will include the following detailed steps that can be visualized as part of the continuum (Figure 2): (1) identify, (2) engage, and (3) navigate.

Figure 2. Intervention steps in the jail-to-community continuum. DCJ: Dallas County Jail; EHR: electronic health record; PrEP: pre-exposure prophylaxis; STI: sexually transmitted infection.



In the "identify" step, when individuals enter the jail, a jail EHR record will be created (or an existing record will be opened for those with prior DCJ incarceration). Our automated algorithm will match the jail EHR to the Parkland EHR and generate an individual HIV risk score. For people with predicted HIV risk above a prespecified threshold that maximizes sensitivity without causing alert fatigue among providers, an automated prompt will appear in the jail EHR for providers to discuss PrEP and order HIV/STI testing. As illustrated in Figure 2, providers will also be prompted to order HIV/STI tests for any patients who report risk factors at intake or during a clinical assessment (eg, transgender identity and requests to be housed with MSM) or who request testing directly. Prompts will persist until orders are completed as a "nudge," a behavioral economic intervention to maximize ordering [83], and results are entered into the EHR.

In the "engage" step, positive HIV tests will prompt referrals to the jail HIV clinic for rapid initiation of antiretroviral therapy according to the current practice, and STIs will be treated based on CDC guidelines [84]. Persons with negative HIV tests will meet one-on-one with a provider or PrEP navigator and receive counseling informed by our PrEP decision-support tool. The navigator we hire will be experienced in working with CL-involved people. Counseling will be person-centered and culturally tailored, with positive sexual health framing.

In the "navigate" step, for patients interested in PrEP, the navigator will review a list of PrEP clinic locations and assist with selecting a provider. Once an individual is released from the DCJ, the navigator will facilitate PrEP linkage by contacting that individual (by phone or SMS text messaging) and providing personalized care navigation. A hotline will be available for released individuals to call for assistance with PrEP referrals. The navigator will continue to follow referred patients for 3 months after any PrEP initiations, recording these contacts and clinical outcomes in REDCap, a secure online data capture system [85].

For this aim of the study, the patient navigator will obtain verbal consent from patients to proceed with a discussion on sexual health and to contact them after release from jail. The navigator will use a script to inform patients about the goals of the project, including the metrics to be collected, and reinforce that the meeting with the navigator is voluntary and will not affect the legal status of the patients.

We will track quantitative and qualitative metrics related to our implementation strategy during a 24-month period of iterative assessment and refinement. Our study metrics map directly to the EPIS framework at key steps in the PrEP care continuum (Figure 2). As shown in Table 1, we will assess quantitative effects, including the number of patients who attend a community PrEP visit, initiate PrEP, and persist with PrEP use for ≥3 months, which is a robust HIV prevention outcome [7]. We will track the rates of new and previously known HIV diagnoses and STIs in the DCJ through EHR chart review.

Feasibility

Feasibility refers to the extent to which a practice change can be successfully used or carried out within a specific setting [86]. We define feasibility as >65% of eligible patients being offered HIV/STI testing and one or more PrEP discussions, our patient PrEP decision-support tool, a PrEP navigation visit, or a PrEP referral in jail.

Penetration

Penetration refers to the extent to which a practice is integrated within a specific setting [86]. For this metric, we will track the

proportion of providers who discuss PrEP or refer to a navigator for at least one eligible patient.

Acceptability

Acceptability refers to the perception among setting stakeholders that a practice is agreeable, palatable, or satisfactory [86]. We will calculate the proportions of patients who accept offers for one or more HIV testing, STI testing, PrEP discussion, navigator contact, or PrEP referral, with acceptance of >80% of test offers and >65% of discussion offers considered acceptable based on prior studies [35,87-89]. We will evaluate differences in feasibility and acceptability among patients by age, sex, gender identity, and race or ethnicity to identify imbalances in the offering and uptake of testing and referrals.

Effectiveness Regarding PrEP Outcomes

Additionally, on a monthly basis, we will measure the proportion of individuals who test negative for HIV, the proportion of this subgroup who receive notifications of their HIV test results, and the proportion of all those tested who are candidates for PrEP based on US Public Health Service practice guidelines for PrEP [90].

Among these PrEP candidates, we will assess how many are released to the community and how many are successfully contacted by the jail navigator after release. We will track the proportion of candidates attending ≥1 PrEP visit after jail release, the proportion prescribed PrEP, and the proportion using PrEP at 3 months after initiation (using direct patient assessments by the navigator). We will complete a run chart, which we will adapt from quality improvement methodologies [91], to evaluate trends in the PrEP care cascade [92] on a monthly basis during the 24-month intervention period and the additional 6-month sustainment period.

Effectiveness Regarding New HIV/STI Diagnoses

We will also track STIs and new and previously known HIV diagnoses in the jail among priority groups and the general jail population. STI positivity will be calculated as positive tests per the total number of tests completed. New HIV diagnosis rates will be calculated as confirmed positive test results in persons without a prior diagnosis of HIV per the total number of tests completed within a given time period. We will use an interrupted time series analysis using monthly data points to compare rates during the 24 months before and 24 months after our intervention is implemented. Our primary analysis will involve a comparison of the longitudinal rates before and after the intervention, and a mixed effects model for interrupted time series will be used as a secondary analysis. We will conduct linear regression analyses to determine if there is a significant difference in new HIV diagnosis rates before and after the intervention.

Sustainment

Sustainability refers to the extent to which a new practice is maintained or institutionalized within a setting's ongoing operations [86]. We will assess how well the strategy components are maintained as part of existing jail processes for 6 months after the formal 24-month study period, including tracking retention in PrEP care for up to 6 months (through navigator follow-up). Our research team includes dissemination consultants, who are medical providers working in jails in Austin, TX; Chicago, IL; and Boston, MA, and who will offer input on refining our strategy components for ongoing use at the DCJ and the potential transfer and integration into other jail settings.

For PrEP linkage, current rates of linkage are essentially zero. Thus, in lieu of a pre/post comparison, we will report the proportion of patients linked to PrEP care during the implementation period with 95% CIs. Power analysis is performed for the interrupted time series analysis of monthly HIV positivity rates, assessing the difference in the mean between the 24 months before and after implementation. Over the preimplementation period, an anticipated 250 tests will be performed monthly with 3 new HIV diagnoses per month. In the postimplementation period, of 500 HIV tests per month, an increase to 9 new diagnoses per month is anticipated due to the focus on individuals identified by the prediction model as being at increased HIV risk. Furthermore, we assume a correlation of 0.2 among monthly observations. Based on a mixed effects Poisson regression model, we can detect the difference in the mean HIV-positive rate between the 2 periods with >80% power at a 2-sided type I error of 0.05. We will also perform subgroup analyses, comparing testing rates by sex, age group, and race or ethnicity.

Evaluation of Qualitative Effects

We will also evaluate the qualitative effects of our implementation strategy through structured observations and discussions at the DCJ to assess changes (positive or negative) in knowledge and opinions of PrEP, workflow, and cross-agency collaboration in line with Dallas County's goal of a coordinated HIV response [93]. Observations will be conducted by individuals with postgraduate training in qualitative methods who have undergone additional training with the DCJ and Parkland Health and who are approved to conduct observations under the protocol approved by the IRB at UT Southwestern Medical Center. Observations will be focused on specific interactions pertinent to the research questions (eg, between the navigator and person soon to be released). Qualitative data on effectiveness and implementation outcomes will be rapidly analyzed in real-time using structured analysis of field notes from observations and discussions. The resulting iterative findings will be presented to a study advisory panel every 4 months to assess evolving attitudes and practices surrounding HIV testing and PrEP (ie, acceptability), gather perceptions of feasibility and penetration of the intervention, and solicit feedback about the ways to improve outcomes.

Ethical Considerations

Each aim of the study has undergone a separate review of procedures and protocols by the UT Southwestern Medical Center IRB, with details of human subject protection outlined in the protocol by aim. This IRB has a prisoner representative, and all IRB-approved protocols were reviewed by Parkland Health and approved by the DCJ correctional health leadership before beginning study activities. To date, the IRB has approved the protocols for aim 1 (STU 2021-0763) and aim 2 (STU 2021-1172). In addition, the Office of Human Research

Protection has reviewed and approved the inclusion of prisoners in human subject research for the overall study protocol in 2022.

For all participants in focus groups and individual interviews in aim 1, the research team has obtained verbal consent. To ensure informed consent, researchers also provided information about the nature and purpose of the study, confidentiality and privacy, HIPAA (Health Insurance Portability and Accountability Act) regulations, potential risks, discomforts and benefits of participation, and the option not to participate or start then stop participating in the interview at any time. In addition, stakeholders were encouraged to contact the study team at any time with questions or concerns they may have about the study. Eligible participants (ie, individuals not employed by UT Southwestern or Parkland Health according to institutional policy) were paid US $25 as compensation for their time for each interview or focus group attended.

Regarding EHR usage for aim 2, all study data were collected from existing EHRs, including medical intake forms at the DCJ and EHRs from Parkland Health and Hospital Systems, to identify potentially eligible subjects for the research. Records were matched based on multiple variables, including patient name, preferred name, date of birth, gender, biological sex, race or ethnicity, and social security number, as available. The medical record data include data collected as part of the medical intake process at the jail and routine clinical care at the jail and Parkland, including demographics, information from clinical encounters, prescription information, laboratory tests and results, and billing information. For those who did not receive medical care or treatment at Parkland Health, only data from the jail EHR were used. There was no additional direct collection of specimens, records, or data from subjects, and the IRB approval allowed secondary analysis without additional consent to identify research subjects and build the prediction model.

Data are not deidentified, as individuals meeting the basic eligibility criteria will be contacted by the researchers for recruitment into the study. No additional research procedures or continued access to identifiable private information will occur until after subjects have given valid consent to participate in the research study. The risk of this activity is minimal to the subjects because the information collected will be limited only to information allowing researchers to determine eligibility for the study and contact information. Only the minimum information necessary to determine eligibility will be recorded. Researchers have been granted access to the medical record data by the institutions and will protect the data they use and record for this activity according to institutional and HIPAA standards for protecting privacy and maintaining confidentiality. If the subjects identified decline participation in the research, the data collected will not become part of the research data. If subjects agree to participate in the research, the identifiable data collected will become part of the subjects' research records and will be stored according to the research confidentiality plan. Because of the nature of the detailed inclusion criteria, it is not feasible for researchers to advertise and screen for eligible subjects. The Office of Human Research Protection highlights this as an acceptable activity to waive informed consent to permit investigators to obtain and record identifiable private information for the purposes of identifying potential subjects [94].

Results

The study was funded by the National Institute of Mental Health in April 2022. Progress has been made on various aims to date. Qualitative interviews have been completed with 26 individuals, including 9 formerly incarcerated individuals, 9 county jail staff, and 9 employees of community organizations (1 individual was both a formerly incarcerated individual and an employee of a community organization). A focus group with 10 additional individuals has also been conducted. All interviews have been transcribed, coded, and analyzed, and a manuscript highlighting the key themes is in progress.

In addition, summaries of field notes for each interview have been organized into key barriers; facilitators; suggested approaches to overcome barriers; resources needed to overcome barriers; and specific strategies to improve risk assessment, HIV testing, sexual health or PrEP education during incarceration, and postrelease linkage to PrEP. Findings from these interviews have been applied to formulate a jail PrEP implementation protocol using rapid qualitative analysis.

An HIV risk prediction model based on jail EHR data to identify individuals most likely to benefit from PrEP has been developed using records from 33,458 individuals who have undergone HIV testing in jail. This model has been optimized using machine learning, has been internally validated, and is ready to be deployed. Future exercises will include integration with health system EHR data from Parkland Hospital and comparisons to parsimonious models, which will guide the iterative development of the model. We anticipate that preliminary study findings on the implementation and effectiveness of the jail PrEP implementation strategy will be available in 2026.

Discussion

Expected Results

We anticipate that the implementation of the multicomponent strategy will promote robust linkage to PrEP care for many individuals at risk for HIV, which currently does not occur at the DCJ. Moreover, we expect to identify a higher number of new HIV infections and STIs than in the 2 years prior to implementation. Our final product will be a well-integrated sustainable multicomponent PrEP implementation strategy that starts upon jail entry and ends with linkage to community-based HIV prevention, which can address major HIV-related inequities for CL-involved populations.

Potential Limitations and Alternative Approaches

In the process of refining the implementation strategy in our second aim, EHR models may be hampered by limited or missing data. We will minimize the missingness of EHR data by combining jail and Parkland data and extending this dataset over a 10-year timespan. We will explore the use of the missingness of EHR variables (which may be a proxy for not being engaged in primary care) as indicators to understand the

effect on model performance. If model performance is suboptimal, we will rely primarily on patient-reported data to identify HIV risk. For EHR alerts, we will proactively address potential alert fatigue [95] by employing rigorous user-centered design principles [96]. We will also train providers on how to respond to alerts about HIV risk, as providers may be unaccustomed to these.

Delays in the generation of electronic HIV risk scores could result in the identification of individuals likely to benefit from PrEP after their release from jail. If this occurs, we expect to identify many of these individuals using patient-reported data. However, the model we have developed will generate scores on day 3 of each person's incarceration, which will mitigate delays. We will also generate future EHR prompts for HIV/STI testing and PrEP if the patient returns to jail, and the navigator will contact the patient to encourage HIV testing and PrEP evaluations with community providers. Though patients may decline visits to discuss PrEP, we will maximize patient interest by training staff to present PrEP in a positive, discreet, and patient-centered manner and will offer our decision-support tool for patients to review independently. Since barriers, such as medical mistrust, transportation, and anticipated stigma, may limit patients' access to PrEP, we will hire and train a navigator who is able to build rapport with diverse populations, use principles of trauma-informed care [97-99], and teach at many education levels. Additionally, we will access existing resources, such as care coordination, offered by community partners.

Study Impact

Despite these possible limitations, this project will generate a valuable approach to prevent HIV in the disproportionately burdened population of CL-involved individuals in the Southern United States. As these individuals often have fragmented health care and may not be reached with approaches targeting primary care or STI clinics [100], our multicomponent implementation strategy has the potential to efficiently reach many persons likely to benefit from PrEP in a nontraditional but well-defined setting with rapid turnover to the larger community. Future projects will focus on adapting this strategy for dissemination to other urban jails, including those represented by our dissemination consultants, in HIV hotspots nationally to maximize its impact on the HIV epidemic for underserved minority communities.

Acknowledgments

The research reported in this manuscript is supported by the National Institute of Mental Health of the National Institutes of Health under award number R01 MH 129185.

Conflicts of Interest

AEN has received research funding from Gilead Sciences. DK has participated in research with funding from Gilead Sciences and Merck to his institution, has received personal funds from UpToDate, Inc and Medscape to develop medical education content on HIV prevention, and has received funds from PrEP4All for travel to an advisory conference.

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Abbreviations

CDC: Centers for Disease Control and Prevention
CL: criminal legal
DCJ: Dallas County Jail
EHE: Ending the HIV Epidemic
EHR: electronic health record
EPIS: exploration, preparation, implementation, sustainment
HARC: HIV/AIDS Re-Entry Coalition
HIPAA: Health Insurance Portability and Accountability Act
IRB: Institutional Review Board
MSM: men who have sex with men
PCCI: Parkland Center for Clinical Innovation
PrEP: pre-exposure prophylaxis
STI: sexually transmitted infection

Edited by A Schwartz; submitted 05.08.24; peer-reviewed by T Poteat, BG Rogers; comments to author 01.10.24; revised version received 08.10.24; accepted 12.12.24; published 18.03.25.

Please cite as:
Nijhawan AE, Kholy J, Marcus JL, Hogan TP, Higashi RT, Naeem J, Hansen L, Torres B, Harris BL, Zhang S, Krakower D
A Multicomponent Strategy to Improve HIV Pre-Exposure Prophylaxis in a Southern US Jail: Protocol for a Type 3 Hybrid Implementation-Effectiveness Trial
JMIR Res Protoc 2025;14:e64813
URL: https://www.researchprotocols.org/2025/1/e64813
doi:10.2196/64813
PMID:

Protocol

Developing and Implementing Provider-Training and Evidence-Based Tools to Support Pre-exposure Prophylaxis (PrEP) Decision-Making and Increase PrEP Adherence Among Young Men Who Have Sex With Men: Protocol for the PrEP Choice Longitudinal Cohort Study

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Abstract

Background: Despite the availability of highly effective HIV pre-exposure prophylaxis (PrEP), uptake and adherence to PrEP among young men who have sex with men (YMSM) remains low, limiting its impact on the prevention of HIV infection. Strategies that incorporate an array of prevention options and provide YMSM and their providers with tailored education and support tools, including tools to support shared decision-making, are needed.

Objective: The goals of the Centers for Disease Control and Prevention (CDC)–funded PrEP Choice study include the development and deployment of CDC guideline–consistent PrEP provider training and the implementation of evidence-based provider- and client-facing PrEP education and support tools. Under this initiative, the CDC funded 2 research projects, Florida State University (the Expanding PrEP in Communities of Color [EPICC] project), and Columbia University (the mChoice project).

Methods: Providers from both projects will complete the PrEP Choice online training, which was developed to educate providers on PrEP options and how to engage clients in open discussions around sexual health and PrEP options. EPICC project providers will also attend online tailored motivational interviewing (TMI) training sessions, and mChoice project providers will view a training video on cultural competency and humility in PrEP care. Following training, each project will enroll a cohort of 400 participants receiving care from study providers and follow them for 12-18 months. Participants will complete online surveys every 3 months and provide biomarkers to assess PrEP adherence. Electronic health record (EHR) data will be collected every 6 months to provide additional information on clinic attendance, PrEP prescriptions, and HIV/sexually transmitted infection (STI) testing. Each project will provide cohort participants with a unique digital health tool to support the PrEP choice and ongoing adherence. The study will assess the effectiveness of training and educational and support tools in practice and the critical factors associated with the successful uptake of and adherence to PrEP by participants. The study will also monitor patterns of PrEP use among YMSM, including types of PrEP and switching between types.

Results: Formative work to develop and prepare the tools for implementation was completed in 2023. The EPICC project began provider training in early 2024, and the mChoice project began in spring 2024. Cohort enrollment for both projects began after provider training began.

Conclusions: Given the changing PrEP landscape, implementation of provider education and tools to maximize uptake and adherence is needed. By delivering culturally competent and interactive provider training on PrEP options, the study will help providers counsel and guide participants on the effective and safe use of PrEP. The digital health tools created will support participant adherence to help them optimize PrEP benefits. Through the cohort design, the PrEP Choice study will provide real-world data about PrEP use that will be critical for informing future guidelines and tools.

International Registered Report Identifier (IRRID): DERR1-10.2196/64186

(JMIR Res Protoc 2025;14:e64186) doi:10.2196/64186

KEYWORDS

pre-exposure prophylaxis; PrEP; PrEP cohort; young men who have sex with men; YMSM; digital health; evidence-based tools; motivational interviewing

Introduction

Background

Young gay, bisexual, and other young men who have sex with men (YMSM) are the population most affected by HIV in the United States. Among all HIV infections diagnosed in 2021, 67% were found in MSM [1]. Racial and ethnic disparities persist in HIV diagnoses among MSM, with 36% of diagnoses among Black or African American (Black) MSM and 33% among Hispanic or Latino (Hispanic) MSM, compared with 25% among White MSM, despite smaller overall populations of Black and Hispanic MSM compared with those of White MSM. HIV can be prevented with the use of HIV pre-exposure prophylaxis, or PrEP [2]. The US Food and Drug Administration has approved the use of 3 antiretroviral drugs for PrEP by MSM: oral emtricitabine and tenofovir disoproxil fumarate (F/TDF) in 2012, followed by the availability of generic F/TDF in 2021; oral emtricitabine and tenofovir alafenamide (F/TAF) in 2018; and long-acting injectable cabotegravir (CAB-LA) in 2021. Clinical trials of sexual event-driven PrEP regimens or 2-1-1 PrEP using F/TDF have demonstrated it to be highly effective for HIV prevention among MSM [3,4]. These options provide MSM with choices about their preferred PrEP regimen; however, little is known about the PrEP choices men make, their switching between PrEP options, and the reasons for these decisions.

PrEP coverage continues to increase markedly among men [5]. However, findings from analyses of limited race and ethnicity data for PrEP users suggest racial and ethnic disparities exist in coverage. These PrEP use disparities are especially concerning in the context of large racial and ethnic disparities in HIV diagnoses, because men who might most benefit from PrEP are not being prescribed it, and among those prescribed, adherence remains suboptimal [6-9]. To accomplish the goals of the “Ending the HIV Epidemic in the US” initiative to reduce new HIV diagnoses by 90% by 2030, increase PrEP coverage to 50% of individuals with indications, and achieve health equity [10], it is imperative to overcome racial and ethnic disparities in PrEP use.

The implementation of effective interventions is needed to increase PrEP initiation, adherence, and persistence among YMSM. YMSM need tailored education with autonomy-supportive communication related to the growing array of PrEP options, and providers who serve these clients also need education and clinical decision-making support. Implementation of resources that discuss all PrEP options and emphasize shared clinical decision-making have the potential to enhance PrEP outcomes among YMSM, including PrEP initiation, adherence, and persistence [11]. Increased understanding of PrEP use patterns, including switching among PrEP options, is needed to optimally support lifetime HIV prevention among YMSM. Using evidence-based PrEP care as a guide, provider and patient education and support tools have been developed to assist in the provision of PrEP care. Evidence-based provider and patient education and support tools (EBTs) are available but are not being routinely used in clinical settings to increase PrEP screening, counseling, initiation, adherence, and persistence by YMSM [2,12,13]. To date, there has been a lack of research on the impact that existing informational materials have on PrEP provision or how tailoring these materials to meet the needs of providers and YMSM from diverse backgrounds could enhance their effects. Further, although EBTs for both providers and YMSM are available, these resources do not acknowledge or incorporate information about a growing arsenal of prevention products nor do they maximize opportunities to engage in a shared decision-making process about these products [14,15].

Provider education can support clinicians to provide recommended PrEP services and to maintain up-to-date knowledge of PrEP options. Patient education using adapted EBTs can help men understand how PrEP can support their sexual health and learn about the PrEP options available to them. Adherence and persistence support tools, such as user-friendly apps, can support men prescribed PrEP to take their medication as directed and to continue to use it for as long as they can benefit from its protection. Increased understanding of PrEP use patterns, including switching among PrEP options, is needed to optimally support YMSM to use PrEP that is appropriate for them at various times in their lives.

Aims and Objectives

The goals of the Center for Disease Control and Prevention (CDC)–funded study, known as the PrEP Choice study, include the development and deployment of CDC guideline–consistent

PrEP provider training and the implementation of evidence-based provider- and participant-facing PrEP education and support tools [13,16]. PrEP support tools include innovative, customized mobile apps. The study will also conduct a longitudinal assessment of YMSM who are initiating or persisting with PrEP to understand their preferences for PrEP modalities and changes in PrEP use over the course of the study. The study will assess the implementation context, assess the effectiveness of provider training and EBTs in practice, and analyze the critical factors associated with successful uptake of and adherence to PrEP by participants enrolled in the study.

Under this initiative, the CDC funded 2 research projects, at Florida State University (the Expanding PrEP in Communities of Color [EPICC] project) and at Columbia University (the mChoice project). The PrEP Choice study is a 5-year initiative; funding began on September 30, 2021. In this paper, we discussed both EPICC and mChoice Studies, as they are supported under the same funding announcement, use the same PrEP training modules, use similar instruments for their longitudinal cohorts, share the same eligibility criteria, and incorporate digital health tools.

Through these 2 studies, we will test the effectiveness of provider training to increase provider knowledge of and comfort with PrEP modalities in clinical practice; evaluate the feasibility and acceptability of implementing provider training; describe the barriers and facilitators impacting the implementation of new PrEP modalities in clinical practice; test the effectiveness of provider training and digital tools to increase PrEP adherence and persistence among YMSM; and describe real-world PrEP use, including factors influencing the selection and change of PrEP regimens.

Methods

Ethical Considerations

This works follows a protocol reviewed and accepted by the Institutional Review Boards of Florida State University (approval number 00003623) and Columbia University (approval number AAAT8812). Participants will provide informed consent prior to beginning any study activities. The consent form includes standard consent sections describing the purpose of the study, the procedures to be followed, and the risks and benefits of participation. The consent form went through multiple reviews by team members to ensure the language was sufficiently simple. A certificate of confidentiality was obtained from the CDC. All data and records will be stored on password-protected servers. No identifiable data will be published.

EPICC project providers will be compensated US $50 for completing the pretraining survey; US $50 for completing online PrEP training modules, tailored motivational interviewing (TMI) training sessions, the posttraining survey, and the first standard patient interaction; and US $50 for the 3-month posttraining standard patient interaction. Cohort participants will be compensated US $50 for the baseline survey and app download, US $50 for an optional onboarding visit, US $25 for the 3-month follow-up survey, US $50 for the 6-month follow-up survey, US $25 for the 9-month follow-up survey, US $50 for the 12-month follow-up survey, US $25 for the 15-month follow-up survey, and US $50 for the 18-month follow-up survey. For home-based dried blood spot (DBS) collection, cohort participants will be compensated US $50 for the baseline, 6-month, and 12-month collections and US $75 for the 18-month collection. A US $50 bonus will be provided to participants who complete the first 3 collections. Participants who complete the exit interviews will be compensated US $50. Providers who complete focus group discussions will be compensated US $75.

mChoice project providers who complete the pre- and postassessment will be compensated US $50. Providers who complete an in-depth interview will be compensated US $100. Cohort participants will be compensated US $40 for the baseline survey and app download, US $45 for the 3-month follow-up survey, US $55 for the 6-month follow-up survey, US $60 for the 9-month follow-up survey, US $70 for the 12-month follow-up survey, and US $80 for the 18-month follow up survey. Cohort participants who complete an in-depth interview will be compensated US $35. Providers who complete an in-depth interview will be compensated US $100.

Study Design

The EPICC project includes 2 distinct aims. Aim 1 includes provider training. Providers will be trained on the use of education tools adapted in the formative work and the process of screening, counseling, initiation, and follow-up with clients interested in or already taking PrEP through our PrEP training modules and will complete TMI training. The effectiveness of the training will be measured quantitatively. Aim 2 is a longitudinal cohort study designed to test the newly adapted education tools through a hybrid type 2 effectiveness implementation cohort to assess PrEP uptake and adherence to PrEP among YMSM and provider provision of PrEP and competence with education tools to increase PrEP services. Aim 2 will include a mixed methods analysis. Figure 1 provides an overview of the EPICC project's design. Formative work can be found elsewhere [17].

The mChoice project includes 3 aims. Aim 1 of the mChoice project is to conduct a hybrid type 2 trial testing the effectiveness of the mChoice clinical intervention to increase PrEP adherence and persistence among YMSM using PrEP. Aim 2 is to conduct in-depth interviews to assess multilevel factors at the patient level associated with selection of a PrEP regimen and switching patterns. Aim 3 is to provide training to health care providers to improve knowledge of PrEP clinical recommendations and enhance provider communication. Figure 2 provides an overview of the mChoice project design. Formative work findings can be found elsewhere [18].

Figure 1. EPICC project design. EPICC: Expanding Pre-Exposure Prophylaxis (PrEP) in Communities of Color; YMSM: young men who have sex with men.

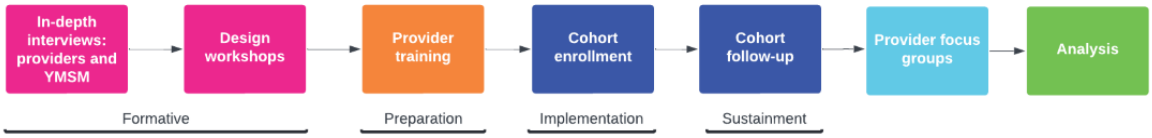


Figure 2. mChoice project design.

Data Collection

Every 6 months, study sites (EPICC and mChoice) will complete a clinic assessment that will include information around PrEP prescriptions issued, clinic services, financial assistance, and PrEP support services. This information will be collected prior to the provider training and will continue for the duration of the study to assess implementation efficacy. There will be a clinic assessment baseline and final, which is completed at the beginning of data collection and at the end and a shorter clinic assessment every 6 months. These assessments will capture data on clinic demographics, PrEP uptake and follow-up and provision of HIV and PrEP education.

The EPICC project's aim 1 provider training consists of the completion of surveys prior to and after training components. Providers are rated on their use of TMI during standard patient interactions immediately after training and three months post training. Aim 2 data collection will occur using surveys every three months, project app paradata, and exit interviews. Additionally, we will conduct focus group discussions with providers at the end of the longitudinal cohort.

The mChoice project's aim 1 data collection will occur using surveys every three months, and project app paradata. Aim 2 data collection will occur using in-depth interviews with a subsample from aim 1. The mChoice project's aim 3 provider training consists of the completion of surveys prior to and after training components and an interview following completion of the training.

Provider Training

Each project will enroll participants for both provider training and the cohort from unique study sites. Figure 3 includes a map of each project's enrollment sites.

The EPICC project team developed online PrEP training modules to educate providers on currently available PrEP options and how to engage clients in open discussions around sexual health and PrEP options. The goal of these open discussions between providers and clients is to encourage shared decision-making on PrEP options. The flexible and interactive modules were created using the Easygenerator online authoring tool, which allows learners to complete their assigned courses over multiple sessions at any time. The interactive features used throughout the modules are designed to keep providers engaged. Some of these features include checks for understanding, embedded videos, and links to external content. Each module also contains at least 1 case-based scenario. These scenarios are based on real-world interactions that study team providers experience during interactions with clients.

The EPICC project team developed these modules using a variety of content sources, including CDC-produced guidelines and materials, research papers, and expert guidance. In addition to modules covering PrEP regimens, we also included modules on the need for PrEP, PrEP screening and startup, postexposure prophylaxis (PEP), and PrEP adherence and persistence. The modules were refined to their final form through an iterative feedback process with subject matter experts within the EPICC project team. Both EPICC and mChoice project teams will use these modules in their respective provider training. Table 1 lists the titles and brief descriptions of each module.

Figure 4 includes screenshots of content within the modules that highlight interactive elements used throughout the course. The video image shown is from "Let's Talk About Sexual Health" [19] produced by the CDC and BeSmartBeWell.com.

In the EPICC project, after completing the online PrEP training modules, providers will attend live, online TMI training sessions led by a member of the motivational interviewing (MI) network of trainers. The training has been split into distinct training modules: (1) introduction to TMI and PrEP choice; (2) TMI spirit, cultural humility, antiracism, and stigma reduction; (3) managing counter change talk and discord with empathy and autonomy support; and (4) eliciting and motivation for PrEP. There will be 2 training sessions lasting approximately 3 hours conducted virtually over 2 days. The training uses videos of

PrEP providers demonstrating TMI integrated with antiracism and cultural humility that were created specifically for this study. The workshops are structured with cooperative learning activities, video examples, and behavioral skill acquisition steps (modeling, verbal and behavioral rehearsal, feedback). After the live, online training is completed, providers will complete a 15-minute standard patient interaction assessment, where a member of the study team will act as a client and the provider will attempt to use TMI techniques during their interaction. The conversation will be coded by a study team member using the MI Coach Rating Scale [20], and a feedback report will be generated and sent to the provider. The report will include strengths and areas for improvement, with video links featuring skills identified as areas for improvement. Three months after completing the TMI training sessions, providers will complete an additional standard patient interaction assessment with the same feedback format. Providers will also complete a brief survey prior to starting the online modules, which will include demographics; PrEP familiarity and attitudes; and PrEP use and future intentions. Providers will complete another survey after the TMI training sessions are over, which will include similar questions to the first survey to assess for change after completing online modules and TMI training.

After completing the online PrEP training modules, providers in the mChoice project will watch a 10-minute video on cultural competency and humility in PrEP care training developed specifically for this study. This module consists of an introduction to cultural competency and humility and exemplifies how these concepts are key components to PrEP care. Like the EPICC project team, sources for the video include information from CDC guidelines, CDC-produced materials, and peer-reviewed journal–cited research papers. For example, the CDC's 5Ps approach to gathering sexual history is highlighted as a critical step in the context of PrEP care. More information about the 5Ps approach can be found on the CDC's website [21]. Useful tips, such as using layperson's terms that are also anatomically correct, making eye contact, and not appearing to be in a hurry, are mentioned throughout. Simultaneously, this module emphasizes the importance of making clients feel comfortable and respected and allowing the client to guide the conversation. This module aims to inform providers about how to best interact with clients and demonstrate racial and ethnic diversity among clients through the use of dynamic graphics. The module also provides training to facilitate provider-client communication so that there can be effective shared decision-making. It will be included in the PrEP Choice provider series launched through Easygenerator.

Figure 3. Map of EPICC and mChoice project enrollment sites. EPICC: Expanding Pre-Exposure Prophylaxis (PrEP) in Communities of Color.

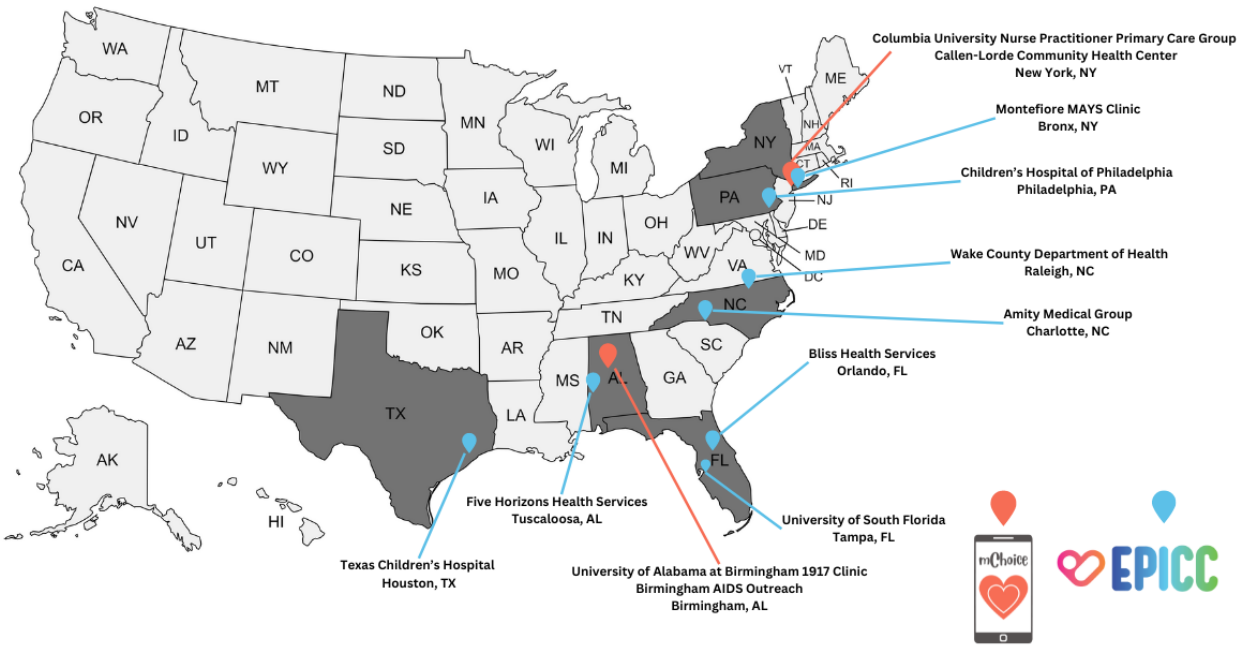


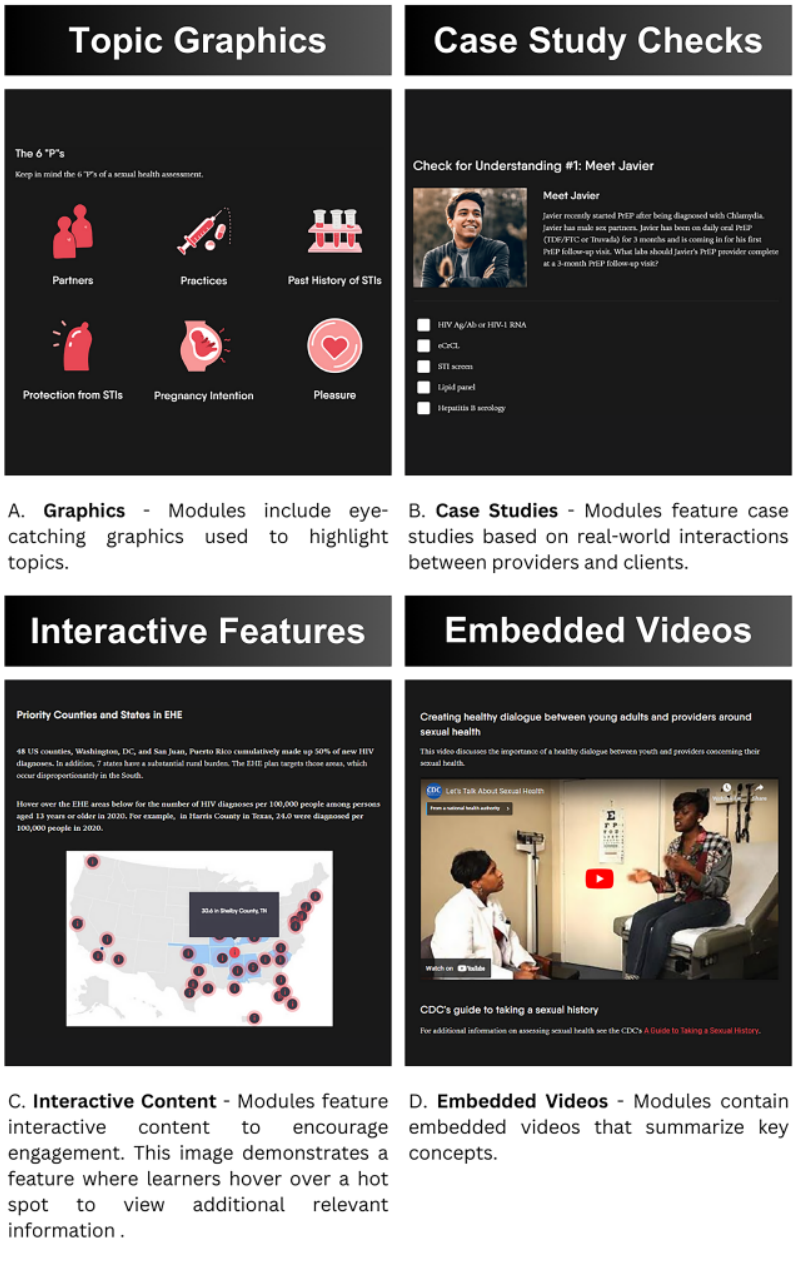
Table 1. Online PrEP[a] training module titles and topics used in EPICC[b] and mChoice Studies.

Module title	Topics covered
Module 1: Why Do We Need PrEP?	HIV epidemic in the United States, the EHE plan, PrEP update in the United States, and PrEP efficacy and effectiveness
Module 2: Who and Why for PrEP	PrEP guideline changes, PrEP screening, and HIV testing recommendations
Module 3: What Is PEP and Who Should Get It?	PEP screening, prescribing, and monitoring
Module 4: Considerations in Choosing Among Oral PrEP Options	Oral PrEP regimens, oral PrEP initiation and follow-up, 2-1-1 or on-demand PrEP, and oral PrEP side effects
Module 5: Considerations in Prescribing and Monitoring Injectable PrEP	Injectable PrEP initiation, follow-up, adherence, side effects, and future PrEP modalities
Module 6: Maximizing PrEP Adherence and Persistence	Adherence counseling components, PrEP implementation, and cost considerations

[a]PrEP: pre-exposure prophylaxis.

[b]EPICC: Expanding PrEP in Communities of Color.

Figure 4. Screenshots and descriptions of interactive content within online PrEP modules used in EPICC and mChoice provider training.



A. **Graphics** - Modules include eye-catching graphics used to highlight topics.

B. **Case Studies** - Modules feature case studies based on real-world interactions between providers and clients.

C. **Interactive Content** - Modules feature interactive content to encourage engagement. This image demonstrates a feature where learners hover over a hot spot to view additional relevant information .

D. **Embedded Videos** - Modules contain embedded videos that summarize key concepts.

Longitudinal Cohort

Both EPICC and mChoice projects will enroll a cohort of 400 participants. Study participation will range from 12-18 months, depending on the study enrollment date. Eligibility criteria include (1) age 18-39 years, (2) the male sex, (3) ever had sex (as a top or a bottom, insertive or receptive) with a person who has a penis, (4) have an active prescription for PrEP (including both new prescriptions at baseline or refills), (5) receive care at 1 of the participating study sites, (6) provide a mailing address within the 50 states where packages can be received, (7) have daily smartphone access, and (8) be fluent in written and spoken English or Spanish. Cohort participants will be recruited by the clinic staff during scheduled visits, through study advertisements placed in clinic waiting rooms, or through study advertisements on social media platforms.

Each project team builds off prior work to adapt their unique digital health tools poised to support PrEP choice and ongoing adherence. The EPICC project builds from the HealthMpowerment (HMP) intervention. HMP is a theory-based status app designed to provide health and wellness information and resources relevant to young people via a mobile optimized platform. HMP was created based on the Integrated Behavioral Model [22-24]. HMP is flexible and easy to adapt for specific populations and health topics. The EPICC project's version of HMP includes resources most relevant for our study population. The mChoice app was created based on the Information System Research framework and builds on formative work to develop a PrEP adherence and monitoring app [25-27]. The mChoice app was built in collaboration with Compliance Meds Technologies (CMT) CleverCap. CMT is an mHealth technology solutions provider that develops adaptable technology to promote health. The CleverCap app is linked to a CleverCap device, which is an electronic pill bottle that records when the cap opens and closes and tracks medication adherence. The CleverCap app was customized to the needs of the mChoice project to support PrEP adherence among YMSM. It offers PrEP resources, such as 2 client-facing PrEP training modules created by the study team and a sexual activity log. It can be programmed for the use of participants who are taking any of the 3 PrEP regimens: oral (daily or event driven) or injectable. Table 2 lists the features of each project's mobile app.

Table 2. Description of EPICC[a] and mChoice digital health support tools.

Feature	EPICC	mChoice
Resources	Educational content across a range of health topics, as well as support for app engagement and behavior change through information and skill building	Participant-facing PrEP training modules, links to the CDC[b] website
Adherence support	Medication tracker to support oral, injectable, or event-driven PrEP adherence	Electronic adherence monitoring through the use of the CleverCap app and device
Sexual behavior tracking	Sexual activity log	Sexual activity log
Connection to care	"Ask the Expert" feature to allow providers to anonymously answer user questions and connect users to resources	Chat function to communicate with the study team
Engagement features	Gamification with badges and avatars earned for completing activities	Adherence statistics for participants taking oral daily PrEP
Integrations with test kits	Yes	N/A[c]

[a]EPICC: Expanding Pre-Exposure Prophylaxis (PrEP) in Communities of Color.

[b]CDC: Centers for Disease Control and Prevention.

[c]N/A: not applicable.

Cohort Procedures

Participants will complete a computer-assisted self-interview (CASI) every 3 months while in the study. Surveys will be hosted on REDCap. EPICC surveys will be distributed through emails and links available within the study app. mChoice surveys will be completed at study sites on a tablet. The surveys will address various topics related to PrEP care engagement, PrEP usage, and PrEP adherence, as well as sociodemographics and risk factors related to PrEP adherence (Table S1 in Multimedia Appendix 1) [7,28-38].

EPICC project participants will complete a home-based DBS collection kit every 6 months while in the study to assess for levels of tenofovir-diphosphate (TFV-DP) and emtricitabine-triphosphate (FTC-TP). Additionally, EPICC project participants can attend an optional virtual onboarding visit with a member of the study team to review key features of the study app and DBS collection instructions. mChoice project participants who report using PrEP containing TFV and FTC will provide a urine sample of 15-30 mL at each visit to measure adherence. After the visit, the staff will use the urine sample for a rapid strip test to interpret adherence results. The staff will upload a picture of the test results to REDCap to send to the lab so that they can perform quality control checks. Participants' urine samples will be used for 2 separate tests: one that measures TFV levels and another that measures FTC levels. Throughout the study period, participants (EPICC and mChoice) will be asked to track their PrEP adherence and sexual behavior in study mobile applications. Electronic health record (EHR) data (EPICC and mChoice Studies) will be collected every 6 months during the study period; variables will include PrEP prescription information, HIV testing, sexually transmitted infection (STI) testing, and results. Clinic site staff will complete medical record abstraction (MRA) using participants' EHRs

every 6 months while in the study. MRA will collect information about PrEP prescriptions, STI testing and results, and HIV testing and results. Table S1 in Multimedia Appendix 1 includes cohort measures.

A subset of EPICC project participants will also complete exit interviews. Questions will focus on understanding factors that influenced participants' selection of PrEP regimens, changes, or discontinuations; perceptions of the counseling they received by providers at PrEP initiation and follow-up; and the receipt of tools or materials that influenced their choice and feasibility/acceptability of the HMP app. The mChoice project team will similarly conduct in-depth interviews with a subset of participants following completion of the intervention to explore experiences with PrEP, reasons for PrEP choices, and impressions of the mChoice intervention.

Postcohort Provider Focus Group Discussions and Interviews

After the cohort is completed, the EPICC project team will conduct 6 virtual focus groups with PrEP providers, clinic staff, and study staff. The purpose of the focus groups will be to gather feedback on overall perceptions of the barriers and facilitators to education tool implementation within their clinical site. Prior to participating in the focus groups, participants will complete a survey that will collect their demographics, whether the provider can prescribe PrEP, and how long the provider has worked at their current clinic.

The mChoice project team will conduct in-depth interviews with participating providers following completion of the PrEP training modules and assessments. The research staff will ask participants about the implementation of the mChoice intervention, any long-term effects of the intervention, opinions of the provider training modules, and recommendations for future implementation of the mChoice intervention.

Primary Outcome Measures

The primary outcome for provider training is PrEP familiarity, PrEP beliefs, and intentions to use PrEP measured at pre- and posttraining. The primary outcome for the cohort is PrEP adherence. For the EPICC project, adherence outcomes will be measured by using blood and will be tailored for oral PrEP modality (daily or 2-1-1) and categorized as protective (1) or not protective (0). The protective level of PrEP in the blood is defined as ≥4 doses taken per week, and the not-protective level is defined as <4 doses taken per week. Adherence outcomes for participants on CAB-LA will be determined by the timely administration of injections. The timely administration of the second injection is defined as within +/–1 week of the target date and within +/–2 weeks of the target date for subsequent injections. For the mChoice project, adherence outcomes, as measured by using urine, will be assessed by testing TFV and FTC levels in urine specimens collected from participants who report daily use of PrEP containing TFV and FTC. The mChoice project will also measure adherence by electronic medication monitoring via the CleverCap device, EHR data, and self-report.

Secondary Outcome Measures

Secondary outcomes for provider training include the feasibility and acceptability of implementing provider training and barriers and facilitators impacting the implementation of new PrEP modalities in clinical practice measured through participant responses during the provider focus group discussions that will occur at the end of the cohort follow-up. The EPICC project cohort's secondary outcome is persistence measures and will be based on (1) the participant's self-report of currently taking PrEP (daily or 2-1-1) or having received the last shot of CAB-LA and (2) the participant having an active prescription for PrEP based on study records or drug levels associated with use within a 1-month window at 6 months, 12 months, and 18 months postenrollment. mChoice secondary outcomes will consist of sexual risk behaviors, HIV status, substance use, and outcomes by the initial PrEP regimen, as reported through follow-up assessments and EHR data.

Statistical Analysis

Specific statistical analyses will be performed for the different projects. Next, we describe the EPICC and mChoice project analysis plans separately.

The EPICC Project

Sample Size and Power Calculations

The sample size for this study was determined based on feasibility after considering the intended analyses and multiple parameter estimates. With 400 participants, the minimum detectable difference in the PrEP adherence and persistence rates was 5.6%, assuming 15% loss to follow-up and a reference rate of 20%, at 0.80 power with a 1-sided test and 0.05 type I error. For baseline to postintervention analyses, simulation-based results indicated the minimum detectable difference from a baseline rate of 20% was approximately 9% (odds ratio 1.6), assuming again 15% loss to follow-up, at 0.80 power with a 1-sided test and 0.05 type I error [39].

Analysis Plan

Baseline participant characteristics will be described for the entire sample and disaggregated by regimen, site/region, ethnicity, level of HIV risk perception, substance use, PrEP experience (naive vs familiar), partner relationship status, and the other variables of interest included in Table S1 in Multimedia Appendix 1.

To determine any differences in discontinuation and nonadherence, we will use Cox proportional hazards to analyze (1) time to first discontinuation and (2) time to first nonadherence by regimen using PrEP adherence measures. To incorporate observations after the first discontinuation or after the first nonadherence, including allowing for the possibility of restarting on PrEP after discontinuation and for periods of nonadherence followed by a period of adherence, we will use a multilevel survival model by including a frailty term in the model to allow analysis of recurrent events [40]. We will follow the same analytic strategy for other dichotomous primary and secondary effectiveness and implementation outcomes. For the composite measure of number of prescriptions (primary implementation outcome), we will fit a multilevel linear or a

generalized linear regression model, again using all the time point data available to assess the strength of the associations between the composite measure for the number of prescriptions and the predictor variables. To examine the trajectories of regimens, we will use generalized linear mixed models (GLMMs) and a survival model to assess the time to each regimen switch.

Provider Training

Mean scores for the pre- and postadministration of PrEP knowledge items, as well as the mean scores for motivational interviewing familiarity and comfort, will be evaluated for significance of difference using the nonparametric Wilcoxon signed-rank test for hypothesis testing of repeated measurements on a single sample [41].

The mChoice Project

Sample Size and Power Calculations

Sample size estimation was based on the number of individuals required in order to detect an odds ratio of 1.7 or greater, based on a previous intervention study [42], in the primary outcome measures (PrEP adherence and persistence) before and after the intervention. We used a GLMM [43] with 80% power and a 2-sided test of .05 significance. We estimated the power and sample size by simulating responses based on the following assumptions: 20% attrition postintervention follow-up, an intraclass correlation coefficient of 0.2 across sites, and correlations in the range of 0.3-0.6 of participants' outcomes at different time points [43]. With these conditions, a sample size of 400 was needed [43].

Primary Outcome

A GLMM, also called an individual growth model and a multilevel model, with an appropriate link function will be used to compare the pre- and postintervention difference for each outcome. The GLMM allows different trajectories for each participant, and this method is appropriate to compare outcome changes after the implementation of the intervention, with the control of baseline values. Analyses will be conducted for the full sample and by study location (New York City and Birmingham) separately [44].

Secondary Outcomes

Similar GLMMs will be used for analyzing secondary outcomes. We will conduct a multigroup comparison in pre- and postintervention differences (the difference-in-difference analysis) using a GLMM by adding the group variable and the group × intervention status interaction (pre- and postintervention) in the GLMM described before. Because the PrEP regimen cannot be randomized, we will use the propensity score method [45] to reduce the between-group bias. We will also examine factors that are associated with the length of time that participants take to change their regimens or associated with the instantaneous rate of change of regimen. Since we will know the date of change of the PrEP regimen (from the EHR data), we will apply a Cox proportion hazard ratio model with time-varying covariates (eg, sexual activity, insurance, side effect) to examine the time to change the regimen.

Provider Training

Mean scale scores for the pre- and postadministration of PrEP knowledge items, as well as the mean time with PrEP patients, will be evaluated for significance of differences using the nonparametric Wilcoxon signed-rank test for hypothesis testing of repeated measurements on a single sample [41]. Categorical data for assessing differences in the proportion of participants in agreement with individual items before and after participating in the knowledge module will be analyzed using the McNemar test of marginal homogeneity [41].

Results

The EPICC project formative work to develop evidence-based tools (Maragh-Bass et al, unpublished data, March 2025) was completed in April 2023 [17]. Provider training enrollment began in January 2024 and was completed in August 2024. Cohort enrollment began in April 2024. As of October 2024, 40 participants were enrolled in the EPICC project cohort. Cohort enrollment is expected to be completed in September 2025, with the final results anticipated in early 2027. Provider focus groups are expected to begin in April 2026, with the final results expected in early 2027.

The mChoice project formative work to develop and evaluate evidence-based tools was completed in January 2024 (Kay et al, unpublished data, March 2025) [18,46]. Provider training enrollment began in June 2024 and is ongoing. Cohort enrollment began in July 2024. As of October 2024, 18 participants were enrolled in the mChoice project cohort. Cohort enrollment is expected to be completed in July 2025. The final results are expected in late 2027.

Discussion

Overview

Posttraining, we anticipate providers will increase competence in using EBTs and providing PrEP support services. We also anticipate participants in the cohort will increase PrEP adherence and persistence. Given the changing PrEP landscape and the availability of new options and formulations, the implementation of provider education and tools to maximize uptake and adherence within their patient populations is needed. By delivering culturally competent and interactive provider training on PrEP options, the study will help providers counsel and guide participants on the effective and safe use of PrEP. The digital health tools created will support participant adherence and help them optimize the prevention benefits of their chosen PrEP regimen. Through the longitudinal, cohort design, the PrEP Choice study will provide real-world data about PrEP use that will be critical for informing future guidelines and tools.

Limitations

This research is limited in its design as a cohort study and not a randomized controlled trial. However, early work to harmonize measures and outcomes across the 2 projects is expected to allow for informative descriptions and the possibility for both pooled and separate analyses, as well as comparison across the entire study. Although multiple study sites across the United

States are included, PrEP Choice is not a nationally representative study and results will not be generalizable.

Conclusion

A multitude of efforts exist to make PrEP more available for people at risk for acquiring HIV infection, especially YMSM. Activities to increase PrEP uptake need to be accompanied by research that assesses its real-world use and identifies strategies to support and maximize its benefits. In addition to improving our understanding of how those at increased risk for acquiring HIV infection use PrEP, the PrEP Choice study will support the design and testing of informed interventions to support PrEP users' adherence and persistence, in addition to initiation.

Acknowledgments

This study is supported by funding from the Centers for Disease Control and Prevention (CDC; awards U01PS005246 and U01PS005229).

The content is solely the responsibility of the authors and does not necessarily represent the official position of the Centers for Disease Control and Prevention (CDC).

Data Availability

The datasets generated and analyzed during this study will be available from the corresponding author upon reasonable request.

Authors' Contributions

All authors contributed to the study design and paper development.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Cohort measures for the Expanding Pre-Exposure Prophylaxis (PrEP) in Communities of Color (EPICC) and mChoice Studies.
[DOCX File , 25 KB - resprot_v14i1e64186_app1.docx]

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Abbreviations

CAB-LA: long-acting injectable cabotegravir
CASI: computer-assisted self-interview
CDC: Centers for Disease Control and Prevention
CMT: Compliance Meds Technologies
DBS: dried blood spot
EBT: evidence-based provider and patient education and support tool
EHR: electronic health record
EPICC: Expanding Pre-Exposure Prophylaxis (PrEP) in Communities of Color
F/TAF: tenofovir alafenamide
FTC: emtricitabine
FTC-TP: emtricitabine-triphosphate
F/TDF: tenofovir disoproxil fumarate
GLMM: generalized linear mixed model
HMP: HealthMpowerment
MI: motivational interviewing
MRA: medical record abstraction
MSM: men who have sex with men
PEP: postexposure prophylaxis

PrEP: pre-exposure prophylaxis
STI: sexually transmitted infection
TFV: tenofovir
TFV-DP: tenofovir-diphosphate
TMI: tailored motivational interviewing
YMSM: young men who have sex with men

Edited by A Schwartz; submitted 11.07.24; peer-reviewed by M Wang; comments to author 06.09.24; revised version received 21.10.24; accepted 03.02.25; published 20.03.25.

Please cite as:
Rainer C, Schnall R, Tanner MR, Galindo CA, Hoover KW, Naar S, Brin M, Martinez A, Jia H, Mendoza M, Hightow-Weidman L Developing and Implementing Provider-Training and Evidence-Based Tools to Support Pre-exposure Prophylaxis (PrEP) Decision-Making and Increase PrEP Adherence Among Young Men Who Have Sex With Men: Protocol for the PrEP Choice Longitudinal Cohort Study
JMIR Res Protoc 2025;14:e64186
URL: https://www.researchprotocols.org/2025/1/e64186
doi:10.2196/64186
PMID:

Protocol

Clinical Safety of Pudilan Xiaoyan Oral Liquid for the Treatment of Upper Respiratory Tract Infection in the Real World: Protocol for a Prospective, Observational, Registry Study

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Abstract

Background: *Pudilan Xiaoyan* oral liquid (PDL) is a proprietary Chinese medicine preparation widely used for upper respiratory tract infection, known for its significant therapeutic effects. However, the safety profiles reported in several observational studies vary, and these studies primarily focus on efficacy rather than specifically addressing safety concerns, thus representing inadequate safety monitoring.

Objective: This study aimed to investigate the incidence of adverse drug reactions (ADRs) associated with PDL and explore the factors contributing to these reactions.

Methods: The study is a prospective, observational, multicenter, hospital-based surveillance study. A total of 17 hospitals from China are involved. The study is expected to enroll a large sample of 10,000 patients aged between 18 and 80 years with upper respiratory tract infection who were prescribed PDL. The patients' data, including demographics, medical history, diagnostic information, medication details, adverse events, and laboratory test results, will be monitored. The occurrence of ADRs will be recorded. The primary outcome is the incidence of ADR. Secondary outcomes are the ratio of patients whose body temperature return to the normal range (cases of body temperature normalization and the duration for achieving normal body temperature within a 3-day period will be documented) and changes in liver and kidney function (occurrence of drug-induced liver injury and acute kidney injury). Descriptive analyses will be performed for the primary and secondary outcomes. A cohort, nested, case-control study design will be used. If one patient has an ADR, then 4 patients without ADRs will be matched as the control group according to gender, age within 5 years, drug batch, and other factors, at a ratio of 1∶4 to compare the symptoms related to ADRs. The differences of ADR incidence among the possible influencing factors will be compared separately to find the factors with large differences. Then, synthetic minority oversampling technique and group least absolute shrinkage and selection operator methods will be used to identify factors influencing the occurrence of ADRs. Finally, propensity scoring methods will be used to control for confounding variables. The progress of each subcenter will be closely monitored, and the incidence of ADR will be systematically calculated. Furthermore, the characteristics and influencing factors of ADR will be analyzed, along with an investigation into its geographical distribution.

Results: The study began on July 17, 2019. Due to the limited number of eligible patients, missed follow-ups, and the huge clinical burden caused by public health events in 2019, the final case will be enrolled on August 30, 2025.

Conclusions: This study will obtain safety results of PDL in the real world and provide guidance on the clinical safety of traditional Chinese medicine formulations.

Trial Registration: ClinicalTrials.gov NCT04031651; https://clinicaltrials.gov/study/NCT04031651

International Registered Report Identifier (IRRID): DERR1-10.2196/65789

(JMIR Res Protoc 2025;14:e65789) doi:10.2196/65789

KEYWORDS

Pudilan Xiaoyan oral liquid; PDL; upper respiratory tract infection; URTI; registry; adverse drug reaction

Introduction

Upper respiratory tract infection (URTI) involves inflammation of the respiratory mucosa from the nose to the lower respiratory tract; it causes localized symptoms that constitute several overlapping syndromes: pharyngitis, common cold, sinusitis, and bronchitis [1]. Bacterial or viral infections may be the cause of URTI, but antibiotics are recommended only for the former [1]. It is a self-limiting viral infection [2]. Currently, considering the treatment of symptoms for URTI and anti-infective therapy [3], the efficacy remains unsatisfactory with notable adverse reactions [4]. *Pudilan Xiaoyan* oral liquid (PDL) is a Chinese patent medicine, collected in the *Chinese Pharmacopoeia*. It has been widely used for URTI and has obtained good curative effect [5,6]. It contains drugs such as *Scutellaria baicalensis*, *Corydalis bungeana*, *Taraxacum mongolicum*, and *Isatis indigotica* [7]. All four herbs have the traditional Chinese medicine effects of removing heat and toxic materials, cooling blood, and reducing swelling. Besides, they also have anti-inflammatory, analgesic, antibacterial, and other biological effects [8]. Despite the efficacy of PDL, it is also necessary to monitor its safety.

In terms of safety, among the biological mechanisms of PDL, *S baicalensis*, *C bungeana*, *T mongolicum*, and *I indigotica* have been identified as herbs with low toxicity. The aforementioned drugs, however effective, are associated with gastrointestinal adverse reactions due to their bitter cold properties. Additionally, *S baicalensis* exhibits limited embryotoxicity and hepatotoxicity and can induce allergic reactions leading to vesicular eruptions [9]. *T mongolicum* primarily contributes to reversible toxicity targeting red blood cells [10], while *I indigotica* possesses nephrotoxic properties and may impose a burden on the urinary system with prolonged use [11]. The formulation of *C bungeana* contains certain hepatotoxic effects [12]. Therefore, it is necessary to investigate the safety of PDL since it is composed of the aforementioned herbal groups.

Monitoring the unintended effects of a drug (pharmacovigilance or drug safety) is crucial due to limited knowledge of rare or late-stage side effects upon market release of new drugs [13,14]. In recent years, numerous related studies have reported the clinical efficacy of PDL; however, there were few independent safety studies on it, most of which were small scale and exhibited significant variations in reported safety outcomes across different studies [15-18], resulting in inadequate understanding of its safety monitoring. In summary, published safety data on adverse effects of PDL therapy were insufficient, thereby impeding the use of standardized recommendations that are necessary for ensuring drug safety.

Although Chinese patent medicine generally exhibits a low incidence of adverse reactions, the evidence pyramid classification derived from effectiveness evaluations primarily considers randomized controlled trials as high-level evidence. However, this classification standard may not fully meet the evidence requirements for postmarketing drug safety evaluation due to limitations such as short intervention courses or small sample sizes, often resulting in an inability to detect ADRs and differences between groups. For the above reasons, this study intends to adopt a large-scale, multicenter, long-term, noninterventional, observational study design to comprehensively analyze and report on the occurrence of adverse events (AEs) [19].

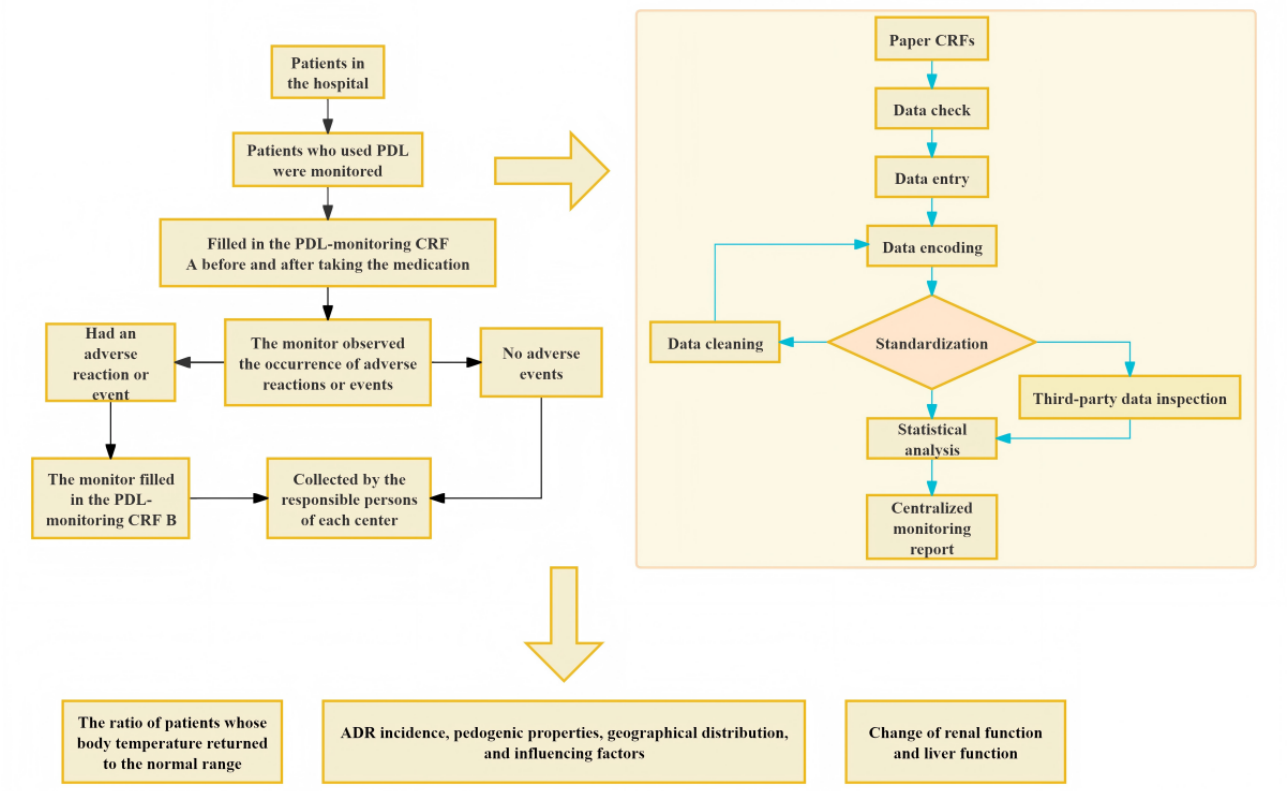
The mechanism of kidney metabolism and excretion of various drugs and toxins is an important cause of drug nephrotoxicity [20], while studies have shown that most of the AEs related to the urinary system were from treatment with PDL [21]. It can be seen that the kidney damage caused by PDL needs further investigation. As hepatic function plays an essential role in drug metabolism [22], clinical studies are necessary to determine the characteristics of PDL-related hepatotoxicity. Additionally, the influencing factors of other PDL-related adverse reactions are still unclear and may be related to the inherent characteristics of the drug itself, improper usage and dosage, improper combination, repeated administration, or use without indications, which need further investigation and study. Furthermore, a comprehensive study regarding the adverse effects associated with PDL use in patients is imperative to optimize the risk-benefit ratio and alleviate strain on limited health care resources.

Methods

Research Design

This is a prospective, observational, multicenter, hospital-intensive monitoring, and continuous registry study. We used the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) checklist when writing our report [23]. The study flowchart is shown in Figure 1.

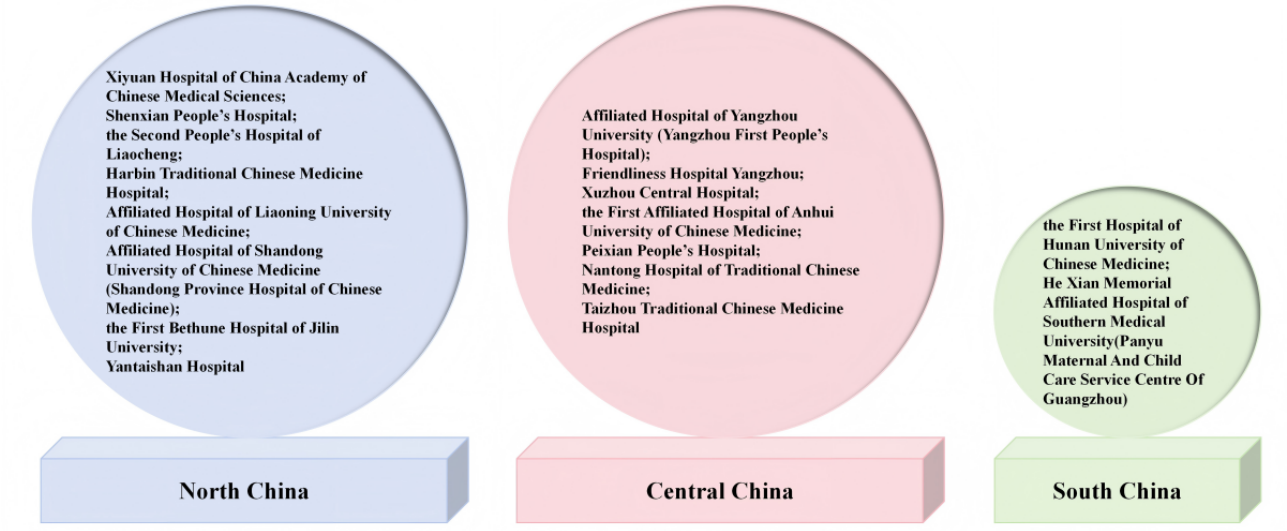
Figure 1. Study flowchart. ADR: adverse drug reaction; CRF:case report form; PDL: Pudilan xiaoyan oral liquid.



Organization

A total of 17 hospitals in China are involved in this study: Xiyuan Hospital of China Academy of Chinese Medical Sciences, the First Hospital of Hunan University of Chinese Medicine, Nantong Hospital of Traditional Chinese Medicine, Shenxian People's Hospital, the Second People's Hospital of Liaocheng, He Xian Memorial Affiliated Hospital of Southern Medical University(Panyu Maternal And Child Care Service Centre Of Guangzhou), Harbin Traditional Chinese Medicine Hospital, Affiliated Hospital of Yangzhou University (Yangzhou First People's Hospital), Friendliness Hospital Yangzhou, Xuzhou Central Hospital, Peixian People's Hospital, Affiliated Hospital of Liaoning University of Chinese Medicine, Affiliated Hospital of Shandong University of Chinese Medicine (Shandong Province Hospital of Chinese Medicine), the First Bethune Hospital of Jilin University, the First Affiliated Hospital of Anhui University of Chinese Medicine, Yantaishan Hospital, and Taizhou Traditional Chinese Medicine Hospital. Figure 2 shows their specific locations.

Figure 2. The geographical location of the 17 hospitals in China involved in this study.Light blue represents North China, light pink represents Central China and light green represents South China.



Sample Size

In accordance with the requirements of the *Guide to Key Drug Monitoring for Manufacturing Enterprises* [24], and referring to the 2013 *Technical Specifications for Intensive Hospital Safety Monitoring of Post-Marketing Chinese Medicine* [25], the "rule of threes" was used for sample size calculation, which states that "if no specific event is observed in X existing cases, there is a 95% likelihood that the occurrence rate of such an event is ≤3/X." Based on the detection rate of rare ADRs (1/10,000 to 1/1000), it is estimated that 3000 cases would need to be collected. However, due to the low probability of ADR occurrences investigated in this study, actual monitoring will be extended to 10,000 cases.

Monitoring Time and Follow-Up

Patients are monitored throughout the medication period in the hospital. The treatment duration of PDL for URTI ranges from 3 to 14 days. This study will include a follow-up period of 7 days after the completion of observation treatment [26], aiming to assess the drug's long-term efficacy and observe any delayed ADRs. The follow-up will be conducted either through face-to-face meetings or via telephone communication. We will use systematic methods and reminders to schedule appointments with patients.

Criteria

The inclusion and exclusion criteria are reported in Textbox 1.

Textbox 1. Inclusion and exclusion criteria.

Inclusion criteria

- Patients with upper respiratory tract infection (URTI) who are administered

  Pudilan Xiaoyan

  oral liquid; the diagnostic criteria for URTI are based on the disease code J06.900 of the

  International Classification of Diseases, 11th Revision
- Aged between 18 and 80 years

Exclusion criteria

- Lactating women, pregnant women, those planning to become pregnant, patients with psychiatric conditions, and others

Instructions for Taking Medicine

In the respiratory and emergency departments of the hospitals under surveillance, the medication of PDL is observed for those aged 18-80 years who strictly follow the prescribing instructions: taking PDL 10 mL at a time, 3 times a day. During hospitalization, the patient must take PDL at least once. The patients will be visited and checked before and after taking the medicine.

Monitoring Content and Data Administration

Monitoring Patient Data, Demographic Information, Diagnosis, Complications, and Medication Information

A collaborative monitoring approach involving doctors, nurses, and pharmacists will be used in this study. They will receive relevant training in surveillance knowledge.

Basic Information Form for Administering PDL

The researchers will record the AE information collected during the study period into the safety monitoring case report form (CRF). All patients will be required to complete CRF A (PDL basic information form). If the monitored patient experiences an ADR or AE during the medication period, the monitor will need to fill out CRF B. We will check the monitoring data; enter, encode, standardize, and clean the data; and then conduct a third-party data inspection. Any discrepancies in the data will be addressed by two data administrators who will resolve them after independently verifying the original CRFs.

Interpretation of ADR Causality

In this study, AEs, ADRs, and serious ADRs will be judged according to the *Administrative Measures on Reporting and Monitoring for Adverse Drug Reaction* issued by the Ministry of Health in 2011 [27]. The evaluation of ADRs follows a 3-level decision-making process, comprising initial reporting by clinical practitioners, assessment by the Expert Committee for ADR Monitoring at the surveillance center, and final determination by panel of senior domestic experts. Based on established assessment criteria, the causal relationship between AEs and PDL will be evaluated according to five key parameters: (1) temporal plausibility, (2) consistency with known mechanisms of action or established adverse reaction profiles, (3) positive dechallenge response, (4) positive rechallenge response, and (5) exclusion of alternative explanations. The correlation between AE and PDL will be divided into six grades: positive, probable, possible, possibly unrelated, to be evaluated, and unable to be evaluated. Those judged to be the first three grades will be classified as ADRs, those judged to be "possibly unrelated" will be classified as AEs, and those judged as "to be evaluated" or "unable to be evaluated" should be rejudged in combination with the original monitoring data. We will conduct thorough evaluations to ultimately confirm the incidence of ADRs associated with PDL. This approach helps to minimize potential biases associated with patient self-reporting and variations in medical practices across different centers. The occurrence characteristics and processes of ADRs will be meticulously documented, with particular emphasis on the timing of ADR onset, the

implementation time of intervention measures for ADRs, and the termination time of ADRs.

Quality Control of ADRs

Each monitoring subcenter will formulate the first-level, quality-control rules and quality-control list according to the content of the monitoring program. The information system of each monitoring unit will be reviewed to ensure that the clinical study data are authentic and traceable. The implementation of the study will adhere to the research protocol and standard operating procedures in order to ensure the authenticity and reliability of the research data. The data collected are presented in Table 1.

Table 1. Basic information form for administering Pudilan Xiaoyan oral liquid[a].

Basic information	Before taking the medicine	After taking the medicine		
		7 days	14 days	21 days
Age	✓			
Sex	✓			
Smoking history	✓			
Occupation	✓			
Expense category[b]	✓			
Pathways to admission	✓			
Drinking alcohol	✓			
Western medicine diagnosis	✓			
Traditional Chinese medicine diagnosis	✓			
Past medical history	✓			
Personal history of allergies	✓			
Allergic manifestation	✓			
Previous other adverse drug reactions or events	✓			
Main drug combination: Western medicine, antibiotics, antipyretic analgesia, proprietary Chinese medicine, or other drugs		✓	✓	✓
Blood routine before and after treatment, white blood cell count, granulocyte, routine urine examination, liver function, renal function, ECG[c] (test sheet within 30 days before treatment), C-reaction protein, influenza virus detection, pathogen detection, and other tests	✓	✓	✓	✓
Adverse reaction occurrence (yes or no)		✓	✓	✓

[a]Patients are visited and examined before and after taking the medication.

[b]Expense category refers to the classification of expenses, such as out-of-pocket (self-funded) costs, expenses covered by medical insurance, and other payment types. It helps in understanding how different types of expenses are categorized based on their funding source or payment method.

[c]ECG: electrocardiogram.

Outcome Measures

Primary Outcome Measure: Incidence of ADRs

The incidence of ADRs is the primary outcome measure, and we will identify factors that contributed to the occurrence of ADRs. The incidence of ADR will be primarily categorized in accordance with the criteria proposed by the Committee of International Organization of Medical Sciences: very common (≥10%), common (1%-10%, including 1%), occasional (0.1%-1%, including 0.1%), rare (0.01%-0.1%, including 0.01%), and very rare (<0.01%) [28], as well as according to the classification of ADR symptoms by the World Health Organization (WHO) [29]. The WHO classification of organs and systems involved in ADRs will also be referenced [30]. The incidence characteristics and regional distribution will be subsequently analyzed, while concurrently investigating the influencing factors (Table 2).

Table 2. Centralized monitoring results of Pudilan Xiaoyan oral liquid in the registered hospitals.

Monitoring result	Description
Categorization	• The ADR[a] was categorized based on general, novel, and severe classifications • The classification was based on the organs and systems affected by the ADR • The symptoms of the ADR were classified
ADR incidence	• The specific event features of each ADR included the incidence rates of various categories and whether they are infrequent or exceptionally rare
Pedogenic properties	• Occurrence characteristics of ADRs specific to each category
Geographical distribution	• The distribution of ADRs is primarily observed in North China, Central China, South China • Each region exhibits distinct characteristics of ADRs
Influencing factors	• Days of medication, age, drug combination, etc

[a]ADR: adverse drug reaction.

Secondary Outcome Measures

The Ratio of Patients Whose Body Temperature Returned to the Normal Range

The cases of body temperature normalization and the duration for achieving normal body temperature within a 3-day period will be documented. The body temperature will be recorded prior to medication, on the first day after medication, and on the second and third days after medication. Daily measurements will be conducted by professional nurses using mercury thermometers. The time of normal body temperature restoration is defined as when the body temperature drops below 37.3 °C after the initial medication administration, with no recurrence observed within a 24-hour period. Thus, the ratio of normalization represented the percentage of cases in which individuals return to a normal body temperature within the total number of cases in the group.

Change in Liver Function

We will observe liver function in at least 3000 patients before and after medication. Liver function indexes will include alanine transaminase (ALT) and aspartate transaminase. To observe whether the above liver function indexes appear abnormal after medication, we will use the 2011 International Association for Severe Adverse Reactions–recommended biochemical diagnostic criteria for drug-induced liver injury [31]. Drug-induced liver injury is defined as meeting one of the following conditions:

1. ALT ≥5× upper limit of normal (ULN);
2. Alkaline phosphatase ≥2×ULN, especially with 5’-nucleotidase or γ-glutamyl transpeptidase elevation, excluding alkaline phosphatase elevation caused by other diseases; or
3. ALT ≥3×ULN and total bilirubin ≥2×ULN.

Change in Renal Function

We will observation renal function in at least 3000 patients before and after medication. The renal function indexes will include creatinine and blood urea nitrogen. To observe whether the above renal function indexes appear abnormal after medication, the diagnostic criteria for acute kidney injury will be defined based on the Kidney Disease: Improving Global Outcomes serum creatinine criteria [32] (at least 50% increase in creatinine within 7 days or a 26.5 μmol/L increase within 48 h).

The time frame for all four result items is 7 days (Table 2).

Statistical Analysis

Data review and cleaning work will take the paper monitoring form as the original record, delete redundant and repetitive parts, supplement missing data, modify wrong values, and report about abnormal values. The basic characteristics of the patients will be included. Descriptive analyses will be performed for the primary and secondary outcomes. SPSS Statistics 26 software (IBM Corp) will be used for descriptive analysis. Data conforming to a normal distribution will be described by means and SDs, and those conforming to a skewed distribution will be described by median, minimum, maximum, and IQR scores. Categorical data will be described by frequencies and percentages. A cohort, nested, case-control study will be used. If 1 patient has an ADR, then 4 patients without ADRs will be matched as the control group according to gender, age with 5 years, drug batch, and other factors, at a ratio of 1∶4 to compare the symptoms related to adverse reactions. In addition, the risk factors of adverse reactions will be analyzed. First, the differences of ADR incidence among the possible influencing factors will be compared separately to find the factors with large differences. Then, synthetic minority oversampling technique and group least absolute shrinkage and selection operator methods will be used to identify factors influencing the occurrence of ADRs, while propensity scoring methods will be used to control for confounding variables.

Ethical Considerations

This monitoring scheme is implemented after the approval of the Ethics Committee of Xiyuan Hospital of China Academy of Chinese Medical Sciences (ethics batch: 2019XL009-1). Patient data included in the analysis were approved by the institutional review committee of each participating agency. Informed patients in this study were exempt from signing the consent application. In addition, the data will be kept confidential, and the researchers who participate in the data

inquiry will need to submit the corresponding application, to ensure that no individual participant or user can be identified in any images in the paper or supplementary materials.

Results

The first case was included on July 17, 2019. Due to the limited number of eligible patients, missed follow-ups, and the huge clinical burden caused by public health events in 2019, the final case will be enrolled on August 30, 2025.

Discussion

Summary

The practice of traditional Chinese medicine in China spans over 2000 years and has consistently garnered high regard for its precise therapeutic efficacy, minimal adverse effects, and cost-effectiveness [33]. As a proprietary Chinese medicine preparation already on the market, PDL had outstanding efficacy in treating URTI [5]. The action mechanism of PDL has been extensively used in clinical practice. However, it is important to acknowledge that there are no completely safe drugs, and every drug administration carries inherent risks. Therefore, the objective of this study was to closely monitor the safety profile of PDL.

The therapeutic safety of PDL is currently being overlooked during the course of disease treatment. Early identification and a better understanding of its adverse reactions will enhance the drug safety profile of PDL and mitigate the therapeutic costs associated with such reactions.

This study is a continuous registry, hospital-intensive monitoring study. Hospital-intensive monitoring allows the evaluation of efficacy and safety in diverse populations under real-world conditions, including sensitive populations that may not be included in premarketing clinical trials, such as pregnant women, ethnic minority groups, older adult patients, children, patients with multiple comorbidities, and those taking multiple medications. The limitation of centralized monitoring in registry hospitals is that it may underestimate the impact of ADRs, as health care professionals may prioritize serious adverse reactions and overlook general adverse reactions. However, this study will implement a 3-level, quality-control approach, using a professional electronic data management system to mitigate missing and misreported data occurrences and ensure the validity and authenticity of the collected information [19].

There are numerous pathological conditions that contribute to drug-induced acute kidney injury, among which the nephrotoxicity of drugs stands as a preventable factor. Enhancing our comprehension of drug safety aids in mitigating the risk associated with drug-induced acute kidney injury. Furthermore, apart from the inherent nephrotoxicity of drugs themselves, administering potentially nephrotoxic medications in high doses or over prolonged treatment durations amplifies the likelihood of renal damage. Additionally, concomitant administration of multiple drugs can synergistically induce nephrotoxicity and consequently lead to kidney injury. Therefore, studying the kidney injury factors of PDL forms the basis for preventing adverse reactions. The Chinese medicine preparation PDL can also induce hepatotoxicity, leading to drug-induced liver damage, which may occur at both therapeutic and overdose doses. This can be attributed to either direct intrinsic hepatotoxicity of the drug or specific (unpredictable) liver toxicity [34], which needs to be further observed and explored.

The monitoring and evaluation of the safety of proprietary Chinese medicine preparations, along with the acquisition of authentic drug safety information, can complement drug instructions, promptly grasp the latest research advancements in related medications, guide their clinical application, and enhance the safety and efficacy of their clinical use.

Conclusions

This study will obtain the safety results of PDL in real-world, clinical applications. Furthermore, monitoring and evaluating the safety of proprietary Chinese medicine preparation is instrumental in providing further clinical guidance on drug use.

Acknowledgments

This trial is supported financially by the National Key R&D Program of China (2022YFC3502004), Funder National Natural Science Foundation of General Program (81973982), Seventh Batch of National Old Traditional Chinese Medicine Experts' Academic Experience Inheritance Project (Chinese Traditional Medicine Teaching Letter [2022] 76), and Fundamental Research Funds for the Central Public Welfare Research Institutes (ZYJGKX202407).

Data Availability

Since this is a protocol, data are not yet available, and information not included in this paper will be provided by the corresponding author upon completion of the trial.

Authors' Contributions

MW and LW prepared the study and the first version of the manuscript. RC participated in the design of the trial. FL collected the information needed for the performance of this trial in each center. ZW, XC, and YL performed a critical revision of the manuscript. YX and LW are responsible for all aspects of the study, including the preparation of the grant application, securing funding, data analysis, and interpretation and preparation of the final manuscript for publication. All of the authors discussed,

read, and revised the manuscript and gave final approval for the publication of this study protocol. The sponsor of this protocol is China Academy of Chinese Medical Sciences, and the responsible party is YX.

Conflicts of Interest

None declared.

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Abbreviations

ADR: adverse drug reaction
AE: adverse event
ALT: alanine transaminase
CRF: case report form
PDL: Pudilan Xiaoyan oral liquid
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials
ULN: upper limit of normal
URTI: upper respiratory tract infection
WHO: World Health Organization

Edited by A Schwartz; submitted 26.08.24; peer-reviewed by X Wu; comments to author 12.12.24; revised version received 05.02.25; accepted 27.02.25; published 21.03.25.

Please cite as:
Wang M, Wang L, Liu F, Chen R, Wang Z, Cui X, Li Y, Xie Y
Clinical Safety of Pudilan Xiaoyan Oral Liquid for the Treatment of Upper Respiratory Tract Infection in the Real World: Protocol for a Prospective, Observational, Registry Study
JMIR Res Protoc 2025;14:e65789
URL: https://www.researchprotocols.org/2025/1/e65789
doi:10.2196/65789
PMID:

Protocol

Tailoring a Skills-Based Serostatus Disclosure Intervention for Transgender Women in South Africa: Protocol for a Usability and Feasibility Study

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Abstract

Background: Transgender women have few interventions to support their HIV prevention and treatment outcomes in South Africa. Further, increased focus should be on intervention development that will reduce HIV transmission within HIV-discordant partnerships, especially for transgender women who navigate gender, sexuality, and relationship stigma. The Speaking Out and Allying Relationships (SOAR) intervention has been developed for sexual minority men to address these outcomes in South Africa. It is a behavioral intervention that is delivered in groups via videoconference to develop coping skills to manage HIV-related stress, assist with disclosure to partners, and establish and maintain safer sex practices with partners. Tailoring SOAR may be feasible for transgender women to support their HIV care while reducing transmission within their relationships.

Objective: This study aims to (1) adapt SOAR for transgender women and test its usability, then (2) assess its feasibility.

Methods: To achieve aim 1, we will use a human-centered design approach to tailor the existing SOAR intervention for transgender women. Interviews and a survey will be administered to transgender women (N=15) to assess intervention preferences. Findings will be used to tailor content like roleplays, scenarios, and media to align with transgender women's lived experiences navigating HIV and relationships. Afterward, we will conduct a usability test with 7 (47%) of the 15 participants to determine intervention understanding and satisfaction. Participants will be transgender women living with HIV and in a relationship with a man who has unknown HIV status or is HIV-negative. All participants will be recruited using community-based approaches. In aim 2, we will examine SOAR feasibility using a 1-arm pilot study. Transgender women (N=20) will be recruited using aim 1 methods and eligibility criteria, with participants completing feasibility surveys and interviews, as well as behavioral and biomedical assessments.

Results: Intervention adaptation began in May 2023 with interviews. Feasibility pilot testing was conducted with 14 transgender women, with study completion in January 2025.

Conclusions: Transgender women need more intervention options that engage their relationships since these can present barriers to HIV treatment outcomes like hindering viral suppression in South Africa. Delivering an existing yet tailored intervention via videoconference expands its reach to transgender women and allows them to engage with others and learn new skills in a secure setting like their homes. SOAR has the potential to improve relationship dynamics and reduce violence, which will in turn enhance HIV treatment and prevention engagement.

International Registered Report Identifier (IRRID): PRR1-10.2196/52121

(JMIR Res Protoc 2025;14:e52121) doi:10.2196/52121

KEYWORDS

transgender women; intervention development; relationships; HIV treatment; South Africa; mobile phones, smartphones; skills-based; serostatus disclosure; HIV; HIV prevention; transgender; treatment outcomes; transmission; HIV-discordant partnerships; behavioral intervention; safe sex; human-centered design; viral suppression; Speaking Out and Allying Relationships; LGBTQ2S; LGBTQ; 2SILGBTQ

Introduction

Background

HIV infections among transgender women are 2.2 higher than gay, bisexual, and other men who have sex with men in sub-Saharan Africa due to syndemics consisting of stigma and discrimination that perpetuate violence and victimization, limiting access to HIV prevention and treatment [1-4]. In South Africa, the HIV incidence for transgender women is 31 cases per 100-person years, with studies showing limited pre-exposure prophylaxis (PrEP) and antiretroviral therapy (ART) access and adherence. Based on other African studies, only an estimated 25% of transgender women are virally suppressed [5-7]. HIV prevalence among transgender women in South Africa mirrors the realities that they share with their peers in other Global South settings, with a 52% mean prevalence documented in 3 South African cities [8]. Transgender women's health and safety remain compromised in South Africa, inhibiting their ability to engage in HIV services to lower transmission risk and improve their overall wellness, and compounding these health outcomes are poor relationship dynamics.

Being in an unhealthy or imbalanced relationship for transgender women can lower their HIV testing behaviors and increase rates of condomless anal intercourse with partners to create trust and intimacy [9-13]. Fear of partner rejection or loss and intimate partner violence may lead transgender women to limit or halt ART use to conceal their serostatus from partners [14-16]. Further, studies increasingly show that transgender women experience negative outcomes of relationship stigma (when partners fear being romantically associated with someone who is stigmatized), which in turn has hindered their ability to discuss HIV treatment with them [15,17]. Although studies with transgender women in South Africa are limited, in the United States, relationship dynamics for transgender women influence HIV risk, in the same ways they do for cisgender women and sexual minority men [17-21]. Additional factors hindering HIV prevention and treatment discussions that transgender may have with a partner include living with them, drug use, alcohol use, education level, and low self-efficacy to use condoms [18]. In sum, cisheteronormative social structures and power dynamics have been shown to result in increased marginalization, increased susceptibility to intimate partner violence, and increased risk of mental issues among transgender women, all hindering HIV prevention and treatment [22-24].

Further, transgender women are less likely to disclose their HIV status to other transgender women and sexual minority men within their social networks, increasing social isolation [25-27]. Only after being out of care and developing AIDS-related illnesses do transgender women disclose their HIV status to an immediate family member in order to secure support for their treatment, but this disclosure does not extend to partners [25,27]. Given a history of HIV care marginalization and discrimination, transgender women often possess inaccurate knowledge and skills in discussing with partners how PrEP and ART adherence, including "undetectable is untransmissible" (U=U) messaging, can work together to reduce transmission and in turn support relationship health [14-16]. Thus, transgender women have ongoing HIV-related stress without the skills to manage this stress and their disclosure to partners and others for support.

The benefits of social and partner support are significant for transgender women. Studies show that transgender women in committed relationships are less likely to engage in HIV-related high-risk behaviors, with researchers suggesting that relationship stability and emotional support lead to more consistent condom use and improved HIV prevention and treatment overall [28-30]. Specifically, higher relationship satisfaction, trust, and commitment were protective factors against HIV transmission among transgender women [17,31]. Additionally, 1 randomized controlled trial found that a social support group intervention further reinforced relationship-related protective behaviors among transgender women [32]. Therefore, a relationship-focused HIV intervention may support treatment and prevention outcomes for transgender women and their partners while garnering the support of family members earlier in their treatment journey.

To address this gap in interventions for transgender women living with HIV in South Africa, the aim of our study is to tailor our existing intervention, Speaking Out and Allying Relationships (SOAR) intervention, with them and then conduct a 1-arm pilot study to assess intervention feasibility in Eastern Cape, South Africa. Specifically, we will tailor SOAR and assess usability for content understandability and satisfaction (aim 1), and then evaluate its feasibility to include retention and any changes in behavioral and biomedical measures (aim 2). We hypothesize that participants will find SOAR feasible, acceptable, and safe to inform a larger efficacy study.

Our SOAR intervention is based on Healthy Relationships (HR), a 5-session, group-based evidence-based intervention to develop individual HIV disclosure risk assessment and safer sexual behavior skills with partners that have demonstrated efficacy in these outcomes in a range of settings [33,34]. The core elements of SOAR are to: (1) develop coping skills to manage HIV-related stress and sexually risky situations; (2) enhance decision-making skills for HIV disclosure to partners; and (3) establish and maintain safer sex practices with partners. The HR intervention was identified based on our preliminary research with sexual minority men and transgender women in South Africa [35]. Additionally, through this preliminary research, we demonstrated that transgender women are willing to complete HIV-related group work and have an interest in mHealth tools, like videoconference modalities, to learn skills in HIV treatment management and disclosure for support

[36,37]. Moreover, harnessing high use rates of smartphones by transgender women for intervention delivery is feasible in South Africa [20,38]. Increased evidence shows that transgender women access web-based social networking sites and use SMS for social networking through mobile and smartphone technologies, creating the potential to tag on ART adherence interventions [39,40]. In our research, we found that HIV-positive sexual minority men and transgender women regularly use videoconferencing to support community networking across rural and urban settings, with 2-hour conversation events focused on HIV, sexuality, and gender [37]. Further, mHealth tools (SMS, chat rooms, and web-based video group interventions) for HIV prevention and treatment in South Africa are part of the national strategic plan [41]. As in the original HR, our SOAR intervention integrates media, scenarios, and roleplays for skill development, and these reflect the experience of South African sexual minority men living with HIV and in relationships. In addition to the standard 5 sessions, we include three 30-minute booster sessions to review action plans over 3 months.

Theoretical Framework

Social cognitive theory serves as the framework for the intervention, which posits that cognition, behavior, and environment interact and influence health outcomes, like HIV risk reduction, disclosure, prevention, and ART adherence. SOAR aims to enhance coping skills for HIV-related stress, self-regulation of disclosure to include risk assessment, treatment, and prevention, and build self-efficacy in healthy behaviors and communication within relationships. Further, the intervention will provide a platform for participants to strengthen coping skills that will support and empower gender affirmation within relationship dynamics that may be experiencing stigma or risk of violence, or desire for improved relationship communication. Within the social cognitive theory model, the intervention will incorporate components such as HIV risk reduction education, treatment education including U=U, HIV prevention strategies like PrEP, and gender affirmation within the context of HIV. Skill-building activities for HIV communication and disclosure risk assessment will be conducted in a confidential group setting. By helping individuals plan for safe sex and consider HIV communication and disclosure to partners, the intervention aims to support ART adherence, empower participants with a sense of agency, and reduce negative feelings associated with their HIV status and internalized HIV stigma.

Our proposed tailoring of SOAR for transgender women is based on high interest to participate among those who attended community outreach activities for recruitment of sexual minority men as part of the original intervention. If this tailoring shows promise of feasibility, then we will conduct a larger randomized controlled trial to assess efficacy and implementation with local agencies that service sexual and gender minority communities in South Africa.

Methods

Study Design Overview

The study will use a 2-fold approach, beginning with intervention tailoring and usability assessment (aim 1) and then a 1-arm pilot study of the intervention (aim 2) to evaluate feasibility. Prior to study initiation, a study coordinator will be hired and trained in study procedures and the SOAR intervention and its delivery approach. The coordinator will be a member of the sexual and gender minority community in Eastern Cape and have a history of HIV program work. Coordinator training will include a review of sexual and gender minority health with a focus on HIV treatment and prevention barriers and facilitators for transgender women, gender-affirming care such as hormone replacement therapy, and relationship dynamics influencing HIV care. Additionally, the coordinator will complete training in good clinical practice and ethics and study procedures including data collection. Finally, the coordinator will be trained in the SOAR intervention which will include both didactic and simulation sessions until competency has been achieved. The study coordinator will conduct all study procedures with mentoring provided by the research team.

Tailoring SOAR for Transgender Women

In aim 1, we will tailor SOAR by using a human-centered design approach. First, we will assess transgender women's preferences and confirm their relationship dynamics regarding HIV. Then, we will evaluate the functionality of the intervention in a videoconference format (Zoom, Qumu Corp), and usability by gauging participants' understanding and satisfaction with the SOAR intervention.

The study will be conducted in Buffalo City Municipality, Eastern Cape, South Africa. In this setting, there is a 46% HIV prevalence among transgender women who live in both urban and rural areas [8]. We will recruit transgender women (N=15) living with HIV and in a relationship for more than a month. Recruitment activities will be conducted by study staff at community events focused on transgender women and sexual and gender minorities. Study staff are members of the sexual and gender minority community and allies, and all completed LGBTQ competency training. Interested participants will be provided study explanation and invited to answer questions in the screening survey. Eligible participants will complete written informed consent in the language of their choosing (eg, isiXhosa, Afrikaans, English). The consent form will outline confidentiality and protections of participant information if they are interested in participating in the study. All participants will receive travel reimbursement and refreshments to complete study procedures.

Preference Assessment and Integration

To assess transgender women's preferences for the intervention, we will conduct in-depth interviews (IDIs). These interviews will delve into influences on HIV treatment including support and relationship dynamics, and gather feedback regarding various aspects of the intervention, including format and delivery. A semistructured question guide will ask questions in four domains: (1) HIV prevention and treatment knowledge;

(2) relationship scenarios involving HIV disclosure and support for role-play development; (3) videoconference delivery preferences; and (4) positive representation of transgender persons in media (web-based, television, and movies) to show during the sessions. Each interview will be 60 minutes long, conducted in the local language (isiXhosa), transcribed verbatim, and translated for analysis. Findings from the analysis will be used to tailor SOAR to the contextual factors influential in HIV treatment and status disclosure for transgender women and to ensure representation of their empowering voices in the roleplays and videos to support skill building.

Usability Testing

Usability testing will involve 2 tasks: pretesting and IDIs with participants. We will recruit 7 (50%) racially and relationship-length diverse transgender women participants from step 1 for pretesting. The pretesting phase will span 5 weeks, with 2-hour sessions each week. At week 8, 3 weeks after the last session, a group check-in session will be conducted via Zoom. Participants will receive SMS reminders for each session and the Zoom session link. All sessions will be completed together to foster positive group dynamics and will include a set of group rules for this purpose, and to protect the confidentiality of participants and their contributions during the sessions. The interventionist will monitor participant engagement throughout the pretesting and follow up with any missed sessions. Participants will provide their smartphone numbers for session reminders, self-assessment, action plans, and partner referrals delivered through Research Electronic Data Capture (REDCap; Vanderbilt University). The sessions and group check-in will be video-recorded for analysis, and participants will receive a data plan to facilitate their participation. After the pretesting phase, IDIs will be conducted with racially and relationship-length diverse participants over Zoom. The interviews will cover 6 usability domains for SOAR, including session functionality, timeliness and appropriateness, clarity of content delivery, document clarity and management, incomplete sessions, and technical transitions between sessions. The individual interviews in isiXhosa are expected to last approximately 50 minutes. Audio recordings of the interviews will be transcribed and translated into English for further analysis.

Data Analysis

To understand SOAR preferences and usability, interview transcripts will be cleaned and confirmed for accuracy before being uploaded into the qualitative data management program, Dedoose, where data will be coded and categorized [42,43]. First, the research team will separately analyze each transcript using predefined codes and open coding, and then discuss coding to confirm alignment and coding distinctions in order to clarify codes [16]. Second, using a thematic approach [44], researchers will analyze the coded transcripts to identify SOAR preferences and usability themes as an iterative process. An additional comparative analysis based on age was conducted to identify any distinctions [44-46]. These discrepancies will be resolved by agreement during research team discussions.

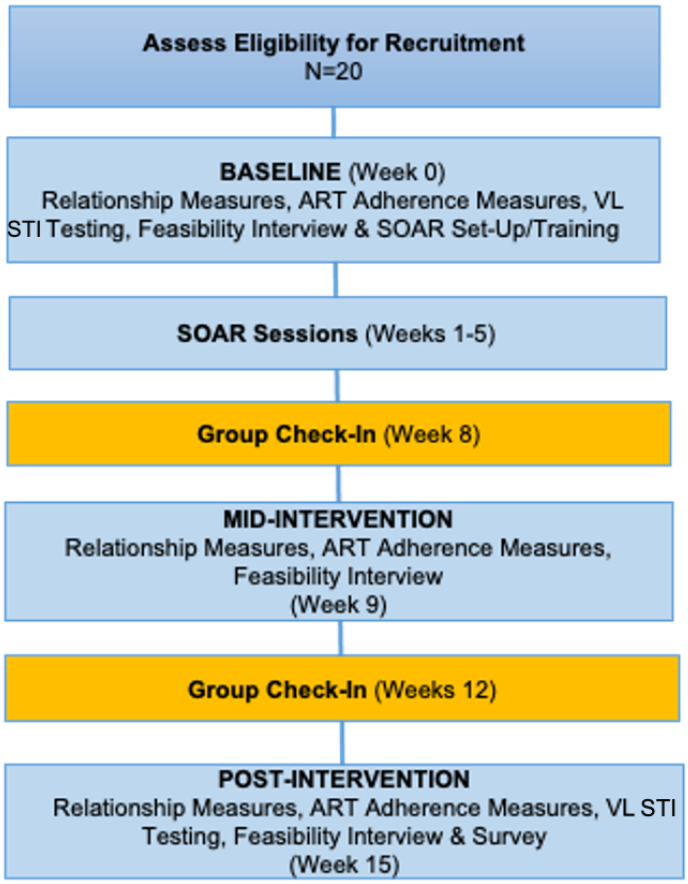
Evaluating the Feasibility of SOAR for Transgender Women

After SOAR has been tailored, in aim 2, we will conduct a pilot study of the intervention using a 1-arm design to determine feasibility, acceptability, willingness, and safety for transgender women (SOAR study design; Figure 1). Also, we will collect data on ART adherence (viral load) and relationship communication to establish a preliminary understanding of outcomes and implementation of measures in a larger study.

We will recruit transgender women (N=20) living with HIV and suboptimally adherent to ART (missed at 2 doses over 2 weeks), to complete the intervention. Additionally, participants must have been in a romantic relationship with a man for more than 1 month and live in Eastern Cape. For screening, participants will complete a rapid HIV viral load test to confirm HIV status.

There will be 5 participants per group for a total of 4 groups. All participants will be recruited and screened into the study by the trained study coordinator, and all recruitment activities will occur at transgender community–focused events. During the consent process, participants will be provided a general overview of the study and informed about the number of study sessions and expected behavioral and biomedical data collection procedures. As in aim 1, all participants will receive a travel reimbursement and refreshments.

Figure 1. SOAR study design. ART: antiretroviral therapy; SOAR: Speaking Out and Allying Relationships; STI: sexually transmitted infection; VL: HIV viral load.



Procedures

Overview

Once enrolled, participants will complete a behavioral survey on REDCap. These measures cover HIV, sexuality, relationship stigma and discrimination, communication in relationships, and HIV prevention and treatment behaviors [47-53]. They will also complete syphilis testing using a rapid diagnostic test (Abbott Determine Syphilis TP), blood draw for HIV viral load, and urine collection for *Chlamydia trachomatis* and *Neisseria gonorrhea* testing. All measures will be administered by study staff.

Afterward, participants will receive training in Zoom, and their smartphones will be assessed and set up for Zoom compatibility. Participants will be notified that they will receive an SMS reminder 12 hours before each session, and then 1 hour before each session, they will receive an SMS with the Zoom link for that session. Also, participants will be informed that during the intervention they will be asked to complete an action plan, and they will receive a partner referral letter via SMS or in paper form (their choice) at the start of the study and can request the letter throughout the study. The referral letter describes the availability of local HIV and mental health services. Each participant will be informed that they will complete 1 SOAR session per week for 5 weeks with 2 check-in sessions afterward.

Group Check-Ins

All participants will be invited to attend group check-ins (n=2) via Zoom. The check-in dates and times will be provided during the last session with connection details (eg, Zoom link) sent via SMS to their mobile devices. Participants will be informed that they will receive a reminder about each check-in session 12 hours before and then 1 hour beforehand.

Each session and group check-in will be conducted by the study coordinator and a research assistant who is trained in the intervention.

Retention Procedures

All participants will be given a card with the study phone number to contact the interventionist if their phone number changes or if they have technical difficulties during the session (the card will not contain information that identifies their participation in the study). The interventionist will phone participants after a missed study visit and SMS each participant monthly to confirm smartphone numbers to support retention.

Measures and Data Analysis

We will use the same measures as outlined in the parent study to include feasibility, behavioral outcomes for ART adherence and relationship communication, and HIV viral load.

Feasibility

The assessment of feasibility encompasses four domains: feasibility [54], acceptability [55], willingness [56], and safety

[57]. Feasibility pertains to the ability to successfully recruit and retain participants, as well as facilitate message exchange and engagement in group sessions [54]. Acceptability refers to participants' preferences and satisfaction with different components of the intervention [55]. Willingness relates to participants' interest in enrolling in a longer study and their likelihood of recommending the intervention to others [56]. Safety focuses on ensuring the confidentiality and security of participant data and communication both within and outside the intervention.[57]

We will assess feasibility using surveys and interviews. The Self-Intervention Evaluation Form and the Client Satisfaction Questionnaire will be administered to evaluate the acceptability [58,59]. A study-specific Likert scale survey will also be developed to assess feasibility, willingness, and safety [60]. This survey will gauge participants' perceived ability to exchange messages, participate in group sessions and check-ins (feasibility), their likelihood of enrolling in a longer study or referring other transgender women (willingness), their willingness to provide referral letters to partners, and their perception of the intervention's confidentiality and security (safety). Also, we will conduct 30-minute interviews with purposively all participants, and these will be conducted at baseline, midintervention, and postintervention [61]. Feasibility will be evaluated by examining participants' attitudes toward various aspects of the intervention, such as video-group interactions, referral letters, and their perceived changes in self-management of ART, HIV risk, and HIV disclosure [62]. Acceptability will be assessed by examining participants' preferences and satisfaction with specific intervention components and the intervention as a whole [62]. Willingness will be measured by assessing participants' willingness to use the intervention consistently from start to finish, their openness to using the intervention in different contexts, and their likelihood of recommending the intervention to others [62]. Safety will be examined by evaluating participants' perceived levels of discomfort with different intervention components and their perceptions of personal safety and the risk of unwanted disclosures [57].

Relationship, ART Adherence, and Biomedical Measures

In this study, we will assess the feasibility of collecting behavioral and biomedical measures and provide a preliminary understanding of outcomes. The SOAR intervention is designed to provide transgender women skills in assessing disclosure and related risks, and association communication skills to discuss HIV with partners. We will administer surveys for relationship satisfaction [63] and communication [64], HIV disclosure [65], and HIV treatment adherence [66] Also, we will assess HIV viral load using whole blood. All measures will be administered at baseline through follow-up.

All data will be analyzed using similar procedures as outlined in aim 1 of this study.

Participants

For both study aims, all transgender women will be over the age of 18 years, be in a relationship for more than a month, own a smartphone, be comfortable with group discussions about HIV, and be HIV-positive with confirmatory testing using OraQuick (OraSure Technologies) during screening. We will enroll with racial diversity to ensure the representation of multiple voices. Our relationship criteria require participants to have a self-reported romantic or emotionally connected partnership with another individual of any sex or gender, and partners must be either HIV-negative or of unknown status. Additionally, all participants need to live in Eastern Cape and suboptimally adhere to their HIV treatment [66].

Ethical Considerations

For this study, aim 1 procedures have been reviewed and approved by the University of Cape Town Review Board (FWA00001938) with reliance on the institutional review board at Arizona State University (STUDY00014539). For aim 2, the study procedures were reviewed and approved by the University of Pretoria Review Board (189/2022) with reliance on Arizona State University (16397). All participants completed written informed consent. All participants will complete written informed consent and will receive R150 (around US $10) as travel reimbursement for completing the study activities and an R150 (around US $10) data plan to support their session attendance. All data will be anonymized when reported.

Results

Staff hiring and intervention tailoring began in May 2023 and were completed in November 2023. During this time, interviews were completed and we identified preferences for the integration of gender-affirming care and South African transgender women's voices (eg, videos) into SOAR sessions. Feasibility pilot testing started in January 2024 and was completed in January 2025. At this time, there are 14 participants who have completed 1-5 SOAR sessions. Primary feasibility results will be used to inform further adaptation and a clinical trial.

Discussion

Expected Findings

The SOAR intervention for transgender women is responsive to South African clinical guidelines for HIV care and addresses barriers to HIV disclosure management and treatment with partners [67]. Specifically, recent clinical guidelines outline a recommendation to deploy mHealth tools for treatment support, as these may allow transgender women to navigate perceived and enacted stigma and discrimination more easily when seeking clinic care [15,16]. Given the established smartphone use in South Africa, and among transgender women, harnessing these tools in HIV interventions is feasible [68]. However, few mHealth HIV interventions have been designed and tested for transgender women [4].

SOAR leverages videoconferencing and group format for delivery. Both modes of delivery have been shown to be highly effective in other settings [69,70], and more research is needed to determine its feasibility with transgender women in South Africa. Further, SOAR has the potential to improve skill-building for HIV status disclosure management that may in turn garner needed support from partners and improve HIV treatment adherence. If partner disclosure and support are not

feasible, then SOAR provides participants with coping skills to manage HIV treatment and identification of other support systems for care.

Given that transgender women have some of the highest HIV incidence rates in South Africa and globally [4], it is imperative that we develop more intervention options based on their lived experiences. Integrating mHealth tools into these interventions can empower participants, as it allows them to control engagement based on their safety and needs. If SOAR is feasible as videoconference delivery for transgender women, then we will propose an efficacy study of the intervention to understand the impact on HIV viral load and quality of life. The intervention has the potential to build relationship skills around HIV treatment for transgender women and their partners who are consistently left behind in the HIV response.

Limitations

The one potential study limitation is smartphone ownership or access. Specifically, although smartphone use is high in South Africa, device costs may be prohibitive for some participants. To facilitate participation such that we have representation of transgender women across socioeconomic standing, we will provide smartphones for participants to borrow, or they may access a tablet with headphones at a community site to attend the sessions.

Acknowledgments

The authors would like to thank sexual and gender minority community organizations and leadership for supporting this study in Eastern Cape, South Africa. This study was funded by a supplemental grant to the parent study, National Institutes of Mental Health, R34MH125790.

Authors' Contributions

The study was conceptualized and designed by JD. CB completed data acquisition with data analysis and interpretation by JD, SN, CB, RPP, and LLAVDM. The writing was completed by JD, SN, and SPP with review and revision by JD, LLAVDM, SPP, RPP, CB, and SN. All authors approve and are accountable for the manuscript content.

Conflicts of Interest

None declared.

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Abbreviations

ART: antiretroviral therapy
HR: Healthy Relationships
IDI: in-depth interview
PrEP: pre-exposure prophylaxis
REDCap: Research Electronic Data Capture
SOAR: Speaking Out and Allying Relationships

Edited by A Schwartz; submitted 23.08.23; peer-reviewed by YG Lee; comments to author 07.06.24; revised version received 18.09.24; accepted 05.11.24; published 26.03.25.

Please cite as:
Daniels J, van der Merwe LLA, Portle S, Bongo C, Nadkarni S, Petrus Peters R
Tailoring a Skills-Based Serostatus Disclosure Intervention for Transgender Women in South Africa: Protocol for a Usability and Feasibility Study
JMIR Res Protoc 2025;14:e52121
URL: https://www.researchprotocols.org/2025/1/e52121
doi:10.2196/52121
PMID:

Protocol

Lung Cancer Screening in Family Members and Peers of Patients With Lung Cancer: Protocol for a Prospective Cohort Study

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Abstract

Background: Low-dose computed tomography (LDCT) screening is promising for the early detection of lung cancer (LC) and the reduction of LC-related mortality. Despite the implementation of LC screening programs worldwide, recruitment is challenging. While recruitment for LC screening is based on physician referrals and mass advertising, novel recruitment strategies are needed to improve the enrollment of high-risk individuals into LC screening.

Objective: We aim to identify whether patients with LC can act as advocates to enroll their family members and close contacts into LC screening and whether this strategy increases screening uptake at the population level.

Methods: We designed a prospective cohort study comprising 2 cohorts constituted between June 2023 and January 2024 with a prospective follow-up of 18 months. Patients with LC (cohort 1) are approached at clinics of the McGill University Health Centre, educated on tools for communicating with family members and close contacts about the benefits of LC screening, and invited to refer their close ones. Referred individuals (cohort 2) are directed to this study's web-based questionnaire to assess their LC risk score with the PLCOm2012 (Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial) prediction model. Individuals meeting the eligibility criteria for LC screening (PLCOm2012 score ≥2% and aged 55-74 years) are directed toward the Quebec LC screening program. Data collected include sociodemographic characteristics, health literacy and smoking status (all participants), patient activation (cohort 1), perceived risk of LC, and generalized anxiety at baseline and at 28 days (cohort 2). LDCT completion within 18 months from referral is assessed from health records. Focus groups will identify the barriers and facilitators in the uptake of LC screening and preventative behaviors based on perceived genetic and clinical LC risks. The primary outcomes are the number of referred participants per survivor of LC and the mean risk of LC of the referred population based on PLCOm2012 scores. The secondary outcomes are the proportion of (1) participants eligible for LC screening; (2) participants eligible for screening who complete LDCT screening within 18 months of referral from a survivor of LC; (3) participants showing interest in genetic testing to inform LC risk; and (4) participants showing interest in a smoking cessation program. Multivariable logistic regression will identify the predictive factors of being referred for LC screening. PLCOm2012 scores will be compared for referred participants and controls from the provincial LC screening program.

Results: Overall, 25 survivors of LC and 84 close contacts were enrolled from June 2023 to January 2024, with followed up through July 2025. The results are expected by the end of 2025.

Conclusions: We describe an approach to LC screening referral, leveraging patients with LC as advocates to increase screening awareness and uptake among their family and peers.

Trial Registration: ClinicalTrials.gov NCT05645731; https://clinicaltrials.gov/ct2/show/NCT05645731

International Registered Report Identifier (IRRID): DERR1-10.2196/58529

(JMIR Res Protoc 2025;14:e58529) doi:10.2196/58529

KEYWORDS

lung cancer; low-dose CT; chest tomography; lung cancer screening; patient advocacy; early detection of cancer; referral and consultation; cohort study; patient empowerment; patient experience

Introduction

Background

Almost three-quarters of lung cancers (LCs) are diagnosed at stages III and IV with poor overall survival [1,2]. LC remains the cancer with the highest mortality rate, with high rates of comorbidities also [3,4]. The projected increase of LC burden in Canada calls for improving its early detection and preventative strategies [5]. Low-dose computed tomography (LDCT) screening of high-risk individuals is promising for early detection and reduction of LC-related mortality [6]. With more than 50,000 high-risk individuals enrolled, the pioneering National Lung Screening Trial has shown a 20% reduction in LC-related mortality with LDCT screening compared to standard chest radiography [7]. Evidence supporting this screening strategy was further supported by the NELSON (Nederlands-Leuvens Longkanker Screenings Onderzoek Trial), Pan-Canadian Early Detection of Lung Cancer Study, and UK Lung Cancer Screening Trial [8,9], leading to recommendations for screening high-risk individuals and the implementation of LC screening programs in North America and Europe [10].

The efficiency of LC screening programs relies on the optimization of the risk-benefit ratio and ensuring high participation rates within individuals with a higher risk of LC. Efforts to improve screening uptake within these groups are necessary as the preliminary uptake rates from pilot programs in the United States, Canada, and Europe were suboptimal, with only 4% to 13% of eligible individuals enrolling in LC screening [11,12]. Recent scoping reviews identified the barriers to LC screening uptake, with the most important barriers being the lack of awareness of screening programs, perceived smoking-related stigma, socioeconomic difficulties, and fear of receiving a cancer diagnosis. Furthermore, individuals facing these barriers have concomitantly higher risk of LC [13,14]. For example, in Canada, the highest rates of LC are clustered among individuals living in rural areas with lower socioeconomic status, who also have lower access to screening programs for those geographical and socioeconomic reasons [15,16]. Strategies to reach those most socially disadvantaged groups are thus imperative to guarantee the efficiency of LC screening.

Survivors of LC are empowered with valuable knowledge on their disease's trajectory, from diagnosis to treatment. By sharing their stories within their communities, they can empower other individuals in similar health states. Due to a combination of both genetic and shared risk factors such as smoking or exposure to radon, individuals with a first-degree relative with a history of LC have a 2- to 3-fold higher risk of LC compared to the general population [17]. In a qualitative study, among individuals eligible for LDCT screening per the US Preventative Services Task Force, Roth et al [18] demonstrated that having friends or family members being treated for LC was a major motivator for being screened themselves.

So far, no previous studies have examined the impact of using survivors of LC as sources of education and referral for peers and family members who may be eligible for screening. We hypothesize that survivors of LC would be willing to refer family members or peers to LC screening, leading to a positive impact on the uptake of both the preventative and screening behaviors of the referred population. This study thus aims to determine the feasibility and acceptability of referral to LC screening through patients with LC referring their close ones to LC screening and to assess the early impact of this novel recruitment strategy on the uptake of LC screening and the patients' outcomes.

Objectives

We aim (1) to examine if patients with LC are willing to refer family members or close contacts to LC screening and if referral is associated with increased patient activation; (2) to examine if targeted enrollment of family members or close contacts of patients with LC for LC screening leads to increased engagement of individuals at higher risk of LC compared to referral through usual care; and (3) to examine the barriers and facilitators on the uptake of preventative strategies and LC screening, based on perceived genetic and clinical LC risks.

Methods

Study Design

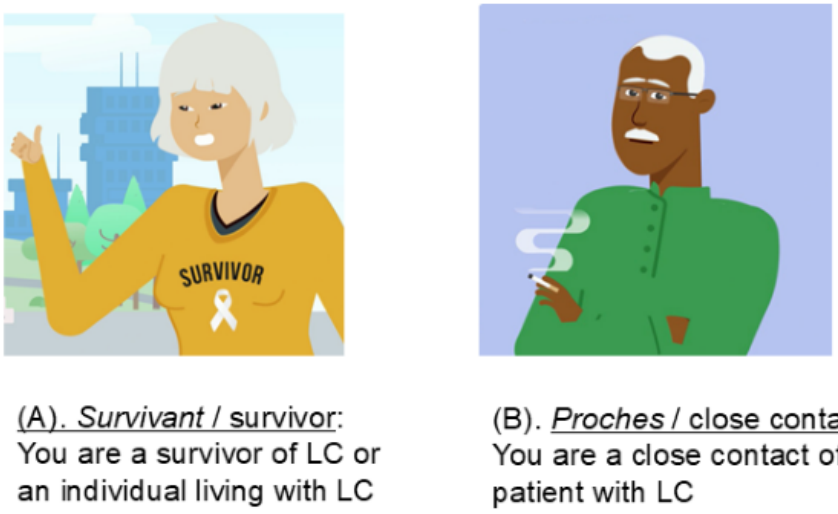
This is a prospective cohort study of 2 separate cohorts.

Participants Eligibility and Recruitment

Cohort 1

The first cohort includes biopsy-proven patients with LC aged older than 18 years at various stages in their disease trajectory, including those undergoing clinical surveillance. Participants in cohort 1 are recruited into this study either through discussion with trained research staff approaching them in the clinical settings or through posters or pamphlets available for viewing in the waiting areas of the clinics. The clinical settings where participants are recruited include the thoracic surgery clinic, pulmonary oncology clinic, pulmonary procedural suites, and chemotherapy infusion centers located at the McGill University Health Centre, one of the largest university hospitals in Montreal, Canada. Recruitment discussions and materials invite these patients to access this study's website [19]. The web page section directed at participants in cohort 1 (Figure 1A) includes educational material on the rationale for LC screening and the methods on how to approach and discuss LC screening with peers and family members.

Figure 1. Screenshot of the web page for survivors of lung cancer and their close contacts. LC: lung cancer.



Patients interested can consent and enroll through this study's website using digital or paper forms. Participants are invited to provide contact information (email or phone number) for the close ones they wish to refer for inclusion in the second cohort of our study. They are also advised to inform their close contacts that they shared their details with the research team and that their informed consent will be mandatory before participation.

Cohort 2

The second cohort includes participants being referred for inclusion into our study by the participants of cohort 1. Referred participants should be aged older than 18 years. Individuals with a personal history of LC are excluded. Referred participants are contacted by our research team through emails, phone calls, or through a recruitment pamphlet mailed for those without internet access. Participants are encouraged to access our study's website [19]. The web page section directed at cohort 2 (Figure 1B) provides general information on LC, its epidemiology, information on LC screening programs and the risk-based eligibility, and information on risk mitigation strategies such as smoking cessation and home radon testing. The enrollment of referred participants is also carried out with a submittable digital form available on this study's website. Participants lacking the digital literacy to enroll by themselves are contacted by the research team to enroll over the phone or through mailed material.

Once enrolled, participants have their 6-year risk of LC estimated with the PLCOm2012 (Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial) risk model [20]. The risk prediction PLCOm2012 model has been extensively validated in previous studies [21,22]. The PLCOm2012 model has also shown adequate properties to discriminate patients with LC in a large cohort of Quebec smokers [23]. Moreover, data from the International Lung Screening Trial have shown that the PLCOm2012 model was more efficient compared to the US Preventative Services Task Force 2013 criteria to identify high-risk individuals to enroll into LC screening programs [24]. Participants who meet the eligibility criteria for the provincial LC screening program (ie, aged between 55 and 74 years and PLCOm2012 score ≥2%) are directed toward the provincial LC screening program to complete LDCT.

Website and Educational Material

This study's website [19] and educational material were developed based on 3 main pillars: accessibility, comprehensibility, and inclusivity. First, we succinctly presented information to account for the health literacy level of the targeted population. Individuals at high risk of LC and with lower education levels are significantly less likely to enroll for LC screening and engage in harm-reduction programs [25], underlining the importance of presenting information comprehensible for all. This study's website content was developed in collaboration with current patients with LC with written material created to be comprehensible at a 5th-grade reading level and above. Second, audiovisual contents are more easily comprehensible and with lower decisional conflict when used as a patient decision aid compared to information presented in textual format [26]. The audiovisual format is also more inclusive of participants with very low literacy. In collaboration with the digital media company Tactica Interactive [27], videos were produced to include the textual information of the website in audiovisual format. Lastly, for participants interested in enrolling in this study but lacking the digital literacy to enroll by themselves, information is provided on this study's website to contact this study's research staff (email address and telephone number).

Outcomes

The primary and secondary outcomes are summarized in Table 1.

Table 1. Study outcomes.

Outcomes	Methods
Primary outcomes	
Number of referred participants per individuals with LC[a] (survivors of LC)	• Questionnaire: cohort 1
Mean risk of LC in the referred population	• Questionnaire: cohort 2 • PLCOm2012 model
Secondary outcomes	
Proportion of participants eligible for the Quebec provincial LC screening program	• Questionnaire: cohort 2 • PLCOm2012 model
Proportion of participants eligible for screening who complete LDCT[b] screening within 18 months from referral	• Provincial health data
Proportion of participants who demonstrate interest in undergoing genetic testing to inform their LC risk	• Questionnaire: cohort 2
Proportion of individuals who demonstrate interest in a smoking cessation program among referred participants who are current smokers	• Questionnaire: cohort 2
Barriers and facilitators in the uptake of LC screening and preventative strategies, based on perceived LC risk	• Focus groups: cohort 1 and cohort 2
Number of visitors on the study's website for referred participants	• Google analytics data

[a]LC: lung cancer.

[b]LDCT: low-dose chest tomography.

Data Collection

Overview

Data are collected using the REDCap (Research Electronic Data Capture; Vanderbilt University) platform [28]. Participants are sent links to complete the web-based questionnaires.

Baseline data collected for all participants include sociodemographic characteristics (age, sex, education level, and ethnicity), health literacy, and smoking status. Health literacy is assessed with the 3-item Brief Health Literacy Screen [29] questions: "How often do you have someone help you read hospital materials?" "How confident are you filling out medical forms by yourself?" and "How often do you have problems learning about your condition because of difficulty understanding written information?" rated on 5-point Likert scales.

Cohort 1

For participants with LC (cohort 1), the phase of LC trajectory (investigative, treatment, or surveillance), tumor stage, performance status (as defined per Eastern Cooperative Oncology Group performance status grading), and their relationship to the referred participants are collected. The degree of self-empowerment they experienced by referring peers and family members for LC screening is assessed using the 13-item Patient Activation Measure (PAM) questionnaire [30]. The 13-item PAM questionnaire is a validated instrument to measure patient knowledge, skills, beliefs, and confidence for self-managing health. Patient activation stands as an important pillar of patient-centered care [31], and evidence has shown that being engaged and active in one's own care is linked to better outcomes [32]. For each participant with LC, the number of unique web page visits is quantified using Google Analytics, and the number of referrals per participant with LC is collected. For participants who refer family members only, supplementary questions are asked to explore the potential barriers: "I don't feel comfortable speaking with friends or close contacts about their health"; "I did not want my friends or close contact who smoke or used to smoke feel judged about their smoking"; "I did not want my friends to worry about their risk of LC"; "Speaking about LC screening and/or LC in general brings up negative emotions for me"; "I don't see or speak with my friends or close contacts very often"; and "This study did not help me feel more comfortable discussing the potential benefits of LC screening."

Cohort 2

For referred participants (cohort 2), the web-based questionnaire collects their known personal history of chronic obstructive pulmonary disease, prior exposure to radon or asbestos, smoking habits, and nicotine dependence using the Fagerström Tolerance questionnaire [33]. Data are used to calculate their PLCOm2012 six-year LC risk. The perceived risk of developing LC is assessed by asking "Compared with others your age, what do you think your chances are of being diagnosed with LC during your lifetime?" rated on a 5-point Likert scale. We also assess whether referred participants believe their risk is high or low due to genetics or smoking exposure and which they think is more important in increasing their lifetime LC risk. Generalized anxiety is assessed at baseline using the General Anxiety Disorder 7-item questionnaire (GAD-7) [34], and a question asks if they believe their anxiety is associated with their perceived risk of LC. We repeat the GAD-7 at 28 days after enrollment to assess the impact of the LC screening risk assessment on anxiety levels. Patients will be asked to give their

consent to access their provincial health records within the 18 months following their enrollment in this study. Extracted data will consist of whether these participants underwent LC screening via LDCT within 18 months after enrollment. No data about the results of the LDCT imaging will be extracted.

Both Cohorts

Focus groups are conducted to explore the perceptions of LC risk (perceptions of genetic risk based on polygenic scores vs perceptions of clinical risk based on PLCOm2012 scores) and their associations with engagement in LC screening and preventative behaviors (such as smoking cessation, radon measurement, and remediation). Qualitative questionnaires and clinical scenarios are presented to this study's participants of both cohorts to explore these themes and elucidate the most prevalent barriers and facilitators toward engagement in preventative behaviors and screening programs. Focus groups will be audio visually recorded and transcribed in verbatims.

Statistical Analysis

Quantitative Analysis

Participants with LC who refer at least one peer for participation will be compared to those who did not refer a peer for participation. To identify the predictive factors of referral, multivariable logistic regression will be used, adjusting for age, sex, educational attainment, health literacy, PAM score, and phase of LC trajectory. The dependent variable in the logistic regression will be referral by patients with LC. Using logistic regression, we will also examine if increased patient with LC activation is associated with increased odds of referral. Chi-square tests and 2-tailed *t* tests will be used for comparisons of categorical and continuous variables.

Referred participants who are eligible for LC screening will be considered as cases. A control group will be selected from patients who were either self-referred or referred by their primary care physician to the Quebec LC screening program and matched by age (1:1). To determine if participants in cohort 2 have a higher risk of LC than the controls, the mean PLCOm2012 scores will be compared using 2-tailed *t* tests in our cohort and in the Quebec LC screening program. The predictive factors of being eligible for LC screening and whether being referred by survivors of LC is associated with increased odds of being eligible will be examined using multivariable logistic regression. We will account for clustering among individuals referred by the same family member using a random effect model.

Spearman coefficients will be calculated to assess the correlations between the actual risk and the perceived risk of LC. Kruskal-Wallis tests will be used to compare actual and perceived risks of LC with different levels of anxiety. Odds ratios and their 95% CIs will be reported. All statistical analyses will be conducted using R (version 4.2.0; R Foundation for Statistical Computing).

Qualitative Analysis

Focus groups consisting of both cohorts will be conducted. For referred participants, the association between their perceived risk of LC based on both their genetic perceptions of risk and their actual clinical risk of LC and undertaking preventative behaviors and screening will be explored.

First, focus groups consisting of both cohorts will be audiovisually recorded and transcribed in verbatims. Responses will be labeled with descriptive codes by 2 independent analysts using NVivo (Lumivero). Interrater agreement and κ coefficients will be calculated to assess intercoder reliability and consensus reached through comparison and discussion within the panel group. The second stage will involve constant comparison, where codes and their content are compared across interviews to discern common and divergent themes. In the final stage, the data will be organized by searching for patterns, variations, and relationships between themes to characterize the entire dataset.

Sample Size

Preliminary data from the provincial LC screening program indicate that 40% of patients either referred to the program by their primary care physician or via self-referral meet the eligibility criteria for LC screening. The McGill University Health Centre receives approximately 800 new patients with LC annually, and the provincial LC screening program receives around 100 referrals each month. With a sample size of 194 referred participants, we will be able to detect a 20% difference in the rates of referral, with a power of 80% and an α value of .05.

Ethical Considerations

This study has been approved by the McGill University Health Centre's Research Ethics Board (MP-37-2023-9041). All participants will provide their informed consent before participation and will be informed that they can withdraw from this study at any time. Informed consent is obtained in either the English or French language through (1) internet-based web forms, (2) phone calls with trained research staff, or (3) completing consent forms in person when approached in one of this study's clinics. To ensure participants fully understand this study's goals when they enroll, three simple comprehension questions are asked being: (1) if this study involves medications (false), (2) if participants will be asked to complete questionnaires (true), and (3) whether they will be asked to refer family and friends (true). If participants have any questions or concerns regarding this study, they can contact our research team via telephone or email at any time (contact information is available on this study's website, pamphlets, and posters).

The REDCap platform used to collect data conforms to the General Data Protection Regulation and Canadian privacy legal and security standards. Access to the REDCap platform is secured with private log-ins and 2-factor authentication. The REDCap database is securely hosted on the Research Institute of the McGill University Health Centre server. No information will be released to unauthorized third parties without prior written approval of the participant except as necessary for monitoring by public health authorities or our institutional research board. Participants will not receive compensation for their enrollment in this study. Those participating in focus groups will be reimbursed on an hourly basis by the Research Institute of the McGill University Health Centre.

Results

Enrollment in the cohorts was conducted from June 2023 to January 2024, with participants being followed up through July 2025. Overall, we have enrolled 25 survivors of LC who have referred 84 of their close contacts to this study. The results of this study are expected to be reported at the end of 2025 through publications in peer-reviewed journals and presentations at relevant national and international conferences.

Discussion

Principal Findings

This paper describes the protocol of a pilot study examining the acceptability, feasibility, and impact of an innovative strategy of referral using patients with LC as advocates to increase the uptake of LC screening among individuals with high risks of LC. Increasing the uptake of LC screening for high-risk individuals is crucial as early detection of LC with LDCT has proved effective in reducing LC-related mortality by 20% and all-cause mortality by 7% [9]. LC screening with LDCT presents unique barriers that hamper the implementation and efficiency of these programs at the population level. In our study, survivors of LC receive education aimed at increasing awareness and enrollment in LC screening programs. We postulate that encouraging survivors of LC to empower and refer their close ones can not only have a positive effect on uptake rates for LC screening but can also improve patient activation and the psychosocial and clinical outcomes of patients with LC themselves.

LC is clustered among individuals with lower socioeconomic status who often also reside in rural areas [15,16,35,36]. The low screening uptake within these subpopulations has been well-established through prior LC screening programs [37]. Determining eligibility for screening is unique to LC screening and requires more extensive shared decision-making discussions between provider and patient compared to other cancer screening programs. As a result, primary care physicians need to dedicate a significant portion of a clinical visit to an LC screening discussion, which can be time-consuming. These subpopulations often face limited access to health care services while concomitantly having a high burden of clinical comorbidities. Thus, health care visits are both limited in frequency and in time as the other comorbidities may require further investigation. A recent study has shown that 67% of primary care physicians would not engage in LC screening discussions if they expected that the discussion would exceed 8 minutes [38]. Placing the referral burden entirely on primary care physicians appears to be unrealistic. These subpopulations with a higher risk of LC may benefit from this approach of encouraging survivors of LC to raise awareness within their social networks and reduce the burden placed on the providers servicing these groups.

As opposed to other cancer screening programs, such as those for breast, colon, and cervical cancers, there is a robust causal association between LC and “self-inflicted” behaviors in individuals at high risk [39]. This perceived smoking-related stigma has a negative psychosocial impact on high-risk patients, leading to self-blame, guilt, and hesitance in discussing their risk of LC with health care professionals and peers [40]. Smoking-related stigma impacts the patient-provider relationships as patients who smoke tobacco are often hesitant to provide an accurate disclosure of their smoking status to their provider and often demonstrate avoidance to discuss topics such as smoking cessation and investigations for ongoing respiratory symptoms. Prior evidence has also consistently shown that this smoking-related stigma leads to delays in seeking medical evaluation when experiencing the presenting symptoms of LC and limits patient involvement in treatment and survivorship care [41]. In turn, this smoking-related perceived stigma leads to hesitancy in seeking enrollment into LC screening programs. Ali et al [42] explored the barriers among high-risk individuals from enrolling in the UK Lung Cancer Screening Trial and determined that current smokers were significantly less likely to enroll in LC screening than exsmokers or never smokers. Compared to nonsmokers, current smokers were more fatalistic and less likely to consider LDCT for LC screening and also less likely to believe early detection would improve their chances of survival [43]. When exploring methods to mitigate the burden of smoking-related stigma, it emerges that current smokers experience the most empathy and can express their emotions more comfortably within support groups made up of other current smokers with similar “lived experiences” [44]. Using preexisting relationships as a forum for open communication and advocacy can therefore be fruitful. Perceived risk of LC can be an important motivator to help balance the negative effects of both practical and emotional barriers and engage in LC screening programs. Interestingly, the perceived risk of LC was positively correlated to the estimated risk of LC in participants from the Pan-Canadian Early Detection of Lung Cancer Study [45]. Furthermore, the perceived risk assessment of LC was associated with higher self-referrals, implying that encouraging individuals to both acknowledge and assess their own perceived risk of LC can be a significant motivator to enroll in screening programs. Using preexisting interpersonal relationships between survivors of LC and close contacts can be fruitful in establishing a forum of open communication to share lived experiences.

This study also aims to show that empowering survivors of LC to engage and motivate close contacts in LC screening and harm-reduction initiatives may have a positive impact on their own clinical outcomes and survivorship. In a recent qualitative study among survivors of LC, the concept of “passing it on”—referring to survivors’ experience with becoming and acting as educators for others—was identified as an important way to address their personal perception of the stigma of LC [46]. Survivors of LC placed significant value on the need to share their stories with their communities, to help family members learn about LC and navigate the health care system. In engaging in a conversation with close contacts regarding LC, they can express how the disease impacted their own well-being from the psychosocial stressors it placed on their mental health, the consequences on their interpersonal relationships, or the physical problems they face daily. Expressing these emotions to their social network may help them feel heard and understood, and in turn, their social network may be more aware and caring of the survivor’s well-being and needs.

Limitations

This study should be interpreted considering the following limitations. First, the recruitment is conducted in clinical settings based on patients receiving in-person care, either through approaching patients with LC directly or via self-referral to our study's website after viewing study-related posters or pamphlets in the waiting areas of clinics. Patients who receive telemedicine follow-up care (such as teleconsultations with health providers and real-time counseling) are then less likely to enroll in this study. This recruitment strategy may introduce a selection bias with a selection of participants in better health states who can participate in this study, living closer to this study's urban health care center, or with a larger social network that supports them in their travel to this study's site. However, this bias appears limited as telehealth for LC care remains marginal at our institution, as also stated in a review of telehealth in LC during the COVID-19 pandemic [47].

Second, when potential participants are approached in person or view our study's recruitment material in the clinics, those accompanying them are exposed to the same discussion and material. Therefore, the referred cohort may be biased to preferentially include the first-degree relatives of survivors of LC as these are the close contacts most likely to accompany patients to their clinical appointments. Friends or more distant relatives of survivors of LC may ultimately be underrepresented in the referred cohort.

To finish, this study is conducted among a cohort of residents in Quebec, where public health care expenses are covered for citizens. The generalizability of the results is limited to similar populations and health care systems, and caution is needed when generalizing results to other Canadian provinces or countries.

Future Directions

Primary care health providers and mass advertising are the current methods of recruitment to LC screening programs. In Canada and the United States, most participants who are eligible for LC screening are being referred to screening programs by a health provider. Barriers related to health care services access then limit the uptake of LC screening, notably in Canada, where approximately 15% of patients are unattached to a regular primary care provider [48]. This lack of providers per population is even worse in Quebec and is expected to worsen with the current population ageing. Developing new strategies to identify and enroll high-risk individuals into LC screening programs is crucial to ensure the success of implementing those programs and, in the end, to improve the patients' outcomes.

Conclusion

Early diagnosis of LC can improve survival rates, and strategies are needed to engage high-risk individuals in LC screening. We believe that patient advocacy has an important value and could be harnessed to identify high-risk individuals to participate in LC screening. Patients with LC have a unique role to play as advocates, and by sharing their lived experience, they could improve the motivation and engagement in LC screening and preventative strategies for their close ones. This study will provide evidence on the feasibility, acceptability, and early impact of this novel referral strategy. The results will be of interest for public health programs and policies, as well as for clinicians, patients facing LC, and their close ones.

Acknowledgments

We thank Tactica Interactive multimedia company for its collaboration in creating the content for this study's website and educational material.

Conflicts of Interest

None declared.

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Abbreviations

GAD-7: General Anxiety Disorder 7-item questionnaire
LC: lung cancer
LDCT: low-dose computed tomography
NELSON: Nederlands-Leuvens Longkanker Screenings Onderzoek Trial
PAM: Patient Activation Measure
PLCOm2012: Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial
REDCap: Research Electronic Data Capture

Edited by S Khan; submitted 18.03.24; peer-reviewed by M Arab-Ahmadi, AT Matthews; comments to author 14.05.24; revised version received 09.11.24; accepted 22.11.24; published 28.03.25.

Please cite as:
Pitrou I, Petrangelo A, Besson C, Pepe C, Waschke AH, Agulnik J, Gonzalez AV, Ezer N
Lung Cancer Screening in Family Members and Peers of Patients With Lung Cancer: Protocol for a Prospective Cohort Study
JMIR Res Protoc 2025;14:e58529
URL: https://www.researchprotocols.org/2025/1/e58529
doi:10.2196/58529
PMID:

Protocol

Assessment and Intervention for Diabetes Distress in Primary Care Using Clinical and Technological Interventions: Protocol for a Single-Arm Pilot Trial

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Abstract

Background: Diabetes distress (DD) is a common emotional response to living with diabetes. If not addressed, DD can have negative impacts on diabetes management, including the progression to mental health conditions such as depression and anxiety. Routine screening and treatment for DD is recommended, with primary care being an ideal setting given that the majority of people with diabetes receive their diabetes care from primary care providers. However, consistent screening of DD does not routinely occur in primary care settings. Research is needed to understand how to effectively and feasibly integrate DD screening and treatment into routine diabetes care.

Objective: This study aims to (1) design and implement individualized technology-supported DD workflows, (2) evaluate the primary outcome of determining the acceptability and feasibility of integrating technology-based workflows to provide treatment for DD, and (3) evaluate the secondary outcomes of changes in DD, depression, and anxiety (baseline, 3 months, and 6 months) in patients receiving screening and personalized treatment.

Methods: In total, 30 English and Spanish-speaking primary care patients with either type 1 or type 2 diabetes will receive screening for DD during clinical visits and subsequent support from an artificial intelligence (AI)–based health care chatbot with interactive tailored messaging. In addition, the use of electronic consultation with a specialist or referral to a behavioral health provider could occur depending on the severity and source of DD. The use of electronic consultations allows providers convenient and timely asynchronous access to a range of specialty care providers. Health outcomes will be measured through changes in validated screening measures for DD, depression, and anxiety. Digital outcomes will be measured through surveys assessing user experience with technology and system usability, and by system performance data. Qualitative data on acceptability and satisfaction with the clinical workflows and technological interventions will be collected through interviews with patients and clinical providers. Descriptive statistics will summarize quantitative outcome measures and responses to closed-ended survey items, and rapid thematic and content analysis will be conducted on open-ended survey and interview data.

Results: Workflows for screening and treating DD have been approved and clinical staff have received training on the process. Electronic surveys for screening measure collection have been created. Data from visit screeners will be entered into the electronic medical record during the medical appointment. Recruitment will begin late June-July 2024.

Conclusions: This study is expected to demonstrate the feasibility and acceptability of integrating individualized workflows for DD into primary care. Improving clinical and digital interventions for addressing DD in primary care can provide alternative

care options for busy clinical providers. This study is intended to deliver whole-person diabetes care to people with diabetes within a primary care setting.

International Registered Report Identifier (IRRID): PRR1-10.2196/62916

(JMIR Res Protoc 2025;14:e62916) doi:10.2196/62916

KEYWORDS

diabetes care; diabetes distress; primary care; healthcare chatbot; artificial intelligence; eConsult; care pathways; clinical workflows

Introduction

Backgrounds

In the United States, diabetes is the eighth leading cause of death [1], with an estimated 38 million people living with diabetes [1]. This chronic condition requires consistent care for effective management to help avoid poor health outcomes [2]. In fact, it is estimated that people with diabetes spend over 8000 hours per year managing their diabetes outside of medical settings [3]. Diabetes distress (DD) is the disruptive and demanding emotional response to these daily demands of living with diabetes [4]. This emotional burden associated with diabetes is pervasive, with one in 4 people experiencing severe DD [4]. DD is associated with negative impacts on engagement in self-care and self-management behaviors, medication adherence, and exacerbation of mental health conditions [5].

Accordingly, the American Diabetes Association recommends that diabetes care be delivered by an interdisciplinary team with a person-centered approach [6] and that it includes regular screening for and monitoring of DD in routine diabetes care for people with diabetes with treatment for DD to be provided by practitioners with specific training to address DD [5]. In addition, a recent white paper by the National Committee for Quality Assurance suggested having a variety of pathways to tailor DD treatment for individuals who screen positive for DD by involving relevant health care professionals and care modalities [7]. Yet, in everyday clinical settings, DD is infrequently identified and only a small number of people with diabetes are asked about how diabetes affects their life by their health care professionals [8]. As primary care is where most people receive their diabetes care, it is a crucial setting within which to assess and address DD [9,10]. However, there remains a lack of consistent screening for DD within primary care, which likely contributes to the emotional burden of diabetes going undetected and untreated [4,11]. Thus, even though DD is highly prevalent and there exist well-validated measures to assess for DD, there is a significant knowledge gap in best practices for implementing DD screening and treatment interventions systematically in primary care. Intervention studies specifically aimed to treat DD have largely been conducted in specialty care settings and not in primary care [5]. Further, among health care providers there remain a lack of awareness of DD and a shortage of trained health care providers who feel adequately equipped to assess for DD and intervene when a patient is experiencing DD [12]. Consequently, there is a clear need to develop scalable and feasible workflows and interventions that can be easily incorporated into primary care settings. Implementing assessment and treatment for DD is a crucial part of incorporating the psychological and emotional aspects of living with diabetes into routine diabetes care. It is part of intentionally incorporating the often-forgotten about psychological and emotional aspects of diabetes care that comprise whole-person care.

Clinical decision support systems (CDSS) have proven effective in prompting providers to deliver recommended care [13]. In general, CDSS improves health care delivery through the use of technology to enhance clinical decision-making, sometimes even using data and observations that are normally unobtainable by providers alone [14]. Clinical decision support technology leverages electronic health records (EHRs), medical knowledge databases, and algorithms to provide patient-specific recommendations, thus enabling providers to make more informed decisions [15]. Benefits can include a reduction in medical errors, enhanced patient safety, improved decision-making, and scalability [15]. The recent integration of artificial intelligence (AI) into health care technology has led to the classification of CDSS as either knowledge-based systems using traditional technology frameworks, or nonknowledge-based systems to indicate the use of AI to transform data into information for the user [16]. Recent reviews of studies that focus on the implementation of nonknowledge-based CDSS in diabetes care have demonstrated significant improvements in patients' blood glucose, blood pressure, and lipid profiles in 71%, 67%, and 38% of the studies, respectively [16]. Technology-based referrals to specialty care electronic consultation (eConsults) have been shown to successfully augment and support care provided in the primary care setting without requiring patients to leave their medical home. Curated health chatbots are an interactive, patient-focused approach to providing patients with important information in an empathic manner at the time of need and point of inquiry, without requiring appointments or waiting for return calls from highly burdened health care professionals. While CDSS can promote diabetes care by facilitating patient self-management, it is hoped that further emerging technology will allow for more efficient and effective management for many people living with diabetes [16].

Research examining the treatment of DD indicates that when DD is specifically targeted that it can be improved, which is important given that DD is known to worsen over time if it is not addressed [17]. eHealth interventions providing support for DD have shown promising results. For instance, a systematic review and meta-analysis concluded that eHealth interventions were effective at significantly reducing DD and that these reductions occurred across a range of different eHealth interventions (eg, telehealth, web-based, and mobile health) [18]. While the eHealth interventions were found to reduce DD, the authors of the meta-analysis indicate the results be

interpreted with caution because of the low number of studies included in the review [18]. Additional research delivering DD interventions through flexible and affordable eHealth avenues requires further exploration. This study is intended to build upon previous research suggesting that digital interventions could provide an avenue for treating DD.

Objective and Aims

The primary objective of this study is to assess the feasibility and accessibility of using health IT integrated into primary care workflows to improve screening and treatment for DD. This project will examine the technical and operational feasibility, patient and provider experience, and behavioral health outcomes of a new technology-supported workflow to conduct screening for DD and provide follow-up treatment by a multidisciplinary team in a primary care setting.

The aims of this pilot study are to (1) design and implement individualized technology-supported DD workflows, (2) evaluate the acceptability and integration of technology-based workflows to provide treatment for DD, and (3) evaluate the change in DD (baseline, 3 months, and 6 months) in patients receiving screening and personalized treatment for it. Symptoms of anxiety and depression will also be evaluated. The primary outcome of this study is to determine the feasibility and acceptability of integrating individualized workflows for DD into primary care.

Methods

Intervention Implementation Process

Preimplementation

The principal investigator (PI) conducted a 1-hour practice-level training session for clinical team members including primary care practitioners, medical assistants, administrative staff, and behavioral health providers. The training topics included an orientation to DD, person-first language when working with people with diabetes, a review of the DD screeners, and a brief introduction on how to support patients experiencing DD. This training was informed by expertise from clinical experts on DD. The training also reviewed the clinical workflow for this study and provided the opportunity for staff and providers to ask questions about the protocol.

Implementation

Patients will complete informed consent to participate in the research study. After being consented, they will attend a scheduled diabetes-specific visit with their primary care physician (PCP). The workflow for the diabetes-specific visit is presented in Figure 1. At clinic check-in, front desk staff or a medical assistant (MA) will provide the patient with the appropriate assessment to complete based on their diagnosis, either the Type 1 Diabetes Distress Assessment System (T1-DDAS) [19] or the Type 2 Diabetes Distress Assessment System (T2-DDAS) [20]. Clinic staff will also provide the patient with the Patient Health Questionnaire-9 (PHQ-9) [21] to assess for symptoms of depression and the Generalized Anxiety Disorder-7 Scale (GAD-7) [22] to assess for symptoms of anxiety. The PHQ-9 and GAD-7 questionnaires are already part of the rooming process and thus not an addition to the established workflow. During the visit rooming process, the MA will enter the results of the screeners (eg, PHQ-9, GAD-7, T1-DDAS, or T2-DDAS) into the flowsheets in the EHR. The EHR used in this study is Epic. Refer to Table 1 for measure descriptions.

Figure 1. Primary care diabetes distress screening and treatment workflow. AI: artificial intelligence; eConsult: electronic consultation; MA: medical assistant; PCP: primary care physician.

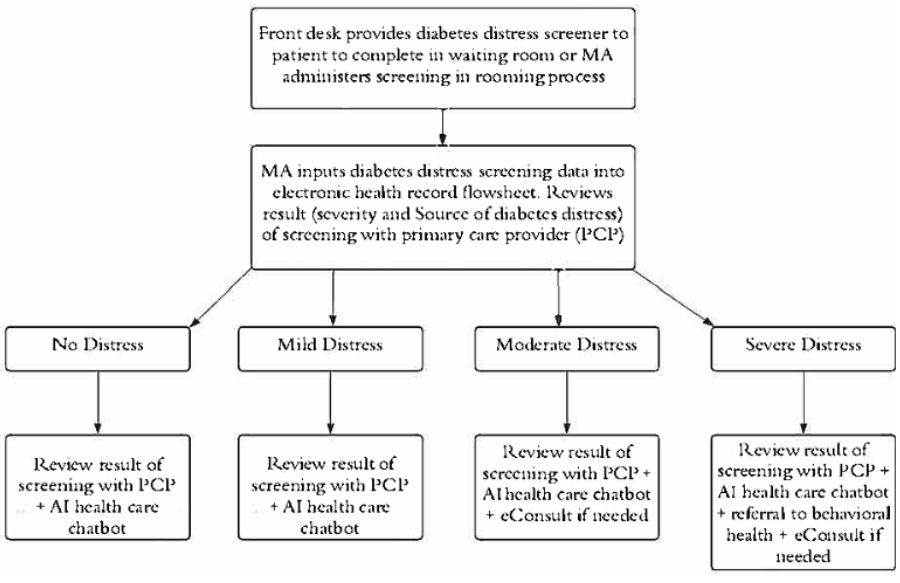

Table 1. Diabetes distress pilot study measures.

Measure	Description	Collection time points
T1-DDAS[a] [19]	• 30 items; 5-point Likert scale. • Assesses the emotional impact of living with type 1 diabetes. Determines the severity and Source of DD[b]. The sources of DD indicate which aspects of living with type 1 diabetes are creating challenges. • The T1-DDAS was validated with adults with type 1 diabetes and has adequate internal consistency on the Core Scale (α=0.95) and Source Scales (α range=0.53-0.88).	• Baseline (at initial clinic visit) • 3 months post screening • 6 months post screening
T2-DDAS[c] [20]	• 29 items; 5-point Likert scale. • Assesses the emotional impact of living with type 2 diabetes. Determines the severity and source of DD. The Sources of DD indicate which aspects of living with type 2 diabetes are creating challenges. • The T2-DDAS was validated on people with type 2 diabetes including both insulin and noninsulin users. Adequate reliability for the Core scale was demonstrated by alpha statistics for noninsulin users (α=0.94) and insulin users (α=0.95). The Core Scale has statistically significant construct validity with the 7 Source Scale criterion variables (all, P<.001).	• Baseline (at initial clinic visit) • 3 months post screening • 6 months post screening
PHQ-9[d] [21]	• 9 items; 4-point Likert scale. • Brief screener assessing symptoms of depression. Amongst a primary care population, the internal reliability was excellent (Cronbach α=0.89) [21]. • The PHQ-8[e] omits question 9 on the PHQ-9, which asks respondents about thoughts of self-harm or death.	• Baseline (at initial clinic visit) • 3 months post screening • 6 months post screening
GAD-7[f] [22]	• 7 items; 4-point Likert scale. • Brief screener assessing symptoms of anxiety. The reliability of the weighted scoring of the items on the GAD-7 has been estimated at 0.91 with internal consistency estimated at 0.92.	• Baseline (at initial clinic visit) • 3 months post screening • 6 months post screening
UMUX-lite[g] [23]	• 2 items; 7-point Likert scale. • Brief measure assessing participant's experience of technology (ie, AI[h] chatbot). Internal reliability estimates for the UMUX-lite range from 0.81-0.87).	• 3 months post screening
System Usability Scale [24]	• 10 items; 5-point Likert scale. • Brief measure assessing the usability of the technology (ie, AI chatbot). Research demonstrates an average reliability using coefficient alpha to be 0.91. Concurrent validity ratings range from 0.22 to 0.96.	• 3 months post screening
Technology Use Assessment [25]	• A 12-item survey assessing user's comfort with and routine use of technology in daily life.	• Baseline (at initial clinic visit) • 3 months post screening
Practice demographics	• Clinic data (ie, number of patients with diabetes, clinical staff, and roles).	• Baseline
AI Chatbot System Performance Metrics	• Engagement and operational metrics recording during the period of system use.	• 3 months post screening
eConsult[i] System Performance Metrics	• Operational metrics recorded during system use from study-specific standardized templates, including the number of patients receiving eConsults, which specialists were eConsulted, what were the consult questions, the time to respond by the specialist, and did the patient follow up with the specialist if referred.	• 3 months post screening • 6 months post screening
Patient demographics	• Includes age, race, ethnicity, gender, sexual orientation, health care insurance type, and comorbid medical diagnoses if applicable.	• Baseline
Qualitative data-clinical staff	• Semistructured interview and survey questions. • Questions assessing experience implementing new workflows and screening patients for DD from clinical staff. A trained qualitative researcher will conduct interviews over the phone or video call according to the semistructured interview guide.	• 3 months post screening

Measure	Description	Collection time points
Qualitative data-patients	• Semistructured interview and survey questions. • Questions assessing participants' experience of being screened for DD, using an AI chatbot, and being referred to targeted providers using eConsults. A trained qualitative researcher will conduct interviews over the phone or video call according to the semistructured interview guide.	• 3 months post screening
Diabetes Distress Provider Time Survey	• Survey form tracking the types of tasks and amount of time spent on tasks related to workflow.	• Primary care physician completes following each participant encounter.

[a]T1-DDAS: Type 1 Diabetes Distress Assessment System.

[b]DD: diabetes distress.

[c]T2-DDAS: Type 2 Diabetes Distress Assessment System.

[d]PHQ-9: Patient Health Questionnaire-9.

[e]PHQ-8: Patient Health Questionnaire-8.

[f]GAD-7: Generalized Anxiety Disorder-7 Scale.

[g]UMUX-lite: Usability Metric for User Experience-lite.

[h]AI: artificial intelligence.

[i]eConsult: electronic consultation.

If there is a negative screen on the T1-DDAS or T2-DDAS, the MA will communicate this to the PCP. The PCP will then provide validation and encouragement based on the skills they learned in the team training. The patient and provider will then collaboratively determine which aspects of DD the patient would like to start to receive information and guidance on from the AI chatbot. Even though the patient is not currently experiencing DD, it is theorized that receiving coping skills and other information from the chatbot will help mitigate future distress. The PCP will send these identified areas through the EHR to the research team so they can send push notification from the AI chatbot to the patient's cell phone in these specific areas.

If there is a positive screen on the T1-DDAS or T2-DDAS, the MA will communicate the severity and source of DD to the PCP. On the T1-DDAS there are 10 sources of distress including financial worries, interpersonal challenges, management difficulties, shame, hypoglycemia concerns, health care quality, lack of diabetes resources, technology challenges, burden to others, and worries about complications [19]. The T2-DDAS indicates specific areas or sources of distress that people with type 2 diabetes may experience [20]. On the T2-DDAS there are 7 sources of distress including hypoglycemia, long-term health, health care provider, interpersonal issues, shame or stigma, health care access, and management demands [20]. The research team has developed specific content areas for sources of distress for both the T1-DDAS and T2-DDAS meant to provide targeted and individualized material to support the needs of patients delivered through the AI chatbot. The study design for levels of DD is the same for type 1 and type 2 diabetes. There are three levels of distress on the T1-DDAS and T2-DDAS: (1) little or no distress, (2) moderate, and (3) high. The levels and source of distress will guide clinical decision-making and intervention pathways that are selected. For each level of distress, the PCP will provide validation and support to patients based on skills they learned during the team training. For little to no distress on the T1-DDAS or T2-DDAS, the PCP will discuss the top 3 sources of distress with the patient and the patient will then obtain a push notification on their cell phone from the AI chatbot on these specific areas. For moderate levels of DD on the T1-DDAS or T2-DDAS, the provider will discuss the main sources of distress with the patient and determine if an eConsult or referral might be indicated based on the needs of the patient in addition to the AI chatbot. An eConsult to the following specialists can include endocrinology, clinical pharmacy, social work or care management, diabetes education, and behavioral health. All these specialty providers are available in the primary care practice where this study will occur. For high levels of DD on the T1-DDAS or T2-DDAS, the PCP will collaboratively determine which areas of distress would be more relevant for the patient to receive from the AI chatbot and determine if an eConsult to any of the above-stated specialties would be indicated and then subsequently discuss and provide a referral to behavioral health if needed. Integrating eConsults into the treatment process allows the PCP to ask a specific clinically oriented question about their patient and obtain an asynchronous response from the specialist. Thus, allowing for shared care decisions between the PCP and specialist without having to refer the patient to an in-person appointment and leading to a possible delay in care [26].

AI Chatbot Intervention

All patient participants, regardless of whether they have DD or the severity of the DD, will be enrolled to receive text messages from the AI chatbot. The AI chatbot will provide education on DD, normalization of DD, suggestions for solution-focused coping strategies, and information provision on patient resources and support. For patients not reporting symptoms of DD, chatbot messaging will be seen as a preventative measure to provide information and build awareness of DD should this arise in the future. For patients reporting DD, the AI chatbot will be seen as a resource to provide suggestions for coping strategies connecting to local support resources and psychoeducational material. Following a collaborative discussion with their PCP on the sources of DD that they would like to receive support on, they will obtain a push notification with the top 3 identified areas of distress. Following this initial conversation, the AI

chatbot will deliver a 12-week curriculum on topics specifically related to DD and the sources of DD (for either the T1-DDAS or T2-DDAS). Participants will receive 3 scheduled text messages on the curriculum content per week throughout the 12 weeks to their cell phone. In between scheduled messages, participants can initiate interaction with the AI chatbot through the text message chain if they choose. Development of the AI chatbot content was overseen and reviewed by DD expert consultants. Participants will not receive messages on topics unrelated to DD or content that was not developed and approved by the study team. In other words, participants will not receive content that is generated by the system or off-topic.

The technology will facilitate error-free delivery of messages via text to user cell phones using an AI chatbot that deploys natural language processing for highly precise communications. We will maximize chatbot precision so that users are more often sent a response from our system that matches the intent of their query. Specifically, we have developed and categorized anticipated "intents"—that is, the specific topics we believe people want to learn or ask about DD and self-management, along with 25-50 variations on ways to ask each question. Question variations allow the system to have enough initial data to learn how to interpret user questions, tolerate misspellings, and recognize the underlying intent of each question. When the system cannot match a response to the question intent, it reverts to a fixed choice (called a "pick list") of responses, for example, "I think you are asking about one of these topics: (1) Cost of diabetes medicine, (2) Cost of treatment, (3) Where to find medications near me. Please type the number corresponding to the topic you wish to explore or try your question again." We rely on data augmentation techniques to create and continuously update a robust library of questions and question variations that the system draws on to generate precise and consistent responses to user queries. We do this through "lemmatization" and "stemming," both processes that group the different inflected forms and stems of a word so they can be analyzed as a single item (eg, runs, run, and running are all forms of the word "run" and thus "run" is the lemma, or root, for all these words). After doing this preprocess work on our prototype dataset, we use Multinomial Naïve Bayes, Linear SVC, and multiclass regression algorithms to anticipate prediction accuracy in correctly matching a response to a question.

eConsult Intervention

The EHR-embedded eConsult system provides a streamlined and timely consultative process that has been shown to improve the quadruple aim-related outcomes and to enhance communication and coordination of care between primary care providers and specialists regarding specific patient areas of concern [27]. The PCP sends a focused question with relevant subjective and objective patient information to a specialist through the eConsult system. The specialist then reviews pertinent information from the EHR and responds to the PCP with guidance and care support with recommendations regarding diagnosis, treatment, and follow-up plans.

Following the patient-specific interaction with the PCP in the diabetes-specific visit, an eConsult with different specialties (indicated above) will be placed through the EHR. The eConsult system is already an established part of routine clinical care since it is embedded in the EHR. eConsults will be used to assist with clinical decision-making and obtaining specialized knowledge and support from various health care professionals based on the specific source of DD. If the patient requires additional support, the eConsult system will allow for a conversion to an in-person or telemedicine visit with the needed specialty.

Poststudy Intervention

Poststudy time point 1 (3 months following initial screening): the research assistant (RA) will send patients a link to complete the screening measures through the patient portal. The screening measures completed at 3 months post screening will assess for DD, symptoms of depression and anxiety, and technology use (refer to Table 1). Outside the clinical setting, the PHQ-8 will be administered instead of the PHQ-9 [28]. The technology measures include the Usability Metric for User Experience-lite (UMUX-lite) [23], System Usability Scale (SUS) [24], technology use assessment, AI chatbot system performance metrics, and eConsult system performance metrics. Qualitative data will be collected at 3 months post screening. Table 1 includes the measures and time points for data collection. The RA will call each patient to conduct a semistructured interview and ask survey questions if patients have not completed surveys electronically within 1 week. The qualitative interview will include questions about participating in screening for DD, experience with the AI health care chatbot and being referred to specialty providers through eConsults. Further, the RA will obtain qualitative data through semistructured interviews and survey questions with 6 clinical staff and both primary care providers who participated in the study. The questions for health care staff or providers will assess their time spent and experience implementing workflows that screen for DD and offer treatment options through provider support, AI health care chatbot, and eConsults.

Poststudy time point 2 (6 months following initial clinic visit): the RA will send patients a link to complete the screening measures through the patient portal at the 6-month time point. The screening measures completed at the 6-month time point are included in Table 1. If patients do not complete the surveys electronically within 1 week, the RA will call to follow up and administer surveys via phone.

Study Design

We propose a pilot clinical trial to be conducted at a suburban multidisciplinary family medicine practice in an academic medical setting. The study is designed to provide feasibility and acceptability data for the development of DD-based screening and treatment using digital and clinical interventions.

Participants

Up to 30 adult English- or Spanish-speaking patient participants with a diagnosis of type 1 diabetes or type 2 diabetes who receive their diabetes care from 2 PCPs at the primary care practice will be enrolled in the study. For Spanish-speaking participants, Qualified medical interpreters are used for translation services that are provided at no cost at the clinic. Qualified medical interpreters are part of routine medical

services. A sample size of 30 is the minimum generally recommended if the underlying population is expected to have a normal distribution [29]. It is also double the minimum recommended number of persons to be included in human factors and usability testing for medical devices, which allows for loss to follow-up or nonparticipation by some individuals in data collection activities [30].

Clinic staff engaged in the new workflows for DD will also be invited to participate in surveys and interviews about their experience with the technology-supported intervention following the completion of the study. Inclusion and exclusion criteria are mentioned in Textbox 1.

Textbox 1. Inclusion and exclusion criteria.

Inclusion criteria

- Age at time of consent 18-89 years;
- Diagnosed with type 1 or type 2 diabetes;
- Patient at the primary care clinic;
- Able to understand English or Spanish;
- Willing and able to sign the informed consent form;
- Willing to be contacted by the study team through the patient portal, phone, or text to complete study measures;
- Ability to reliably send and receive text messages.

Exclusion criteria

- Participation in another study that might interfere with participation in this study;
- Unable to follow the study procedures for the duration of the study or is deemed unacceptable to participate in the study per principal investigator judgment;
- Participant or participant's immediate family member is an employee of the health care chatbot company providing services for the study;
- Planning to move in the next 6 months;
- Planning to change primary care practices in the next 6 months.

Data Collection and Outcome Measures

Both qualitative and quantitative methods will be used to assess study outcomes at the patient level, practice level, and technology system level. Patient-level health outcomes include DD, depression, and anxiety measured at baseline, 3 months, and 6 months using the T1-DDAS or T2-DDAS, PHQ-8, and GAD-7. The T1-DDAS was selected to be used in this study because it is the most updated and comprehensive assessment tool for determining DD in people with type 1 diabetes. The T2-DDAS was used as a measure because it is the most comprehensive and contemporary survey tool to determine DD among people with type 2 diabetes. The PHQ-9 and GAD-7 are commonly used brief screeners in primary care [21,22]. User experience with technology will be assessed through the administration of the UMUX-lite at 3 months, the SUS at 3 months, and a technology use assessment at baseline and 3 months. The SUS is widely adopted as a reliable measure of usability across technology types and in a variety of populations. The UMUX-lite represents a user experience-focused usability measure that has proven to correlate well with the SUS in overall usability and is appropriate for use with health technologies. The technology use assessment was previously developed by a member of the research team for use in discerning technology adoption and use patterns with primary care patients [25]. In addition, qualitative data from interviews and responses to open-ended survey items will be collected from practice staff, PCPs, and patients to determine the acceptability and feasibility of implementing screening and technology-supported treatment for DD. Interviews will be conducted by a trained qualitative analyst according to a semistructured interview guide, recorded and transcribed using artificially intelligent transcription software (Otter.ai), with human adjudication of transcripts to avoid error (refer to Multimedia Appendices 1 and 2 for interview guides). Positive experiences with the digital interventions will be determined by participant responses to the qualitative interview questions. Further, PCPs will complete the DD Provider Time Survey to track activities and time spent on workflow tasks. Acceptability with the eConsults will be evaluated by standard data collection protocols in the EHR. eConsult data will capture the patient-specific inquiries and requests from PCPs and responses given by specialists. AI chatbot performance data will be collected from the chatbot system and used to evaluate engagement with the AI chatbot according to the People at the Center for Mobile Application Design framework [31]. Table 1 lists the measures to be collected for this study in detail.

A number of the validated measures have existing published versions in both English and Spanish including the T1-DDAS, T2-DDAS, PHQ-8, and GAD-7. For outcomes measures including the UMUX-lite, SUS, and the technology use assessment that did not have an available version in Spanish, we had a system-verified language translator assist in translating these materials from English into Spanish.

Data Analysis

Quantitative Data Analysis

The study team will use standard statistical packages (eg, R [R Foundation for Statistical Computing]) to conduct data analysis. Descriptive statistics (means, SD, frequency distributions, and proportions) will be used to summarize baseline patient characteristics, clinical and behavioral outcomes, and other quantitative outcome measures and responses to closed-ended survey items. As a feasibility study, it is not powered for inferential analyses or power analyses, but the results are expected to inform future work. Based on results from similar studies, a 60% (18/30) threshold will be used to determine technical and operational feasibility and user acceptability, that is, 60% (18/30) of participants remain engaged with the technology solutions throughout the duration of the study, and 60% (18/30) of participants report positive experiences and satisfaction levels with the program overall [32]. The study has been planned to minimize the amount of missing data overall and thus anticipates the use of maximum likelihood methods to estimate missing values for statistical analysis. We will use this data to calculate an effect size to power a larger study.

Qualitative Data Analysis

This study's acceptance is determined by patient and health care provider user experience through interviews, clinical team member feedback, and responses to user experience surveys. An overall positive rating on tailored survey items or positive themes identified from qualitative data represents acceptability for this study. The program will be deemed acceptable among participants overall if 60% (18/30) or more of participants report positive ratings and themes. Qualitative analysis of open-ended survey data and interview data will be conducted using rapid thematic and content analysis to assess user experience by identifying and exploring common topics and themes that emerge from participants' responses. The rapid analysis will be informed by the Consolidated Framework for Implementation Research and will use a dual-read approach and matrix classification method with 2 reviewers, who will discuss classification decisions to achieve consensus [33]. Enough participants are included in the planned sample size to ensure qualitative analyses will reach thematic saturation overall.

Ethical Considerations

Approval and Study Consent

This study has been approved by the Colorado Multiple Institutional Review Board (protocol #24-0186). The PI and primary care providers will assemble a patient list from the Diabetes Registry in the EHR and send this to the RA. The RA will outreach to potential participants via the patient portal in the electronic medical record, by email, and by phone using scripted language to invite patients to participate. As part of enrollment, the patient will opt-in to receive text messages from the AI chatbot. If a patient declines to participate, this will be documented for evaluation purposes so that the same patient is not reapproached in association with a future scheduled clinic visit. If the patient expresses interest in participating, the research team will complete informed consent and study enrollment before a future clinic visit. As part of the consent process, patients will agree to a chart audit by the research assistant within 4 weeks of their initial visit to ensure all initial measures are completed.

Safety and Potential Risks

The procedures used in the proposed research study pose no greater than minimal risks to patients and practices involved in the study. The AI chatbot is a nongenerative system meaning that it does not independently develop content. The primary clinical team has generated the content and reviewed it with expert consultants on DD. Further, no Protected Health Information is requested from patient participants or sent from the AI chatbot. The AI chatbot operates on HIPAA (Health Insurance Portability and Accountability Act)-compliant infrastructure under a business associate agreement between the health care system where this study is taking place and the AI chatbot company. During the course of this study, patients could experience worsening of their symptoms of DD as a result of interacting with the AI chatbot and discussing the emotional and psychological aspects of diabetes with their medical provider. However, we do not expect that these are likely risks for patients participating in the study in part because messages provided by the chatbot have been prewritten and approved by clinicians and the chatbot is not using in-the-moment generative AI technologies to respond, such that it cannot create separate content or go off-script. If these concerns arise through a review of messages and chatbot interactions or as reported by patients, the PI will review and refer as appropriate to other health care providers for follow-up. The clinic where this study will take place has fully staffed behavioral health providers integrated into the practice who will be available to discuss any concerns that providers and patients may experience.

Compensation

Patient participants will receive a small financial incentive at 2 separate time points. They will receive two US $25 gift cards (totaling US $50). The first US $25 gift card will be given after enrollment in the study and completing the first set of surveys. The second US $25 gift card will be given after completing the 3-month postscreening questionnaires. Providers will receive no direct financial incentive. The primary care clinic where this study will take place will receive a financial incentive for participating in and attending the team training.

Results

Implementation Status

The PI met with clinic leadership to describe the project and obtained buy-in from the team. Workflows were developed that outline study design and patient flow (refer to Figure 1). The PI conducted a team training with the clinic where this study will take place as well as met with the PCPs that will be participating in this study to provide education and training on DD, an overview of validated measures for DD (eg, T1-DDAS and T2-DDAS) and conversational tools that can be used to support people with diabetes and DD.

T1-DDAS and T2-DDAS scoring were incorporated into the EHR through an EHR build. The PI collaborated with the EHR administrative team on requesting the 2 DD measures be

incorporated into the EHR. This was done during the annual optimization and training period, namely the Epic Sprint program [34]. This program is intended to improve the users' experience of the EHR and assist with updates and requests. The DD measures were built into the EHR as flowsheets so that data could be entered and scored in the EHR.

Chatbot content specific to DD was developed with assistance from 2 leading diabetes psychologists with expertise in DD. The AI chatbot was field tested by the primary research team and the project was reviewed with patients with diabetes through a patient advisory committee including 8 members and feedback was incorporated in refinements of the chatbot content. Key feedback that was incorporated included the frequency of chatbot messages and the time of day that chatbot messages would be sent. The primary research team field-tested the chatbot by sending and receiving text messages to their cellular phones and documented any errors, challenges, or missing content that they experienced. This information was reviewed and discussed with the chatbot vendor and incorporated into the chatbot analytics and content library. The field testing and feedback process was repeated twice.

Recruitment Status

Patient recruitment is anticipated to begin during late June-July 2024. Recruitment will likely take place through January 2025.

Data Collection Timeline

We anticipate that data collection will be completed by July 2025.

Research Status

Institutional review board approval was obtained on March 15, 2024. We have signed contracts with RAs that will be performing the duties of providing outreach to eligible patients, obtaining informed consent from patient participants, and administering screening tools at the 3-month postscreening and 6-month postscreening time points. In addition, RAs will ensure that data collection from patient screeners is complete and documented appropriately. Following 3 months post screening, research assistants will conduct the semistructured interviews and administer the survey questions to both patients and clinical staff. At the 6-month study time point, the primary team will send the remaining screeners to patient-participants. The primary research team has been meeting weekly since November 2023 to develop the research plan and discuss project tasks.

Technology Status

Licensing agreements and institutional risk assessment approval for the AI chatbot were obtained before patient recruitment. The AI chatbot was initially beta-tested by the primary research team and patients with diabetes to determine if messages could be delivered on a schedule and if the system could get replies back. The beta test revealed that additional content related to suicidality and "hating having diabetes" was needed, more training on the model to correctly match intents to the content library was needed, and that more of the intents had existing content in the chatbot library but that improving the link to these was still needed. The clinical research team developed content related to suicidality including providing crisis resources and directions to seek emergency services if needed. The introductory chatbot disclosure message was reviewed and indicated that the chatbot is not a replacement for medical treatment and to contact 911 for medical emergencies. Before the study launch, the primary research team retested the chatbot system to ensure that the updates had been completed.

eConsults are an active clinical care option for PCPs at our institution, fully integrated into the EHR and in use by over 28 specialties [35]. As a result, they are a readily usable aspect of this study. For our study, specialists available by eConsults will include behavioral health, social work, care management, diabetes education, pharmacy, and endocrinology.

T1-DDAS and T2-DDAS were created and incorporated into the EHR as flowsheets. The PHQ-9 and GAD-7 are already embedded in the EHR. The results of the DD screeners will be able to be pulled into visit documentation, facilitating care coordination with eConsulted providers. In addition, flowsheet data can be tracked over time and will be easily accessible for providers to review during and after patient visits.

The chatbot performance metrics will be monitored throughout the course of this study and evaluation of the chatbot functionality is part of the feasibility. The study team will monitor for communication failures and in the event of longer-term impact will contact participants directly.

Funding Status

Funding for this study was secured from the Peer Mentored Care Collaborative in January 2024. The duration of the funding was 1 year.

Discussion

Expected Findings

This pilot study is expected to demonstrate the acceptability and feasibility of implementing screening and treatment for DD in a primary care clinic. Through this study, workflows will be developed and implemented to screen for DD at a diabetes-specific visit. Following screening for DD, patients will engage in a clinical conversation with their PCP about the results of the screening measure. A tiered approach will be used to determine the type of intervention that is suggested to the patient. All patients (regardless of DD screening result) will receive access to the AI chatbot. Patients might also receive an eConsult with another health care specialist (eg, social work, clinical pharmacy, care management, behavioral health, endocrinology, and diabetes educator) to support the specific Source of DD. If levels of DD are in the high range, patients may also receive a referral to a behavioral health provider.

We anticipate that the use of technological interventions such as the AI chatbot and eConsults will be experienced positively by participants. It is expected that participants will view the AI chatbot as beneficial to their diabetes care and will find it easy to use. The semistructured interviews will specifically request feedback on participant experience using the AI chatbot. The use of eConsults will allow PCPs to increase collaborative communication among the interdisciplinary team and provide participants with additional specialty services if needed. Having

increased coordination among their primary care team will likely be seen as beneficial and helpful to participants. Existing research indicates that specifically targeting DD for intervention has positive benefits on the severity of distress [17]. Further, eHealth interventions for DD have been shown to be effective for improving diabetes-related distress [18].

This study is expected to increase provider and staff awareness and knowledge of screening for and intervening with DD through team and provider training. The training will provide opportunities for learning important psychological and emotional aspects of patients with diabetes that often go overlooked in clinical care. Clinical conversations focusing on the emotional side of living with diabetes are expected to be a new experience for patients in this study. While this might be a new type of clinical interaction, obtaining validation, normalization, reassurance, and empathy from their medical provider will likely be seen as a helpful and rewarding experience. Living with diabetes is a challenging undertaking that under the best of situations requires nuanced interventions from providers and constant attention and monitoring on behalf of patients and their caregivers. Having a supportive environment to discuss challenging lived experiences is intended to improve the emotional burden of diabetes. This finding is anticipated given that emerging evidence suggests that how health care members speak to people with diabetes can impact the development or exacerbation of DD [12].

Even though DD has become increasingly viewed as an important aspect of diabetes care, there remains limited data on treatment approaches. Current literature points to the importance of addressing DD but interventions specifically focused on DD are needed [36]. Most studies do not examine DD as a primary outcome but deliver interventions focused on managing diabetes more broadly [36,37]. This study will provide interventions that are meant to target DD specifically. The primary research team intends to continue pursuing funding opportunities to conduct larger studies in DD assessment and treatment in primary care settings. Future research would expand the assessment and treatment of DD to entire practices involving the whole care team to provide consistency in whole-person diabetes care delivery.

DD significantly impacts clinical, behavioral, and psychosocial outcomes in people living with diabetes. The majority of people with diabetes receive their diabetes care in primary care. However, assessment and treating DD do not routinely occur in primary care settings. The use of several interventions, including supportive dialogue with PCPs, an AI chatbot, and eConsults, will assist in delivering individualized treatment and support for DD without contributing to increased workload for primary care practices. Learning how to provide screening and treatment for DD in primary care settings is crucial to improving the care of people living with diabetes. Health care systems should cultivate environments that promote open discussions about emotional health. This may include training staff to establish a welcoming atmosphere, integrating whole-person considerations into standard assessments, and ensuring that patients feel at ease when sharing their experiences. Embedding the assessment and treatment for DD within primary care workflows is intended to invite providers and patients to consider the broader impact of living with diabetes.

Limitations and Challenges

Given the current state of rapid evolution for AI technologies and associated policies governing AI use in practice, obtaining institutional approval to use AI chatbot technology as part of patient care requires an extensive review process. While health care technology continues to be seen as a scalable and feasible form of care delivery, administrative barriers can make implementation and usage challenging. Overcoming some of these barriers will likely contribute to increased uptake of technology.

Potential barriers to the implementation of new interventions into primary care practices can include lack of leadership buy-in, lack of communication regarding the rationale for the intervention to all practice staff and providers, and workflow barriers. We have thoughtfully approached each of these barriers through our preimplementation work highlighted above, including practice-level training. The PI also met with clinic and health system leadership before the start of the study to secure support for the project. In addition, the study was designed to seamlessly integrate into already existing practice workflows that were being used for depression and anxiety screening. The integration of DD measures into the EHR was intended to further reduce implementation barriers.

Potential barriers to implementing our protocol in other primary care settings include differing resources. Access to eConsults is not universal and alternative protocols would need to be developed depending on practice settings. Furthermore, not all clinics have integrated behavioral health teams easily accessible. It is likely that providers and staff in other primary care settings may also require training on the diagnosis of DD given its emerging status within the spectrum of care for patients with diabetes. The results of this study could help inform what resources (eg, personnel and training) would be needed to successfully integrate DD assessment and treatment into diverse primary care practices.

A potential limitation of eConsult use is the increased, noncompensated workload on primary care providers, who must act on the e-consultant's recommendations for each patient. Primary care is a fast-paced setting that is often stretched for resources, staffing, and time. Further, primary care is a diverse setting with varied access and structures to care delivery. Consequently, it is unlikely that a single approach or method of care is appropriate in all primary care settings. With significant variability in primary care, interventions need to have adequate flexibility to have a chance to be incorporated successfully into this care environment. Feasibility studies offer an opportunity to determine if interventions can be flexibly disseminated into primary care in a scalable fashion. For the AI chatbot, we anticipate a limitation to be the imperfect matching of responses to participant questions. We are mitigating this limitation by setting expectations upfront with participants and using the dataset to iteratively improve chatbot responses over time with use. We chose this curated content route versus an open generative AI approach to minimize potential risks from chatbot hallucination or inaccurate responses.

Given that this is a feasibility study with a small sample size, and we are not powered for inferential analyses, the results of this study will not be generalizable. However, the results of this study will be used as preliminary data for a larger trial.

Conclusions

Creating and disseminating workflows for screening and treating DD in primary care is an important component for delivering whole-person diabetes care. The use of an AI chatbot to deliver individualized treatment and support for DD and eConsults providing additional specialty support are expected to help increase support and treatment for DD without contributing to an increased workload for primary care practices. This study is intended to help us begin to understand how to implement DD screening and treatment in primary care settings in a scalable and real-world manner.

Acknowledgments

The authors thank the Peer Mentored Care Collaborative within the University of Colorado School of Medicine for funding this research, and the Primary Care Diabetes Lab Patient Advisory Council for their review and insights provided. We would like to thank our expert consultants, Lawrence Fisher PhD, ABPP, and Danielle Hessler PhD. This manuscript is original work and is not under review for any other publication.

Data Availability

Data sharing is not applicable to this article as no datasets were generated or analyzed during this study.

Authors' Contributions

MK, TKO, and SLM conceptualized the study. EK and JFG were involved in the dissemination of the project. DS and JFT supervised the project and provided feedback. AS assisted with a literature search and adding content to the manuscript. MK drafted the manuscript and designed the figure and table. All authors reviewed and approved the final version of the manuscript.

Conflicts of Interest

TKO has received funding through the University of Colorado for work related to diabetes technology but has no COI related to DD, eConsults, or the use of an AI chatbot. SK has received research money for diabetes technology but no COI regarding diabetes distress.

Multimedia Appendix 1
In-depth interview with patients.
[DOCX File , 35 KB - resprot_v14i1e62916_app1.docx]

Multimedia Appendix 2
In-depth interview with providers/staff.
[DOCX File , 35 KB - resprot_v14i1e62916_app2.docx]

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Abbreviations

AI: artificial intelligence
CDSS: clinical decision support systems
DD: diabetes distress
eConsult: electronic consultation
EHR: electronic health record
GAD-7: Generalized Anxiety Disorder-7 Scale
HIPAA: Health Insurance Portability and Accountability Act
MA: medical assistant
PCP: primary care physician
PHQ-9: Patient Health Questionnaire
PI: principal investigator
RA: research assistant
SUS: System Usability Scale
T1-DDAS: Type 1 Diabetes Distress Assessment System
T2-DDAS: Type 2 Diabetes Distress Assessment System
UMUX-lite: Usability Metric for User Experience-lite

Edited by A Schwartz, T Leung; submitted 17.06.24; peer-reviewed by R Nooripour, C Spates; comments to author 29.11.24; revised version received 23.01.25; accepted 23.02.25; published 31.03.25.

Please cite as:
Kostiuk M, Moore SL, Kramer ES, Gilens JF, Sarwal A, Saxon D, Thomas JF, Oser TK
Assessment and Intervention for Diabetes Distress in Primary Care Using Clinical and Technological Interventions: Protocol for a Single-Arm Pilot Trial
JMIR Res Protoc 2025;14:e62916
URL: https://www.researchprotocols.org/2025/1/e62916
doi:10.2196/62916
PMID:

Protocol

Integrating Virtual Reality, Neurofeedback, and Cognitive Behavioral Therapy for Auditory Verbal Hallucinations (Hybrid): Protocol of a Pilot, Unblinded, Single-Arm Interventional Study

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Abstract

Background: Current treatments for schizophrenia and other psychotic disorders have limited efficacy, with high rates of nonresponse to “gold standard” treatments. New approaches are therefore urgently required.

Objective: The aims of this pilot study are to investigate the feasibility, acceptability, safety, and usability of Hybrid treatment (primary aim); and to explore Hybrid’s treatment efficacy and engagement of treatment targets (secondary aim). The primary aim will be assessed via face-to-face user experience surveys on a (self-assessed) 5-point Likert scale (and qualitative open-ended questions) examining: (1) acceptability, (2) helpfulness, (3) engagement, and (4) perceived safety. We will also examine consent and completion rates, and the number of sessions attended. Our threshold for moving on to efficacy trials will be at least 70% of our participants to rate 3 and above (which corresponds to agree or strongly agree) that the intervention package was acceptable, feasible, and safe. The secondary aims will be assessed by observing whether individuals achieve self-directed modulation of high-β neurophysiological activity (neural target) and progression upwards through the VR-based exposure hierarchy (psychological target), and by assessing symptom change scores. This study developed a new treatment approach for auditory verbal hallucinations, a major symptom of psychotic disorders, that integrates advances in psychological therapy (cognitive behavioral therapy for psychosis), technology (virtual reality, VR), and neuroscience (electroencephalography-based neurofeedback).

Methods: Hybrid takes a “symptom capture” approach using individually tailored VR-based exposure exercises. Participants (N=10) will receive the intervention package weekly over 12 face-to-face sessions. Here, participants will be progressively exposed to symptom triggers and develop methods of downregulating neural activity associated with these symptoms (neurofeedback component) while concurrently receiving clinician-delivered cognitive behavioral therapy for psychosis.

Results: As of February 2025, Hybrid has commenced (unblinded) recruitment activities from Orygen clinical services in Northwestern Melbourne, Australia. A total of 75 individuals have been approached and 64 individuals have been prescreened (41 individuals were deemed eligible, 15 individuals were ineligible, and 8 individuals declined or did not respond to contact attempts) and 5 individuals have been included in the study. Of the 5 individuals who have commenced the Hybrid treatment, 4 are actively engaged in the program and 1 individual has withdrawn. We expect recruitment to conclude in July 2025 and for the results to be published in 2026.

Conclusions: The Hybrid study is piloting a novel approach that has the potential to address the shortcomings of current treatments for psychotic symptoms. If there is favorable evidence for the acceptability, feasibility, safety and usability of Hybrid, the study team will move on to efficacy trials.

Trial Registration: Australian New Zealand Clinical Trials Registry ACTRN12624000357550; https://tinyurl.com/24ey8hpy

International Registered Report Identifier (IRRID): PRR1-10.2196/63405

(JMIR Res Protoc 2025;14:e63405) doi:10.2196/63405

KEYWORDS

psychosis; first episode psychosis; schizophrenia; virtual reality; neurofeedback; EEG; auditory verbal hallucinations; voices; cognitive behavior therapy; youth mental health; pilot study; paracusias; paracusis; treatment; medication; psychotic disorder; efficacy; neuroscience; psychology; hybrid; adolescent; Australia

Introduction

Overview

Psychosis is the distinguishing feature of schizophrenia spectrum disorders and a frequent manifestation of mood and substance use disorders [1]. It is characterized by alterations in thoughts and perceptions, often taking the form of positive symptoms such as delusions, hallucinations [2], and disorganized thinking [3], as well as negative symptoms such as blunted affect, poverty of speech, and withdrawal from social and occupational activities [4]. First episode psychosis (FEP) onset most commonly occurs in late adolescence and early adulthood [5], with auditory verbal hallucinations (AVHs) being the most prevalent type of positive symptom reported in this clinical population (≈80%) [6,7]. AVHs are typically characterized by hearing voices that are perceived as distinct from the person's own thoughts. Such experiences are often a cause of significant distress and disruption to daily functioning [8], making AVHs an important target for treatment. Furthermore, evidence supports the benefits of early intervention following the first onset of psychotic symptoms with the duration of untreated psychosis (ie, the time between first psychotic symptoms to antipsychotic treatment) consistently predicting poorer long-term outcomes in longitudinal studies [9,10].

Current Treatments for Psychosis

Current treatment recommendations for psychosis include antipsychotic medications, psychosocial support, and psychological treatment, specifically, cognitive behavioral therapy for psychosis (CBTp) [11-13]. Unfortunately, all currently available treatments are only moderately effective. First, the efficacy of antipsychotic medication for the treatment of positive symptoms of psychosis is not optimal. For example, while commonly prescribed antipsychotics can be significantly more effective than placebo, these medications are accompanied by side effects such as weight gain, sedation, and extrapyramidal symptoms which lead to high incidences of patient nonadherence [2]. A 2019 meta-analysis including 16 randomized controlled trials of antipsychotics and >6200 patients with schizophrenia found that 38% (n=2364) of patients met the criteria for nonresponse and two-thirds showed only "minimal improvement" [14]. Second, the effect sizes for psychological treatments, such as CBTp, tend to be small (≈0.4) and limited in long-term efficacy [2]. Both pharmacological and psychological interventions have higher rates of nonresponse [14] and disengagement [15] in patients with earlier onset of illness highlighting the importance of targeting FEP populations and developing effective and reliable treatments for early intervention. New treatment development, both pharmacological and psychological, is therefore urgently required.

"Cold Cognitions"

One of the limitations of psychological therapies such as CBTp may be that they tend to rely on abstract self-reflection (or "cold cognitions") which can be detached from the actual in vivo experience of symptoms (or "hot cognitions") [16]. This limitation may be particularly relevant for young people in the early stages of psychotic disorder, many of whom find it challenging to engage in this form of self-reflective therapy [17]. Borrowing from the "symptom capture" approach used in other mental disorders, the effectiveness of CBTp may be improved if it is applied while the symptom is actively occurring [18] and collaboratively addressing the symptom that has been activated. The benefit of actively eliciting "hot" cognitions has been demonstrated in the treatment of anxiety disorders and obsessive-compulsive disorder (OCD) [19]. In these disorders, "exposure and response prevention" (ERP) is a key feature of gold-standard psychological treatment [20]. This therapeutic approach involves actively eliciting a degree of anxiety by exposing the patient to symptom triggers and addressing the cognitive and behavioral reactions together with the therapist. Once a degree of mastery and tolerance has been achieved over a low-level, anxiety-inducing trigger, the patient and therapist collaboratively proceed to higher levels of an exposure hierarchy.

Virtual Reality

One advance in technology that may help anchor treatment to the in vivo experience of symptoms is virtual reality (VR). VR

is an interactive computer-generated experience in which the user wears a headset that immerses them in a simulated environment. The VR system is able to create sensory illusions that mimic reality and elicit brain and behavioral responses that parallel those that occur in the real world [21]. VR environments have been found to be useful in the treatment of mental disorders such as social anxiety (for review see Chard and van Zalk [22]), phobias (for review see Kothgassner et al [23]), posttraumatic stress disorder (PTSD; for review see Maples-Keller et al [24]), and as a treatment of psychotic symptoms such as paranoia [25] (see Valmaggia et al [26] for review). Similar to cognitive behavioral therapy (CBT) for anxiety and OCD, this therapeutic technique is founded on exposure principles, where a person is presented with feared, anxiety-provoking, or symptom-inducing stimuli in a graded manner within a controlled environment to enable them to gradually develop strategies to cope when triggers arise in the course of daily life. VR studies for PTSD have found that immersion (ie, a subjective sense of presence in the VR environment) and personalization of the VR environment (ie, tailoring the VR environment to the person's specific and idiosyncratic triggers) may lead to better outcomes, as therapy is more likely to generalize to real-world situations [27]. Indeed, a meta-analysis of VR-assisted exposure therapy for anxiety disorders showed a large overall effect size for VR exposure therapy compared with (mostly waitlist) control conditions (Cohen *d*=1.11, SE 0.15, 95% CI 0.82-1.39) [28]. Furthermore, research on the use of VR for psychosis treatment has indicated the approach can be feasible, acceptable, and effective for improving some symptoms including positive symptoms such as paranoia and hallucinations [29].

For the specific treatment of AVHs, the small number of VR trials to date have all involved avatar therapy, a related approach that involves the creation of a computerized, audio-visual avatar that mimics the hallucinated voices normally experienced by participants, either on a computer screen [30] or using a head-mounted display [31,32]. During these sessions, the participant is supported by the therapist to engage in a dialogue with the created personalized avatar and to develop strategies to respond to the voices. At the same time, the avatar voice and expressions are gradually adjusted from their normal content/tone (eg, abusive) to be friendly and supportive, controlled by the therapist [33]. A 2020 meta-analysis showed favorable results for avatar therapy in patients with schizophrenia compared with supportive counseling on measures of mental state, level of insight, and quality of life [34]. However, while avatar therapy involves artificially recreating an analog AVH experience, the use of the VR environment to elicit symptoms naturally (as is used in traditional ERP treatments) has not yet been explored.

Neurofeedback

Another technological advance, neurofeedback, has proven useful in the treatment of a number of disorders and has shown promising results for psychotic symptoms [35,36]. Neurofeedback is a technique in which individuals use a brain-computer interface to control their own brain activity by receiving real-time feedback on their neural activity. Neurofeedback has most commonly been provided via electroencephalography (EEG) or real-time functional magnetic resonance imaging (rtfMRI). In an example of EEG neurofeedback, individuals receive real-time information on their brain activity, often presented as a bar graph, where the height of the bar represents the power of oscillatory activity in a given frequency band (eg, α or β) measured in terms of power (ie, amplitude squared). This visual display allows participants to try to gain control over their brain activity by manipulating the visual feedback. Participants are typically provided with directions or mental techniques to control their brain activity, are encouraged to apply and adapt their own strategies, and to use the visual feedback display as a guide [37].

The ability of healthy individuals to manipulate their neural activity using neurofeedback has repeatedly been demonstrated [38-40] and is suggested to have positive impacts on cognitive and emotional domains, including the improvement of working memory [40], intelligence [38], and identification of emotional prosody [41]. This has led to neurofeedback's clinical application to a range of psychiatric or neurological disorders, with meta-analyses reporting benefits for attention deficit hyperactivity disorder [42], depression [43], PTSD [44], subclinical OCD [45], and epilepsy [46]. The findings in patients with medication-resistant epilepsy are particularly striking, with neurofeedback demonstrating efficacy in averting seizures once patients learn to anticipate their onset, and with a transfer effect evident even years later [42,46].

The use of neurofeedback in psychotic disorders is increasing in popularity, with a small number of studies published to date (for review see [36]). All studies have found that patients with schizophrenia were able to self-regulate their neural activity, although evidence for a transfer effect (that is, the ability of participants to employ the strategies they have learned during neurofeedback to control their neural activity in the absence of neurofeedback) has yet to be clearly demonstrated. A particularly promising study using rtfMRI indicated a transfer effect for patients with schizophrenia with treatment-refractory AVH after a 2-week training period [47]. Interestingly, the posttraining increase in functional connectivity between brain regions associated with AVH (the left superior temporal gyrus and inferior prefrontal gyrus) was associated with a reduction in AVH symptoms over the training period. As Nan et al [48], recently concluded, "these positive outcomes suggest that such intensive neurofeedback training may provide new insight into the treatment of schizophrenia and thus deserves further study to fully examine its scope."

While rtfMRI-based neurofeedback (like that used in the aforementioned study) can be costly and uncomfortable (due to the space restrictions), EEG-based neurofeedback offers the benefits of portability, cost-effectiveness, and higher patient acceptability. EEG has the further advantage of capturing oscillatory dynamics associated with neural functioning, which cannot be detected using functional MRI owing to the slow temporal latency of the hemodynamic response [49,50]. For patients with FEP, studies on EEG frequency bands (α: 8 to 12 Hz; β: 13 to 30 Hz; θ: 4 to 7 Hz; δ: 0.5 to 4 Hz; low γ: 30 to 50 Hz; and high γ: 50 to 90 Hz) have reported several abnormalities across all 6 bands [51]. Oscillations in the high β band range (approximately 18-30 Hz) are associated with autonomic nervous system hyperarousal and anxiety, which are recognized

as one of the most common subjective features of AVH [52,53]. Previous studies have found that reducing high β band activity (and hyperarousal) is associated with a decrease in psychotic symptoms in patients with schizophrenia, including AVH [48,54,55]. Thus, the use of EEG-based neurofeedback targeting high β band activity represents an important target for the treatment of AVH.

The Hybrid Study

This study, Hybrid, will investigate the potential of a novel treatment approach to AVH in young people with FEP that, if successful, could be incorporated into an individual's broader health care program. Our integrative model combines psychological therapy (CBTp), new immersive technologies (VR), and neuroscience (neurofeedback) in an individualized symptom capture (or ERP) treatment approach. The term "Hybrid" is used to reflect the integrated approach of treatment where each element has been selected to strengthen the effectiveness of the treatment regime as a whole.

A pilot study is required to investigate the following aims: (1) to determine whether Hybrid is feasible, acceptable, and safe; (2) to examine participants' experience of the intervention package and whether it can be modified to increase probability of clinical utility; (3) to explore if there is a signal of clinical benefit in response to Hybrid treatment; and (4) to examine whether Hybrid engages specific neural (modulating high β band activity) and psychological (moving up a symptom-eliciting exposure hierarchy) targets (proof of concept). Hybrid will be an unblinded, single-arm intervention study.

Methods

Participants

Ten participants with a diagnosed FEP will be recruited via telephone from Orygen's Early Psychosis Prevention and Intervention Centre, headspace youth mental health services, and the Orygen Clinical Trials Unit database which serve the Northern and Western suburbs of Melbourne, Australia. Help-seeking participants with FEP from the community will also be recruited. Recruitment will involve phone calls, email, and SMS contact with potential participants. Participants will receive a manually initiated reminder SMS or phone call the day before participation sent by the study clinician or research assistant.

Inclusion Criteria

The inclusion criteria are as follows:

- Aged 15-26 years inclusive.
- Sufficient fluency in English to engage in psychological therapy with an English-speaking therapist, and to understand the study assessments.
- Ability to give informed consent and adhere to study procedures. Parental or guardian consent will be obtained for participants younger than 18 years.
- Psychotic threshold AVH in lifetime as measured by the Comprehensive Assessment of At Risk Mental States (5 or 6 on the severity and ≥4 on frequency for longer than 1 week [56]).
- A rating in the past year of ≥1 on the Psychotic Symptom Rating Scales hallucinations scale [57], corresponding to voices occurring at least once/week. The purpose of this is to ensure that participants with reasonably frequent hallucinations are included in the study, as the experience of symptoms during Hybrid sessions will optimize the study's test of outcomes of interest.

Exclusion Criteria

The exclusion criteria are as follows:

- Documented history of head injury, seizures, or other significant neurological illness.
- Documented history of intellectual disability.
- Visual impairment precluding the ability to view VR scenarios.

Ethical Considerations

Ethics approval for Hybrid has been obtained from The Royal Melbourne Health Human Research Ethics Committee (number 2022.116). This study has ethics approval via the Melbourne Health Human Research Ethics Committee (HREC/76936/MH-2022) for research involving humans and access to patient medical records and information. Participants (or their caregiver/guardian if younger than 18 years) must provide informed consent to participate in the Hybrid treatment. Participants are free to withdraw at any time, with the knowledge that doing so has no impact on their routine treatment. All data from the study is deidentified and only the study investigators have access to this information. This means that each participant's data will have a unique code which only the study team members will have access to. Each participant will be reimbursed AUD $50 (US $31.72) per research interview visit as well as AUD $20 (US $12.69) per EEG recording session.

Data Management and Imputation Strategy

To address attrition or missing values, we will code these as "N/A." The current follow-up protocol is designed to maximize data collection; however, if the missing data are substantial, we will apply multiple imputation methods.

Key Components of the Hybrid Treatment Model

Psychological Therapy

The CBTp approach used in Hybrid relies on hierarchical exposure principles in order to trigger cognitive and affective reactions that occur while experiencing symptoms, that is, "hot cognitions" during symptom activation [58]. As outlined above, this approach may maximize the impact of psychological therapy, as has been observed in other disorders.

Virtual Reality

The VR paradigm that will be used to elicit AVH is inspired by Stinson et al [59] who used a real-world setting comprising computer-generated characters of both sexes and several ethnicities and background sounds simulating the environment. Our VR approach is based on the CBTp framework, beginning with developing a shared understanding (functional analysis) between the participant and therapist of the antecedents of

hallucinatory episodes (eg, presence of other people and lack of meaningful activity) and habitual responses to them (eg, talking back to voices, avoidance). The participant and therapist will then select a template scenario from preexisting VR environments (eg, supermarket and bedroom) developed in consultation with a small group of current and previous service users. Various aspects of the VR environment will be modified to personalize it for the antecedents the individual has identified and to create a hierarchy of symptom-provoking situations. These will include such aspects as the number of people present, proximity and gaze intensity of people, context (interpersonal interaction, indoors, outdoors, time of day or night), sounds, and the presence or absence of "safety strategies" to manage symptoms (eg, mobile phone). For each participant, there will be 5 scaled variants of the personalized scene graded on a 0-100 scale of subjective distress (ranging between 0 and 20 [low], 21 and 40 [moderate], 41 and 60 [high], 61 and 80 [very high], and 81 and 100 [severe]). There are a number of benefits of the VR approach. (1) It provides a controlled environment that can be stopped at any moment, which is not always feasible in real-life exposure settings. (2) It can be designed in a manner that is highly personalized to the individual, which may maximize therapeutic potential. (3) It is a treatment approach that may be particularly suited to young people, given its engaging and interactive nature. (4) It is becoming increasingly feasible for translation into clinical services, given the dramatic reduction in the cost of VR equipment and the fact that VR devices are becoming increasingly portable.

Neurofeedback

EEG will be used to provide real-time neurofeedback to participants while experiencing AVH.

EEG will be acquired using the Muse Headband 2 attached to the Oculus Rift S VR headset. The Muse Headband 2 acquires EEG via 4 electrodes placed over the prefrontal (forehead) and temporal-parietal areas of the brain (electrodes AF7, AF8, TP9, TP10 in the traditional 10-20 electrode system) and collects data at a sampling rate of 500 Hz (with a fifth reference electrode in the position of FPz). The Muse device has been shown to yield frequency-based components of the EEG signal comparable to the research-grade EEG system Biosemi Active Two with the additional benefit of live-streaming capabilities and neurofeedback integration [60]. In Hybrid, the neural target will be the neurophysiological activity associated with autonomic nervous system hyperarousal, specifically, power in the high β range (18-30 Hz) as discussed above (see below for further details).

Intervention Design

Hybrid consists of a Preparation phase (face-to-face, approximately 2 weeks) followed by an implementation phase (12 weekly face-to-face sessions based on previous VR study designs [31,61-63]). Figure 1 shows a visual representation of the Hybrid intervention design and Figure 2 presents the schedule of assessments.

Figure 1. Hybrid design. CBT: cognitive behavioral therapy; VR: virtual reality.

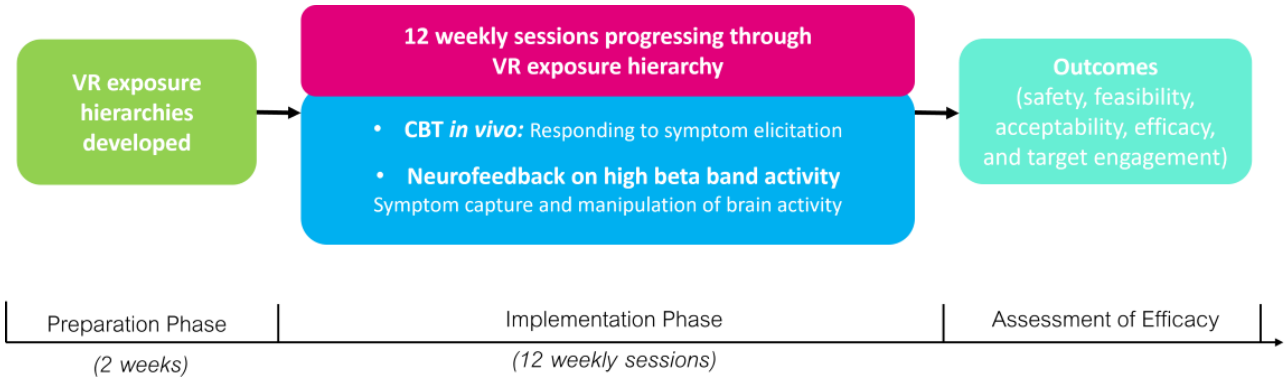
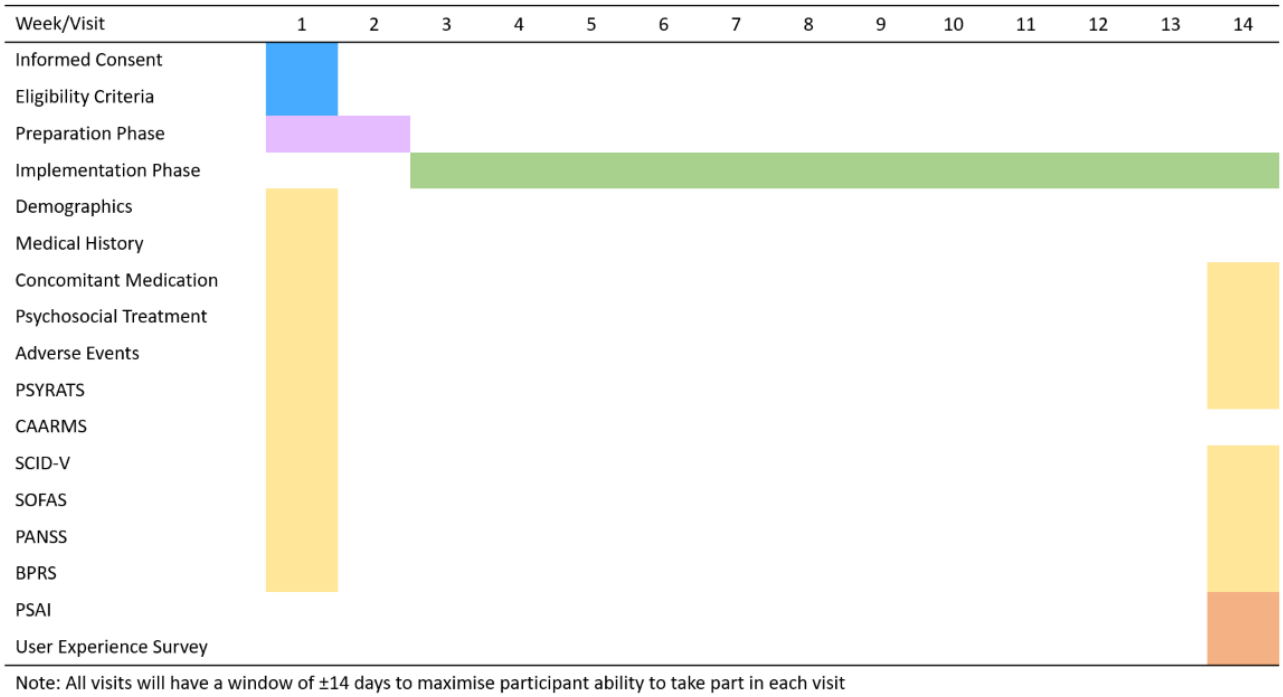


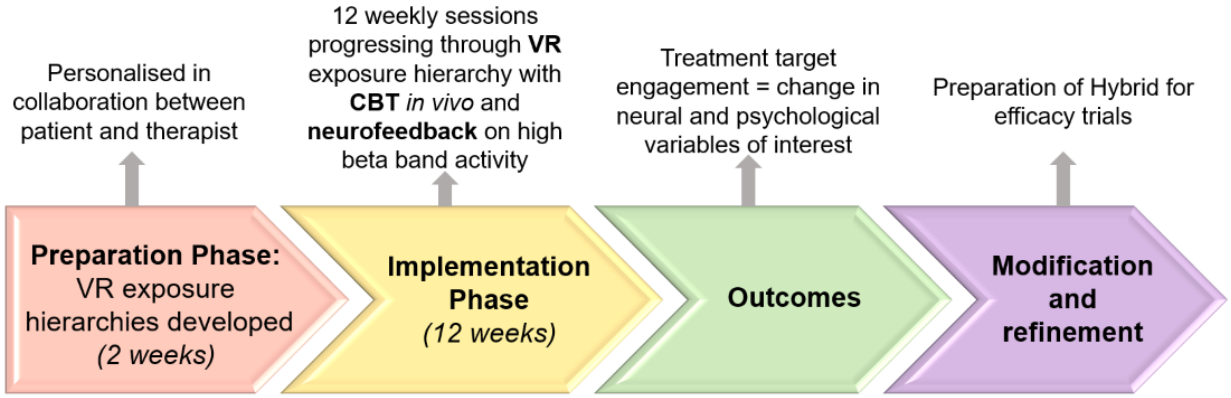
Figure 2. Hybrid schedule of assessments. BPRS: Brief Psychiatric Rating Scale; CAARMS: Comprehensive Assessment of At Risk Mental States; PANSS: Positive and Negative Syndrome Scale; PSAI: Pilot Study Assessment Instrument; PSYRATS: Psychotic Symptom Rating Scales; SCID-V: Structured Clinical Interview for the DSM-V; SOFAS: Social and Occupational Functioning Assessment Scale.



Preparation Phase (Weeks 1-2) Development of the VR Exposure Environment

The preparation of the VR exposure hierarchy will be embedded within a CBT framework by using an adaptation of the standard CBT for voices approach [64]. As mentioned above, the participant and therapist will develop a hierarchy of VR environments personalized for the antecedents identified as symptom-provoking. An example of a VR exposure hierarchy is provided in Figure 3. In developing this hierarchy, the participants will rate the degree of subjective immersion ("presence") they felt in the VR environment using the Immersive Technology Centre-Sense of Presence Inventory [65], a widely used measure in this field. VR environments will only be used if they are rated as inspiring at least "moderate presence," as this has been found to increase therapeutic effectiveness [27]. Once the VR exposure hierarchies have been developed, participants will commence the implementation phase.

Figure 3. Hybrid VR exposure hierarchy example: Shopping Centre template. Example of VR hierarchy exposure levels (left) based on the shopping center template. The participant is exposed to the exposure environments via the VR headset while concurrently speaking with their therapist (cognitive behavioral therapy for psychosis) and receiving neurofeedback of high β band activity via a visual display of a thermometer (right). VR: virtual reality.



#	Exposure Level	Subjective Distress	VR Environment
5	81-100	Maximum	Crowded shopping center, critical gazes, indistinct noises
4	61-80	Very High	Crowded shopping center, people passing by, looking occasionally
3	41-60	High	Interaction with cashier at checkout, people heard in the distance
2	21-40	Moderate	Walking in supermarket aisles, passing people, supermarket music playing
1	0-20	Low	Leaving shopping center, in car park, nobody around

Implementation Phase (Weeks 3-14)

The implementation phase will consist of weekly sessions delivered over a 12-week period (SD 14 days, Figure 2) and consists of the following two components: (1) CBT in vivo (in response to the VR exposure) and (2) neurofeedback simultaneously presented to the participant via the VR device. The VR apps and sessions can only be accessed by the clinician and administered in person. During these weekly sessions, the therapist will be able to view the VR scenario (via an external monitor) and the neurofeedback thermometer, hear the auditory input, and provide guided assistance to the individual.

Cognitive Behavioral Therapy in Vivo (in Response to VR Exposure)

The participant will start at the lowest level of their exposure hierarchy and progressively work up the hierarchy over the course of the sessions. The standard approach in ERP interventions will be adopted, which is to achieve a reduction in subjective units of distress to 30/100 before progressing to the next step in the hierarchy. While the participant is exposed to the symptom-eliciting VR scenario, they will engage in CBTp with their therapist (the participant will be wearing "open backed" headphones, allowing them to hear the therapist as well as sounds coming from the VR environment). The CBT will be standard, manualized CBT for voices [64,66,67] dealing with the "hot" cognition reactions elicited by the VR scenario. Key elements include reassurance regarding lack of threat, challenging appraisals of AVH (eg, their perceived power, threat, or dominance; reducing submissive or reactive behaviors), actively responding to AVH, and developing a sense of control over AVH by attempting to delay or reduce their volume or distract from them with a variety of strategies (eg, humming and visualization). Sessions will last 30-45 minutes and will be stopped at any point if requested by the participant.

Neurofeedback Simultaneously Presented to Participant Via the VR Device

While the participant is being exposed to the VR scenarios and engaging in CBT with a therapist, they will receive visual neurofeedback of electrophysiological activity (power) in the high β band (18-30 Hz) range as measured via EEG. The neurofeedback will be provided to the participant via a single visual image of a thermometer in the corner of the VR scene (ranging from 0 to 100 "degrees"). The temperature of this thermometer is based on the individual's "baseline" neural activity within the high β band range which is measured at the start of each session prior to entering the VR scenario. The thermometer will increase in "temperature" if high β band power increases. The therapist will inform participants that this thermometer is a visual representation of their current stress levels which will give them a real-time objective indication of how their brains are reacting to the Hybrid therapy. Participants will be instructed to keep their eyes open (so as to remain exposed to the VR scenarios) and to keep the thermometer below the 50-degree reading (ie, "half way"; regulating their neural activity in the desired direction) as an additional motivating goal. In keeping with other neurofeedback studies [18], they will be instructed to devise their own strategy for modulating this neural activity but will be informed that they can discuss different strategies with their therapist. If the thermometer measurement is maintained in the lower half ≥50% of the session time, participants will be made aware of the success of their

efforts as positive reinforcement at the end of each of their weekly sessions.

Integration of Multiple Technologies in One Innovative Treatment Package

Combining the treatment components in Hybrid will engage multiple treatment targets and possible pathogenic mechanisms (psychological, neurophysiological, and neurobiological) simultaneously. There is also likely to be a synergistic effect through the interaction of the individual treatment components that will make the package more than the sum of its parts. To illustrate, the real-time neurofeedback provided to participants and therapists in response to the VR exposure exercises will feed into the content of the CBT therapy, because the participant and therapist will be able to discuss the direct impact the exposure exercises are having in an immediate, non-retrospective fashion. This preserves the benefits of dealing with "hot" cognitive and affective reactions. In turn, the CBT will assist the young person in developing strategies for modulating their neural activity in response to the VR exposure exercises. Moreover, the neurofeedback will dynamically reinforce and boost the effect of CBT via participants being able to see in real time that the CBT is helping change their brain activity. This will create a salient and durable learning experience, contributing to a "real world" transfer effect and motivating the use of CBT skills in the absence of neurofeedback. This tridirectional impact of the treatment components—the way the individual items work together—will amplify their individual contribution to therapeutic gain.

Measures

Primary Outcomes

Feasibility and Acceptability of the Hybrid Model

A Pilot Study Assessment Instrument developed by Orygen researchers based on the user experience approach will assess (1) acceptability, (2) helpfulness, (3) engagement, and (4) perceived safety. Items are rated on a self-assessed 5-point Likert scale. Acceptability and feasibility will also be determined by assessing consent and completion rates, the number of sessions attended, the number of dropouts, and completion rates of measures. A high rate of elicited AVH is required to facilitate "hot" cognitions so that the symptoms are targeted directly rather than through abstract self-reflection.

Safety of the Hybrid Model

Safety will be assessed by recording adverse events or serious adverse events.

Usability of the Hybrid Model

Assessing the experience and usability of the VR environments was conducted using the user experience survey, a specifically adapted 18-item questionnaire from other Orygen VR studies for this study. This measure will be completed at the end of the Hybrid intervention (week 14 of the study). At this point, participants will also complete a semistructured interview about their experience of the intervention and suggestions for modifications to the treatment package.

Threshold of the Hybrid Model

Our decision to move on to efficacy trials will be based on the user experience survey, which uses a 5-point Likert scale. We will require at least 70% of our participants to rate 3 and above (which corresponds to agree or strongly agree) that the intervention package was acceptable, feasible, and safe.

Secondary Outcomes

Auditory Verbal Hallucinations

The hallucinations scale of the Psychotic Symptom Rating Scales will be used to assess changes in AVH severity, frequency, and distress.

General Psychopathology

The Brief Psychiatric Rating Scale [68], Structured Clinical Interview for the *DSM-5* (*Diagnostic and Statistical Manual of Mental Disorders* [Fifth Edition]) [69], Social and Occupational Functioning Assessment Scale (SOFAS) [70], and the Positive and Negative Syndrome Scale (PANSS) [71] will be used to assess change in general psychopathology and symptoms.

Psychological Treatment Target

The highest level in exposure hierarchies was achieved in each session. For each participant, the final target score of each of these measures will be the average over the 12 implementation phase sessions.

Neuropsychological Treatment Target

This will be operationalized as the difference (ie, change) between the first half and the second half of the VR exposure exercises in average power of high β band activity. A mean score will be used for analysis and will be given by the average change in ratings over the sessions attended.

Planned Analyses

As this study is a pilot study designed to generate initial data to guide future research, a power calculation has not been conducted. A sample size of 10 participants is consistent with similar proof-of-concept and pilot studies [44,48].

Primary Analyses

Means and SDs of acceptability, feasibility, safety, and usability measures and the percentage of participants showing different levels of ratings on the Pilot Study Assessment Instrument will be reported. Thematic analysis of the semistructured interviews will also be conducted. The number of adverse events and serious adverse events will be reported and reviewed.

Secondary Analyses

Clinical Efficacy

Effect sizes, paired *t* tests and Wilcoxon analysis of clinical rating changes before and after the intervention will be computed, which will inform future efficacy trials.

Target Scores

Means, SDs, and 95% CIs of neural (average β band power) and psychological (exposure hierarchy level) target scores will be reported. The magnitude of the changes in both scores will reflect the degree of target engagement achieved. A mean score

will be used for analysis and will be given by the average change over the first half (mean of weeks 3 to 8) and second half (mean of weeks 9 to 14) of the sessions attended.

Further Analyses

Whether greater engagement of neural and psychological targets is associated with greater change in clinical measures will also be explored. This finding would indicate a treatment mechanism that could be systematically tested in future studies.

Results

As of February 2025, Hybrid has commenced (unblinded) recruitment activities from Orygen clinical services in Northwestern Melbourne, Australia. A total of 75 individuals have been approached and 64 individuals have been prescreened (41 individuals deemed eligible, 15 individuals ineligible, and 8 individuals declined or did not respond to contact attempts). Of the 41 individuals who were prescreened as eligible, 9 individuals consented (16 individuals declined and 8 individuals did not respond) and 5 individuals have been included in the study. Of the 5 individuals who have commenced the Hybrid treatment, 4 individuals are actively engaged in the program and 1 individual has withdrawn. The demographic information for these 5 participants are as follows: aged 21 to 27 (mean 24, SD 2) years; 5 male sex at birth consisting of gender identity of 2 cisgender males, 1 transgender male, 1 nonbinary, and 1 questioning their gender. We expect recruitment to conclude in July 2025 and for the results to be published in 2026.

Discussion

Anticipated Findings

Hybrid introduces a new treatment approach that integrates CBTp with VR and neurofeedback. This integration of treatment components may augment each individual element in such a way that it maximizes the impact of each individual component. We anticipate that this will produce durable skill-building and a "real world" transfer effect that motivates the use of Hybrid strategies in everyday life. In addition, individuals should see a reduction in AVH distress, severity, and frequency as evidenced by symptom change scores at the end of the treatment package.

We predict that Hybrid will be successful in achieving this based on the fact that the treatment package will be as follows. (1) Engaging and acceptable: previous studies have shown that young people in the early stages of psychosis find neurophysiological assessments highly acceptable and the neurofeedback and VR components of Hybrid leverage "gamification" [72,73] (ie, using game design and mechanics to encourage active participation) in the treatment of mental disorders. (2) Easily implementable given the increasingly affordable and portable nature of the tools used in the Hybrid intervention (EEG and VR). (3) Empowering: young people develop self-directed control over their symptoms, as opposed to being an "object" of treatment, which is often how other treatment approaches, such as pharmacotherapy, are experienced [74]. As has been recognized [75] previously, neurofeedback can be a means of "taking back control" of the brain by promoting strategies to manage symptoms that come "from the inside" and can be used at any point in the course of everyday life. (4) Focused on individual symptoms rather than diagnostic categories. This is in keeping with the current trend in psychiatric research away from disorder-bound approaches toward transdiagnostic and symptom-based risk factors [76,77]. Therefore, Hybrid could represent a breakthrough in clinical research for effective treatments for psychosis and, if successful, would significantly improve clinical outcomes in young people with AVH.

In terms of study limitations, we highlight that our use of the PANSS and SOFAS as measures of symptoms and functioning may be suboptimal for fine-grained assessment of symptomatology (such as for the negative symptoms) and function. We note that the main aim of this study is to assess the feasibility and acceptability of the Hybrid treatment and we plan to include additional, more fine-grained measures in future studies. We chose to use the PANSS and SOFAS based on many previous studies in early psychosis populations using these measures and increasing our comparability to previous research [70,71]. Second, our clinical assessments are structured to minimize the burden on the individual, therefore, certain features which may be of significance (eg, past history of trauma or eating disorders) were not assessed, but may affect responsiveness to the Hybrid treatment. In subsequent trials, a more thorough assessment of psychopathology may be included to address this. Finally, by virtue of design, we cannot make inferences about any other symptoms associated with psychosis (eg, paranoia and disorganized thinking) as we were targeting AVH in these efficacy trials. Future studies could expand to target other psychotic symptoms.

Conclusion

This pilot study aims to demonstrate the safety, feasibility, and acceptability, as well as establish proof of concept for Hybrid treatment. This initial study will provide valuable information as to whether the Hybrid treatment protocol could be modified and whether moving on to efficacy trials is indicated.

Acknowledgments

We would like to thank Tamar Wong for his significant contribution to the VR component of the Hybrid study. We also extend our gratitude to Hybrid research participants. The study is funded by an NHMRC Investigator Grant (2026484) awarded to BN.

Data Availability

The datasets generated or analyzed during this study are available from the corresponding author on reasonable request.

Authors' Contributions

JS contributed to writing the original draft, project administration, conceptualization, supervision, and investigation. ER was responsible for reviewing and editing the manuscript. MA-J, IB, ID, SL, JL, NT, AT, GW, and SW were involved in conceptualization, with IB also contributing to manuscript review and editing. LB and JL provided supervision. ID contributed to the methodology. CE and BM handled project administration, with BM also involved in investigation and manuscript review. HPY conducted a formal analysis. BN contributed to conceptualization, manuscript review, and editing, and secured funding.

Conflicts of Interest

None declared.

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Abbreviations

AVH: auditory verbal hallucination
CBT: cognitive behavioral therapy
CBTp: cognitive behavioral therapy for psychosis
DSM-5: Diagnostic and Statistical Manual of Mental Disorders (Fifth Edition)
EEG: electroencephalography
ERP: exposure and response prevention
FEP: first episode psychosis
OCD: obsessive-compulsive disorder
PANSS: Positive and Negative Syndrome Scale
PTSD: posttraumatic stress disorder
rtfMRI: real-time functional magnetic resonance imaging
SOFAS: Social and Occupational Functioning Assessment Scale
VR: virtual reality

Edited by A Schwartz; submitted 18.06.24; peer-reviewed by LB Glenthoj; comments to author 03.09.24; revised version received 14.10.24; accepted 25.02.25; published 01.04.25.

Please cite as:
Spark J, Rowe E, Alvarez-Jimenez M, Bell I, Byrne L, Dzafic I, Ellinghaus C, Lavoie S, Lum J, McLean B, Thomas N, Thompson A, Wadley G, Whitford T, Wood S, Yuen HP, Nelson B
Integrating Virtual Reality, Neurofeedback, and Cognitive Behavioral Therapy for Auditory Verbal Hallucinations (Hybrid): Protocol of a Pilot, Unblinded, Single-Arm Interventional Study
JMIR Res Protoc 2025;14:e63405
URL: https://www.researchprotocols.org/2025/1/e63405
doi:10.2196/63405
PMID:

Protocol

Assessing Patient-Reported Satisfaction With Care and Documentation Time in Primary Care Through AI-Driven Automatic Clinical Note Generation: Protocol for a Proof-of-Concept Study

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Abstract

Background: Relisten is an artificial intelligence (AI)–based software developed by Recog Analytics that improves patient care by facilitating more natural interactions between health care professionals and patients. This tool extracts relevant information from recorded conversations, structuring it in the medical record, and sending it to the Health Information System after the professional's approval. This approach allows professionals to focus on the patient without the need to perform clinical documentation tasks.

Objective: This study aims to evaluate patient-reported satisfaction and perceived quality of care, assess health care professionals' satisfaction with the care provided, and measure the time spent on entering records into the electronic medical record using this AI-powered solution.

Methods: This proof-of-concept (PoC) study is conducted as a multicenter trial with the participation of several health care professionals (nurses and physicians) in primary care centers (CAPs). The key outcome measures include (1) patient-reported quality of care (evaluated through anonymous surveys), (2) health care professionals' satisfaction with the care provided (assessed through surveys and structured interviews), and (3) time saved on clinical documentation (determined by comparing the time spent manually writing notes versus reviewing and correcting AI-generated notes). Statistical analyses will be performed for each

objective, using independent sample comparison tests according to normality evaluated with the Kolmogorov-Smirnov test and Lilliefors correction. Stratified statistical tests will also be performed to consider the variance between professionals.

Results: The protocol has been developed using the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) checklist. Recruitment began in July 2024, and as of November 2024, a total of 318 patients have been enrolled. Recruitment is expected to be completed by March 2025. Data analysis will take place between April and May 2025, with results expected to be published in June 2025.

Conclusions: We expect an improvement in the perceived quality of care reported by patients and a significant reduction in the time spent taking clinical notes, with a saving of at least 30 seconds per visit. Although a high quality of the notes generated is expected, it is uncertain whether a significant improvement over the control group, which is already expected to have high-quality notes, will be demonstrated.

Trial Registration: ClinicalTrials.gov NCT06618092; https://clinicaltrials.gov/study/NCT06618092

International Registered Report Identifier (IRRID): DERR1-10.2196/66232

(JMIR Res Protoc 2025;14:e66232) doi:10.2196/66232

KEYWORDS

primary health care; patient satisfaction; artificial intelligence; medical records systems; computerized; patient-centered care

Introduction

Background

In the medical field, medical record writing is an essential task that requires time and accuracy on the part of health care professionals. The medical record, which includes the patient's medical history, any symptoms they have had, treatments performed, and other relevant details, is a critical component in making appropriate medical decisions and ongoing patient follow-up [1].

In the modern health care context, there has been a transition to the digitization of these records, giving rise to the concept of the electronic medical record (EMR). An EMR is the electronic representation of a patient's medical record, created and maintained by health care professionals. This digital approach has not only revolutionized the way medical information is stored and accessed but has also improved the efficiency of medical care by facilitating the retrieval of relevant data at the point of care [2,3]. EMRs provide a centralized platform for medical information management, allowing for more accurate tracking and more coordinated care [4].

Traditionally, health care professionals have spent a significant amount of time writing medical records [5], which can affect the efficiency and quality of care they provide. This manual task is not only time-consuming but can also lead to documentation errors, omissions, or inconsistencies in the information recorded. A descriptive study published in the *Annals of Internal Medicine* in 2020 conducted a detailed assessment of the amount of time doctors spent using EMRs during outpatient visits. In this study, which included comparisons of 1482 doctors, it was found that doctors were actively using EMRs for 43% of the total time they were online [6]. It has also been shown that all this can contribute to an increase in burnout among professionals [7,8].

In recent years, the field of artificial intelligence (AI) has experienced significant advances in natural language processing and speech recognition [9,10]. These advances have enabled the creation of automated tools and systems that can accurately and efficiently transform speech into text. In the health care setting, this technology has the potential to streamline and improve the writing of medical records, freeing up time for professionals to focus on direct patient care [11,12]. However, this technology was necessary but not sufficient, and it was not until the advent of generative AI that a key part of the process could be completed to obtain sufficient quality for practical use [13,14].

Another important aspect is the issue of data privacy and security [15]. The implementation of AI systems in clinical practice must comply with strict regulations regarding the protection of patient health data. This includes ensuring the security of data transmission and storage, as well as compliance with data privacy regulations, and the General Data Protection Regulation [16]. In the case of AI use, these requirements must go further, given the additional risks of training models with data in health care, which in the worst cases can result in data hacking or the inclusion of strong biases in the algorithms [17,18].

Several companies and academic institutions have developed prototypes and pilot systems for the automated writing of medical records from the doctor-patient conversation in English (Nuance DAX, Amazon HealthScribe). These tools use advanced algorithms and AI models trained on large amounts of clinical data to extract and record relevant information [19].

Relisten

In this context, the Spanish company Recog Analytics has developed Relisten [20], an automated clinical note-writing system designed to handle real-world consultations, supporting multiple languages and offering integration with EMRs.

Through a natural conversation between the health care professional and the patient, this AI-powered tool uses recordings to extract relevant fields corresponding to key sections of the medical history in a structured way and then send them to the Health Information System (after correction and approval by the health care professional). A detailed description of the algorithm's architecture can be found in

Multimedia Appendix 1, providing technical insights into its design and functionality.

Methods

Study Objectives

This study has the following objectives: (1) to evaluate the perceived quality of care reported by patients with the use of an AI-powered solution in the consultation, measured through anonymous satisfaction questionnaires at the end of each consultation (Multimedia Appendix 2); (2) to assess the satisfaction of health care personnel with the care provided in consultations, measured using an anonymous satisfaction survey at the end of the study (Multimedia Appendix 3) and a structured interview; and (3) to assess the time spent by health care personnel on entering records in the EMR, measured by statistical tests comparing consultations with and without the tool.

Overview, Design, and Hypotheses of Study

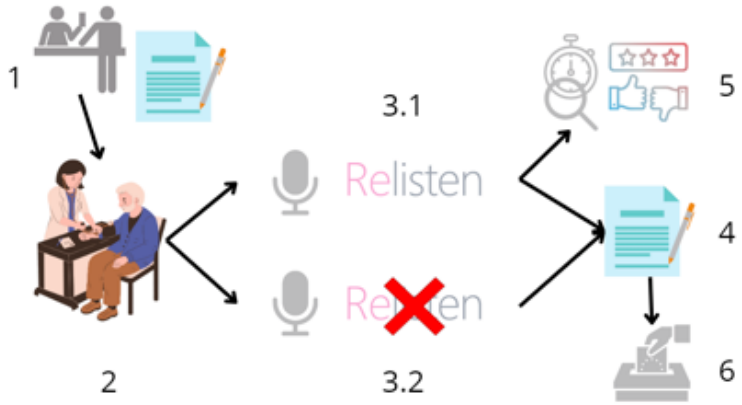
A proof-of-concept (PoC) analysis will be carried out in the context of a multicenter study, where several health professionals (nurses and physicians) from different primary care centers (CAPs) will use the AI-powered tool in consultations (under informed consent of the patient) and will survey patients and the professionals themselves.

The project is structured in three main phases: (1) preparation: this includes the demonstration and initial training of the participating professionals, the preparation of the technological infrastructure (microphones), and the coordination for carrying out the surveys, with an approximate duration of 2 weeks; (2) development: this consists of the use of an AI-powered solution during consultations, as well as data collection, including audios, clinical notes, and survey results, lasting approximately 20 weeks; and (3) data analysis and presentation of results: this phase involves the processing and analysis of the data collected, followed by the presentation of the results obtained, and lasts approximately 2 weeks.

The measurement of the objectives will be carried out using the following methods: (1) perceived quality of care as reported by patients using an anonymous patient survey after each consultation, in a patient-blinded study (patients are not told beforehand whether the AI-powered tool has been used in the consultation; this fact is outlined by a graphic mark in the surveys in which the tool has been used); (2) satisfaction of health care personnel: an anonymous survey will be conducted at the end of the study. This will qualitatively evaluate the tool's impact on consultations, focusing on aspects such as its general usefulness, ease of use, the quality of notes generated, its perceived ability to improve attention during consultations, and the extent to which it saves time. In addition, the study will incorporate structured interviews with primary care health care professionals (nurses and physicians) to explore their experiences with the tool in depth. The interviews will include questions about the above concepts, as well as at least an additional request to the health care professional to identify limitations and improvements to the tool. (3) Time spent entering information into the EMR. To determine the magnitude of savings, 2 measurements taken during the PoC will be compared: the time the health care professional spends typing in the consultation and the time the health care professional spends reviewing and correcting notes generated by the AI-powered tool.

Figure 1 facilitates the visualization of the development of the study in consultations.

Figure 1. Steps involved in the study workflow.



The steps mentioned in Figure 1 include:

1. Patient consent at reception: the patient arrives at the CAP and is attended to at the reception desk, where he or she is given the information sheet and the informed consent form, which he/she will return signed if he/she agrees to participate in the study.
2. Consultation begins: the patient arrives for consultation and the doctor confirms their participation.
3. (3.1) Use of Relisten: the consultation is carried out, alternating between consecutive patients (simple randomization). Recording and using the AI-powered tool to provide full patient care. In this mode, the health professional does not take notes during the consultation and proceeds to step 5.
4. (3.2) Standard documentation: recording it and writing it at the same time in the electronic record as usual. In this mode the AI-powered tool is only used as a consultation recorder to calculate the typing time of the health care professional, using these consultations as a control group.

5. Note review or writing: the doctor hands the survey to the patient and says goodbye.
6. Satisfaction surveys: the doctor reviews the notes generated by the AI-powered tool, recording the time required for that task directly on the tool's website, copies and pastes them into the electronic record, and rates the notes generated by the tool for that consultation.
7. Anonymous survey submission: the patient deposits the completed survey anonymously in the box provided.

The study team hypothesizes that the use of an AI-powered tool improves the perceived quality of care by allowing health care professionals to spend more time interacting directly with patients and less time on clinical documentation. This translates into more patient-centered care and a measurable improvement in both patient and staff satisfaction.

Setting of the Study

The study population will be made up of patients who are visited in person at CAPs in Catalonia, both in emergency and control consultations, whose professionals (nurses and physicians) participate in the study. The participating primary care centers are CAP Amposta, CAP Centelles, CAP Artés, CAP Sallent, CAP Súria, and the Consorci d'Atenció Primària de Salut Barcelona Esquerra.

Given the nature of the tool and its applicability to most of the practice settings, there will be no previous selection of patients, but any patient who comes for consultation with the professionals participating in the study will be eligible.

Participants eligible for inclusion in the study must have provided written informed consent, be involved in face-to-face medical or nursing consultations conducted in Catalan or Spanish, and be aged 18 years or older.

Participants will be excluded from the study if they are unable to understand the nature of the study, lack fluency in Catalan or Spanish, do not provide consent to be recorded, or if any technical issues, such as internet service downtime, compromise the recording process.

The study included patients in unscheduled visits (emergency), first visits (with history taking), and follow-up for chronic disease.

The SPIRIT guidelines were followed when designing the research (Multimedia Appendix 4) [21].

Sample Size and Randomization

To calculate the sample size, the 2 objectives that require such calculation are considered:

1. For the patient satisfaction surveys, proposed on a Likert scale from 1 to 5, we are faced with the problem of comparing independent samples. Assuming normality in the difference of the samples (a hypothesis that will be verified during the statistical tests), the formula for the determination of the required sample size is the following:

Where Z_α and Z_β represent the Z-table values for confidence level and test power, respectively, sigma is the SD of the (estimated) differences, and d is the effect size to be measured. For this study, standard values for α=.05 (95% confidence) and β=.8 (80% test strength) are selected, σ=1 is estimated as an extreme case to ensure that the results will be statistically significant, and d=0.25, as the minimum improvement we want to demonstrate. The result is n=395.21 for each group, so we set the number of patients to be analyzed to 400 with the AI-powered tool and 400 without the tool.
2. For time-saving, applying a similar procedure with the same standard values, σ=90 seconds and d=30 seconds, we obtain n=111.15 for each group, so we set the number of consultations to be analyzed to 120 with the AI-powered tool and 120 without the tool.

Since the groups are the same and there is no interconnection between the measurement of both objectives, it is possible to use the same consultations for both, and therefore the total number of patients required will be the larger of the two above, resulting in n=800 (400 patients with the AI-powered tool and 400 without the tool). The randomization was carried out in a simple format, given the sufficient sample size and the fact that the aim is to validate the hypotheses at a general level, although for information purposes the study also shows intermediate results stratified by type of consultation (first or follow-up) or by a health professional.

Data Collection

The data collection process involves the following:

1. Satisfaction surveys completed by patients at the end of the consultation (with the AI-powered tool as a test and without the tool as a control). The survey will be given to the patient on paper by the health professional inside the doctor's office at the end of the visit. They will be collected anonymously in a box upon exiting the office, in a visible and accessible place. This involves single-blinded data collection (the patient does not know whether the AI-powered tool is being used, although the health care professional does). These questionnaires will be available in Catalan and Spanish.
2. Quality surveys at the end of each consultation by health care professionals, on a scale of 0-10 with the possibility of including open-ended comments, will be carried out directly through the AI-powered tool's digital platform. These questionnaires will be available in Catalan and Spanish.
3. Satisfaction surveys completed by health care professionals at the end of the study, as well as interviews to better understand the impact and limitations in a qualitative manner.
4. Recordings of conversations between the patient and health care professional (Recog will delete the recordings at the end of the study).

These items align with study objectives and are detailed in the Multimedia Appendices 2 and 3.

Qualitative data will be collected using open-ended survey surveys for patients and health care professionals and structured interviews with professionals. These data will be analyzed using thematic analysis.

The study variables are mentioned in Textbox 1.

Textbox 1. Study variables.

Independent variables

- Indicator of whether the artificial intelligence (AI)–powered solution has been used in the consultation (no typing during the consultation; yes or no)
- Identifier of the health care professional involved (user code stored in the AI-powered tool)

Dependent variables

- Results for each survey question, on a scale of 1-5.
- Time saved during consultations is measured by comparing the writing time in the 2 scenarios: one where doctors manually write notes during the consultation (non–AI-powered audios) and another where they review and correct notes generated by the AI-powered tool. For the non–AI-powered audios, investigators listen to the recordings and measure the exact time the professional spends writing. In AI-assisted consultations, the doctors use the platform to time their note corrections. By comparing these two measurements, the study aims to quantify the time-savings offered by the AI-powered tool, with each recording being analyzed individually for accuracy. This has been chosen because other forms of measurement (such as automatically measuring silences) may introduce greater biases (silences due to circumstances other than note taking) than human interpretation. Although logically it is not a perfect measure either, the savings impact is expected to be sufficiently significant for these random errors to have a very small impact in relative terms.

  In addition, health care professionals are asked to include, through the AI-powered tool's digital platform, possibly relevant comments about the consultation they have just carried out, such as when a consultation has been carried out in multiple languages, with one participant speaking in Spanish and another in Catalan.

Statistical Analysis

The main hypotheses of the study focus on evaluating the reported quality of care and saving time in the writing of clinical notes. To assess the improvement in reported quality of care, the normality of the sample will be checked using the Kolmogorov-Smirnov test with Lilliefors correction. Student *t* test for independent samples will be applied in the case of normality, or an equivalent nonparametric test otherwise. Key survey items, including patient-reported satisfaction with time spent, the attention received, and perceived care quality, as well as health care professional satisfaction with reduced administrative burden, ease of use, and note quality, will be analyzed to test for significant differences.

In terms of time savings, 2 aspects will be measured separately: the relative time (in percentage) that the professional spends writing notes during the consultation without using the AI-powered solution, and the relative time that the doctor spends reviewing the notes generated by the tool. Similarly, the normality of the sample will be checked using the Kolmogorov-Smirnov test with Lilliefors correction, and the Student *t* test or its nonparametric equivalent will be applied as appropriate.

Since the sample is not randomized, a sensitivity analysis will be conducted to account for potential selection bias. All statistical analyses will be performed using RStudio, considering a confidence level of 95% and a statistical power of 80%.

Confidentiality

In this study, confidentiality will be rigorously protected by several procedures. The patient surveys, which will be conducted anonymously upon exiting the consultation, will be transcribed by the Recog staff into a Microsoft Excel file for subsequent analysis, without any identifying data. The audios collected during the consultations will be automatically stored in the AI-powered tool platform, guaranteeing their security by storing them in the S3 (Simple Storage Service) service of Amazon Web Services, with controlled access, encryption, and without identifiers that allow patients to be identified. The professionals' comments will be stored in Amazon Web Services DynamoDB tables, also with controlled access, thus ensuring the confidentiality of all the information collected.

In no case is the objective of the study to train the algorithm with the data obtained, since the algorithm is already trained. The models applied are speech-to-text models, originally trained on multilingual datasets [22] and a large language model trained on generic datasets in multiple languages, public and private, not specified by the model developer. Notes are written in the project and no medical analysis is being performed by AI. The initial tests have shown the correct capability of the complete software for this task, which we seek to validate more extensively with this project. The initial stages of the algorithm use machine learning techniques, such as advanced speech-to-text models for transcription. The subsequent steps, including structuring the extracted information into relevant clinical fields, rely on a combination of rule-based processes, predefined templates, and generative AI models.

Ethical Considerations

This study was approved by the University Institute for Primary Care Research Jordi Gol Health Care Ethics Committee (Code 3/286-P). The research adhered to institutional guidelines for studies involving human subjects, including those requiring the recording of patient interactions and subsequent analysis. Written informed consent will be obtained from all participants before their inclusion in the study. Participation was entirely voluntary. No monetary or material compensation was provided to participants. All participants will complete a written informed consent. Upon arrival at the CAP, the Admissions administration staff will offer the patient the chance to participate in the study. The participant will be given the information sheet attached to the informed consent form, where he or she will be informed

about the purpose of the study and the handling of the data. If the patient authorizes his or her participation, he or she must complete and sign the informed consent form and give it to the clinical professional with whom the consultation is to take place.

Results

This study was preregistered on ClinicalTrials.org. Recruitment began in July 2024, and as of November 2024, a total of 318 patients have been enrolled at participating CAPs. The recruitment process is proceeding more slowly than expected and to ensure sufficient sample size the recruitment period has been extended until March 2025. This adjustment enables comprehensive data collection without compromising the study's objectives.

Discussion

Principal Findings

The implementation of AI-based technologies in health care has been a topic of growing interest in the last decade. These technologies promise to improve the efficiency and quality of health care, but their adoption depends largely on empirical evidence to support their benefits.

This study seeks to contribute to that evidence base by evaluating a specific tool that has the potential to alleviate one of the main sources of administrative burden for health care professionals: the writing of clinical notes. By freeing up time that would otherwise be spent on administrative tasks, an AI-powered tool could enable health care professionals to focus more on direct patient care, thereby improving the quality of care.

The results of the project will serve to validate the usefulness of an AI-powered solution in daily practice, from the perspectives of improving the perceived quality of care and saving professionals' time, which could amount to more than an hour a day that could be invested in attending to more patients, promoting adherence with the same patients, or other value-added tasks.

If the result of the study is favorable, the tool is technically prepared to be integrated with IT systems, is scalable to thousands of queries in parallel and has been designed from the ground up with absolute priority to data security and privacy (the tool deletes queries minutes after processing to avoid being a target for cyberattacks; it is not a database, just a processor). It is therefore considered that its implementation may be feasible, the first step being to validate its capabilities in this study.

While our study is one of the first to evaluate the use of an automated clinical note-writing system based on AI algorithms in day-to-day clinical consultations in primary care, previous research has explored similar technologies in other medical specialties. For example, a 2024 study assessed the accuracy of AI-generated clinical notes using ChatGPT-4 (OpenAI), finding that such tools can produce notes comparable in quality to those taken by physicians [23]. In another study, the Permanente Medical Group (United States) implemented AI scribes for more than 10,000 physicians and found that this technology reduced documentation time, improved doctor-patient interactions, and achieved high satisfaction among both patients and physicians [24].

Limitations of the Study

One of the main limitations of this study is that the sample is not randomized, which may introduce selection bias. To address this, a sensitivity analysis will be performed to ensure that any potential bias is minimized. Related to the sample size, while substantial for a PoC study with 800 participants, may still be considered relatively small.

Another important limitation is the variability introduced by the participation of different health professionals, who can generate a significant variance in the results obtained, both in patient satisfaction and in the time saved in the consultation. Although patients were blinded to the use of the tool, their reported satisfaction may still be influenced by other factors such as the health care professional's behavior or consultation dynamics. To mitigate this effect, it has been decided to involve a reasonable number of professionals, seeking a balance between reducing variance and avoiding an excessive burden on participants, although this will still be a limiting factor.

Another possible bias is in the measurement of time saved. This is calculated as the difference between the time spent on a consultation without the AI-powered tool to write the notes and the time needed to review the notes generated by the tool in another consultation. However, there will always be an inherent bias, as it is not possible to reproduce the same consultation exactly, and the professional's previous knowledge may influence how quick they are in carrying it out. In addition, the measurement of the time the professional spends writing may not be completely accurate. In addition, while we assess the time spent on writing clinical notes, another potential limitation lies in the time spent reviewing the notes generated by the tool. This measurement may be influenced by external factors, such as interruptions (eg, being called to the door, receiving phone calls, etc), which could result in prolonged review times without the actual time being spent on reviewing the notes. The start and end points of the review period are based on when the professional clicks "start review" and "finish review," but interruptions could lead to inaccurate time recordings. In addition, another limitation is the risk that doctors rely too much on AI-generated notes without thoroughly reviewing them, which could lead to inaccuracies. Although doctors are instructed to verify the notes as soon as possible following the consultation to avoid this, individual differences in review diligence could have an impact on the results. Despite these challenges, an analysis of these errors has been performed and it has been concluded that their impact will be significantly lower than the effects that are intended to be measured, so the results, with the proposed sample, can be considered valid. However, if any extreme values are identified during the analysis, they will be excluded.

Conclusion

We anticipate that patients participating in the study will perceive an improvement in the quality of care they receive and

that there will be a significant reduction in the time spent taking clinical notes. Although we expect the generated notes to be of high quality, it remains uncertain whether a significant improvement over the control group, which is already expected to have high-quality notes, will be demonstrated. Ultimately, this proof-of-concept study seeks to explore the potential benefits of integrating AI in primary care settings.

Acknowledgments

We thank all the primary care centers that participated in this study, as well as the health care professionals and patients who volunteered. We would also like to thank the Recog Analytics technical team for their ongoing support during the development and implementation of Relisten. This project has had no external funding except for the development of the tool by the company Recog Analytics.

Data Availability

The datasets used and/or analyzed during the current study will be available from the corresponding author on reasonable request.

Authors' Contributions

JV-A, CA, and DHH made significant contributions to the methodology, investigation, and writing (original draft and review & editing of the work). They also supervised and validated the project. AC, ES-F, MLB, CFP, IM, RA, OC, RF, JA, CM, MMM, MG, and SN critically reviewed the manuscript, ensuring accuracy, clarity, and intellectual rigor, and approved the final version for publication, participating in writing and validation. AG coordinated and supervised the project, critically reviewing the intellectual content, approving the final published version, and participated in project administration and supervision.

Conflicts of Interest

CA, DHH, and ACC are employees of Recog Analytics, the company that developed Relisten. While the study was funded by Recog Analytics, to minimize potential bias, the analysis of the results will be conducted independently by authors not affiliated with the company. We have a collaboration agreement with Recog Analytics for this research project. This agreement ensures compliance with data privacy regulations, prohibits fine-tuning of the algorithm using study data, and mandates the deletion of all temporary data immediately after processing. The tool is used solely for research purposes and its inclusion in this study is based on its potential to support primary care professionals by reducing administrative burden and improving workflow efficiency.

Multimedia Appendix 1
Algorithm Architecture.
[DOCX File , 101 KB - resprot_v14i1e66232_app1.docx]

Multimedia Appendix 2
Health Professional Satisfaction Survey.
[DOCX File , 20 KB - resprot_v14i1e66232_app2.docx]

Multimedia Appendix 3
Patient Satisfaction Survey.
[DOCX File , 17 KB - resprot_v14i1e66232_app3.docx]

Multimedia Appendix 4
SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) checklist.
[PDF File (Adobe PDF File), 86 KB - resprot_v14i1e66232_app4.pdf]

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Abbreviations

AI: artificial intelligence
CAP: primary care center
EMR: electronic medical record
PoC: proof of concept
S3: Simple Storage Service
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials

Edited by A Schwartz, T Leung; submitted 16.09.24; peer-reviewed by H Isto, B Eapen, B Mesko; comments to author 16.12.24; revised version received 27.12.24; accepted 07.03.25; published 07.04.25.

Please cite as:
Vidal-Alaball J, Alonso C, Heinisch DH, Castaño A, Sánchez-Freire E, Benito Serrano ML, Ferrer Pascual C, Menacho I, Acosta-Rojas R, Cardona Gubert O, Farrés Creus R, Armengol Alegre J, Martínez Querol C, Moreno-Martinez M, Gonfaus Font M, Narejos S, Gomez-Fernandez A
Assessing Patient-Reported Satisfaction With Care and Documentation Time in Primary Care Through AI-Driven Automatic Clinical Note Generation: Protocol for a Proof-of-Concept Study
JMIR Res Protoc 2025;14:e66232
URL: https://www.researchprotocols.org/2025/1/e66232
doi:10.2196/66232
PMID:

Protocol

A Reminder App to Optimize Bladder Filling During Radiotherapy for Patients With Prostate Cancer (REFILL-PAC): Protocol for a Prospective Trial

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Abstract

Background: Many patients with nonmetastatic prostate cancer receive radiotherapy, which may be associated with acute cystitis, particularly if the volume of the urinary bladder is small. Three studies showed bladder volumes <200 ml or <180 ml to be associated with increased urinary toxicity. Therefore, it is important to maintain bladder volumes greater than 200 ml during as many radiation fractions as possible. Several studies investigated drinking protocols, where patients were asked to drink a certain amount of water prior to radiotherapy sessions. This may require considerable discipline from the patients, who are predominantly older adults. Adherence to a drinking protocol may be facilitated by a mobile app that reminds patients to drink water prior to each radiation session. This study investigates the effect of such an app on bladder filling status in patients with prostate cancer undergoing external beam radiotherapy (EBRT) alone.

Objective: The primary goal of this study is to evaluate the impact of an app that reminds patients irradiated for prostate cancer to drink 300 ml of water prior to each radiotherapy session on the number of fractions with bladder volumes <200 ml during the radiotherapy course.

Methods: This ongoing phase 2 aims to recruit 28 patients treated with EBRT alone for nonmetastatic prostate cancer. Radiotherapy will be administered using normo-fractionation, with doses ranging from 70 to 80 Gy in 35 to 40 fractions of 2 Gy, preferably with volumetric-modulated arc therapy (VMAT). Treatment volumes include the prostate with or without the seminal vesicles.

Results: Recruitment for this trial will start in March 2025 and is planned to be completed in October 2026. The study is scheduled to conclude in December 2026.

Conclusions: This trial is the first to evaluate the impact of a reminder app on the number of radiotherapy fractions with bladder volumes <200 ml in patients undergoing irradiation for localized prostate cancer.

Trial Registration: Clinicaltrials.gov NCT06653751; https://clinicaltrials.gov/show/NCT06653751

International Registered Report Identifier (IRRID): PRR1-10.2196/68179

(JMIR Res Protoc 2025;14:e68179) doi:10.2196/68179

KEYWORDS

prostate cancer; external beam radiation therapy; radiation toxicity; bladder filling; mobile app

Introduction

Prostate cancer is one of the most common solid malignancies worldwide [1]. Most patients with nonmetastatic disease receive either prostatectomy or radiotherapy. Radiotherapy is often performed with normo-fractionated (5 × 2 Gy per week) external beam radiotherapy (EBRT) alone or EBRT plus a high-dose-rate brachytherapy boost [2]. For normo-fractionated EBRT alone, the recommended total dose is between 74 and 80 Gy, corresponding to 37 to 40 fractions of 2 Gy [2]. Prostate cancer radiotherapy may be associated with significant acute urinary toxicity such as cystitis, particularly if the volume of the urinary bladder is small. A total of 3 studies showed that bladder volumes <200 ml or <180 ml, respectively, were associated with increased acute or late urinary toxicity [3-5]. In a retrospective study by Pisani et al [3], which included 280 patients treated with EBRT for prostate cancer, bladder filling (volumes <200 ml vs ≥200 ml) was an independent predictor of grade ≥2 acute urinary toxicity. A prospective study by Pinkawa et al [4] assessed the quality of life in 80 patients irradiated for prostate cancer at different time points. At follow-up between 6 and 10 weeks after radiotherapy, pain with urination was reported less frequently by patients with an initial bladder volume of ≥180 ml compared to <180 ml. In another prospective study from Germany, 193 patients received training via a biofeedback mechanism to achieve a bladder volume between 200 and 300 ml at each radiation session [5]. The results showed that reproducible bladder volumes >180 ml were associated with a significant decrease in grade ≥2 acute urinary toxicity. In another study, a planned bladder volume >200 ml and daily filling between 82% and 113% were associated with reduced intrafraction motion of the prostate [6]. Moreover, in the study by Smith et al [7], optimal bladder dose constraints were missed more frequently if the bladder volumes were <200 ml. Therefore, it is important to maintain bladder volumes >200 ml at as many radiation fractions as possible.

In a recent study by our group that investigated the bladder volumes at each of the first 35 radiation fractions in 72 patients receiving EBRT alone, the mean and median numbers of radiation fractions with bladder volumes <200 ml were 17.8 (SD 12) and 16.5 (IQR 7.5-29.5) fractions, respectively [8]. On the other hand, in a subgroup of 37 patients with a bladder volume of at least 200 ml before the start of the radiotherapy course, the mean and median numbers of radiation fraction with bladder volumes <200 ml were only 9.4 (SD 8.3) and 8 (IQR 2-16), respectively. The mean and median were significantly higher in the subgroup of 35 patients with bladder volumes <200 ml, at 26.7 (SD SD 8.5) and 30 (IQR 22-34), respectively. Therefore, there is a medical need for improvement, especially in the latter subgroup.

Several studies have investigated the role of drinking protocols [5-7,9-17]. Patients were asked to drink a certain amount of water prior to computed tomography (CT) simulation and radiotherapy sessions. In these studies, the amount of water ranged between 200 and 600 ml, and the time interval until the CT simulation or radiation session was between 30 and 60 minutes [5-7,9-17]. However, drinking a certain amount of water at a specific point in time may require considerable discipline from patients, who are predominantly older adults. These considerations led to the idea of developing a mobile app that reminds patients to drink a certain amount of water prior to each radiation session. The idea of testing a reminder app in this context was based on our experience with such an app during our previous Interreg project NorDigHealth [18,19].

This study investigates the number of radiation fractions with bladder volumes <200 ml in a prospective cohort of patients using a reminder app. Additionally, it evaluates whether the use of the reminder app significantly reduces the proportion of radiation fractions with bladder volumes <200 ml compared to a historical control group without app support. After several ethical discussions, we decided to compare the cohort of the single-arm phase 2 trial to an appropriate historical control group after careful matching rather than performing a randomized phase 3 trial. Since the responsible individuals at the contributing centers were confident that the reminder app would improve bladder filling in the phase 2 cohort, they deemed it unethical to withhold the app from approximately 50% of the patients participating in a randomized phase 3 trial. The main goal of this prospective phase 2 study is to evaluate the impact of a reminder app on the number of fractions with bladder volumes <200 ml during radiotherapy in patients irradiated for prostate cancer. The app reminds the patients to drink 300 ml of water 45 minutes prior to each radiotherapy session. The primary end point is the number of radiation fractions with bladder volumes <200 ml after 35 fractions of radiotherapy. Additionally, the following end points will be evaluated: (1) the number of radiation fractions with bladder volumes <200 ml at the end of radiotherapy, (2) patient satisfaction with the reminder app, and (3) the impact of the reminder app on the use of health technology.

Methods

Trial Design and Duration

This is a single-arm prospective study performed in 1 university hospital, 2 academic teaching hospitals, and 1 private practice. It will investigate the effect of a reminder app on the number of radiation fractions with bladder volumes <200 ml during a course of radiotherapy for the treatment of prostate cancer compared to a historical control group [8]. The control group is considered appropriate for comparison with this study cohort, as these patients were treated very recently (in 2022 or 2023)

with external beam radiotherapy alone in 3 of the 5 centers participating in this study. The control group underwent a cone beam computed tomography (CBCT) session prior to each radiation fraction, enabling bladder volume assessment with the same level of precision as in this study. To ensure comparability of the total number of fractions administered in the prospective study with those in the historical control group, the primary end point is restricted to the first 35 fractions administered. The recruitment of all 28 patients is planned to be completed within 20 months. The follow-up period will end directly after the radiotherapy course, which is scheduled to take 7 to 8 weeks. This equals a total running time of 22 months for the study. In accordance with the previous study assessing the number of radiation fractions with bladder volumes <200 ml during a course of radiotherapy for treating prostate cancer, the following characteristics will be recorded to allow adequate comparison with the historical control group: (1) bladder volume at CT simulation, (2) BMI, (3) age, (4) prostate volume prior to radiotherapy, (5) Karnofsky performance score, (6) risk group of prostate cancer, and (7) antihormonal therapy [8]. All patients in the phase 2 cohort and the historical control group must have a bladder volume <200 ml at CT simulation.

Patient Selection

This trial will be performed in patients with prostate cancer receiving definitive normo-fractionated radiotherapy. Patients will be adequately informed about their diagnosis and the nature, significance, and scope of the trial. Patients will only be included after completing the pretherapy evaluation, meeting all inclusion criteria, and not meeting any exclusion criteria (Textbox 1).

Textbox 1. Inclusion and exclusion criteria.

Inclusion criteria:

- Histologically proven prostate cancer
- Indication for definitive normo-fractionated radiotherapy
- Possession of and ability to use a smartphone
- Bladder volume at computed tomography (CT) simulation <200 ml
- Age ≥18 years
- Written informed consent
- Capacity of the patient to consent

Exclusion criteria:

- Radiotherapy of pelvic lymph nodes
- Expected noncompliance

Patient Interventions

For all patients, radiotherapy will be administered using normo-fractionation with 70 to 80 Gy in 35 to 40 fractions of 2 Gy, given 5 days per week (overall treatment time 7-8 weeks), preferably with volumetric-modulated arc therapy (VMAT) [2]. Treatment volumes include the prostate with or without the seminal vesicles.

Radiotherapy for prostate cancer may be associated with acute side effects, including dermatitis, cystitis, proctitis, diarrhea, and fatigue. If grade 3 toxicity occurs according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5, radiotherapy may be delayed for a maximum of 7 days without consequences [20]. If it is delayed for more than 7 days, participation in the study will be terminated, and the coordinating investigator must be informed.

Patients may receive concurrent systemic agents as part of their anticancer treatment, regardless of their participation in this trial [2]. These agents will be indicated and prescribed by treating medical oncologists or urologists outside this trial.

The following parameters will be recorded prior to the start of radiotherapy: medical history including micturition disorders, medication including anticancer treatment, physical examination, age, body height and weight, Karnofsky performance score, bladder volume and prostate volume at CT simulation, tumor stage, histology, Gleason score, prostate-specific antigen, risk group, planned radiation dose and dose per fraction, number of fractions, radiation boost, treatment volume, radiation technique, experience with smartphones, and need for support regarding the use of the reminder app. Throughout the trial, bladder volumes will be assessed by staff members prior to the radiotherapy course (based on CT simulation) and before each radiation fraction using CBCT. Adverse events will be assessed on an ongoing basis according to CTCAE version 5 [20]. At the end of the radiotherapy course, patients will be asked to complete a questionnaire assessing their satisfaction with the reminder app and the impact of its use on their attitude toward health technology.

Safety Management

An adverse event is any event experienced by a patient or participant in a clinical trial that does not necessarily have a causal relationship with the treatment. It can include any adverse or inadvertent occurrence (including notable laboratory findings), symptom, or illness that occurs during the treatment period, regardless of whether there is a causal relationship. Existing illnesses that deteriorate during the trial should also be reported as adverse events. Events covered by the documentation for concomitant diseases and radiation-related

acute toxicities of Grade ≤2 do not have to be additionally documented as adverse events. Serious adverse events are those that fulfill one of the following criteria at any dose level: lethal, life-threatening, requiring hospitalization or extent of a hospital stay, permanent or significant disability, birth defects or malformations, any medically significant event, or any event necessitating surgery to prevent one of the aforementioned concomitant illnesses. Hospitalization should be defined as necessary for treating the adverse event. Hospital stays that are part of the treatment outlined in the protocol or due to a planned, elective operation are not classified as serious adverse events. Likewise, an elective hospitalization to facilitate the trial process does not count as a serious adverse event.

Sample Size Calculation

The primary goal of this study is to assess the impact of an app that reminds patients irradiated for prostate cancer to drink water before each radiotherapy session on the number of fractions with bladder volumes <200 ml during the radiotherapy course. This study also aims to demonstrate that this number is lower than without using an app (historical control group). To allow for a skewed distribution of the primary end point, the Wilcoxon-Mann-Whitney test will be applied for confirmatory statistical analysis. Sample size calculation is based on the article by Noether [21]. In the external historical control group consisting of 35 patients, the mean number of radiation fractions with bladder volumes less than 200 ml was 26.7 (SD 8.5), and the median number was 30 (IQR 22-34). A decrease in this mean value by roughly 30% (to 18.7 fractions) is considered clinically relevant. For illustrative purposes, translating this decrease into a nonparametric effect size framework (assuming normal distribution) leads to a probability of roughly 0.25 that the number of fractions <200 ml with the reminder app will be larger than without the app. Based on this effect size, a sample size of 25 patients in the prospective trial is required for comparison with the historical control group to ensure 90% power to reach statistical significance with a 2-sided Wilcoxon-Mann-Whitney U test and a 5% significance level. Assuming that roughly 10% of the enrolled patients will not be eligible for the primary analysis as they received less than 35 fractions, a total of 28 patients should be enrolled.

Statistical Analyses

All data recorded in the case report forms describing the study population, efficacy, safety, and quality of life will be analyzed descriptively. Categorical data will be presented in contingency tables with frequencies and percentages and 95% CIs. Continuous data will be summarized with at least the following: frequency (n), median, quartiles, mean, SD (standard error), minimum, and maximum. The number of participants with protocol deviations during the study and listings describing the deviations will be provided. Chi-square tests will be used to compare percentages in a 2 × 2 contingency table, replaced by the Fisher exact test if the expected frequency in at least 1 cell of the associated table is less than 5. Stratified 2 × 2 contingency tables will be analyzed using Cochran-Mantel-Haenszel tests. Logistic regression models serve as multivariable methods for binary end point data. A comparison of ordinal variables between treatment arms will be performed using the asymptotic Wilcoxon-Mann-Whitney test, replaced by its exact version in case of ordinal categories with a small number of categories and/or sparse data within categories. Any shift in the location of quantitative variables between study groups will be performed using the Wilcoxon-Mann-Whitney tests. All patients who start the radiotherapy and provide data on the primary end point will be analyzed (full analysis set). The data analysis will be performed according to the statistical analysis plan, which will be finalized prior to database lock and any statistical analysis.

The primary study end point is defined as the number of radiation fractions with bladder volumes less than 200 ml after 35 fractions of radiotherapy. Descriptive measures of location and dispersion will be used to describe the results of the prospective study. The impact of patient characteristics on the primary end point will be assessed by Wilcoxon 2-sample tests. These characteristics include age (<75 vs ≥75 years), Karnofsky performance score (70-80 vs 90-100), BMI (<30 vs ≥30=obesity), prostate volume prior to radiotherapy (<60 vs ≥60 mL), risk group of prostate cancer (low to intermediate vs high), and antihormonal therapy prior to and/or during the course of radiotherapy (no vs yes). For confirmatory analysis, the prospective study will be compared with the historical control group through a 2-sided Wilcoxon-Mann-Whitney 2-sample test and a significance level of 5%. A high degree of comparability is expected between the prospective trial cohort and the retrospective patient data set. However, potential heterogeneity among the study populations will be identified by comparing patient characteristics with Wilcoxon-Mann-Whitney tests. Homogeneity will be assumed if all resulting *P* values are above 20%. Any factor indicating a tendency toward heterogeneity (ie, *P*<.20) will be included in a multivariable count data Poisson regression model with the number of radiation fractions with bladder volumes <200 ml as a dependent variable and the respective factors and binary factor (prospective study vs historical control) as the independent variables. If there is evidence of overdispersion, the Poisson model will be replaced by a negative binomial model.

Additionally, secondary end points will be subjected to statistical analysis. Since no comparison with historical data is possible, these analyses will focus on descriptive statistical analysis only. Patient satisfaction results will be used to decide whether the app needs modifications. In the case of a dissatisfaction rate >20%, app modifications will be made. If the app has a dissatisfaction rate >40%, it will be considered not useful.

Ethical Considerations

The examinations to be carried out as part of this trial are all considered standard procedures. There are no additional laboratory investigations or X-rays to be done, or any other examinations that could be potentially burdensome for the patient. The trial protocol was approved by the ethics committee of the University of Lübeck, Germany (file 2024-519), and the trial has been registered at Clinicaltrials.gov (NCT06653751). Prior to inclusion in the trial, each patient will be fully informed about its contents and procedures. If the patient has received the necessary information and the investigator is sure that the patient has understood this information, they will be asked to provide their consent via signature. The patient will receive a

copy of their information and the signed informed consent forms. The investigator will also inform the patient that they have the right to withdraw consent to participate in the trial at any time and without providing any reasons. Patients will be informed that the data collected as part of the trial will be documented anonymously and then forwarded for scientific evaluation.

The trial will be conducted in accordance with the principles laid out in the Declaration of Helsinki. Data will be collected in accordance with the regulations set out in the Data Protection Act. All findings from the clinical trial will be stored on electronic data storage devices and treated with utmost confidentiality. Organizational measures have been taken to prevent the data from being sent to unauthorized people. Patients will only be identified via their individual patient numbers throughout the entire documentation and evaluation phase, and any identifiable data will not be used.

For the personal activation of the app for each study participant, Nextlabel OHG will receive the participant's e-mail address. To ensure the protection of all e-mail addresses, a contract has been signed between the Sponsor (University Medical Center Schleswig-Holstein) and Nextlabel OHG. The contract includes an approved data protection concept. Nextlabel will not have access to any patient data that are not pseudonymized. Amendments to the study protocol may only be implemented if approved by the responsible ethics committees. Only the coordinating principal investigator may carry out such changes. However, all coinvestigators will contact the coordinating principal investigator if modifications are deemed necessary. If any changes are made to the study protocol, all investigators will be informed after ethics committee approval, and the notice must be confirmed.

Data Management and Monitoring

All data relating to patients will be recorded pseudonymously. Each patient will be identifiable only by their unique patient number, date of birth, and sex. A patient identification list will only be kept in the relevant trial centers and will not be forwarded to the sponsor. Data collection will be done using the study-specific data documentation forms that must be filled in using a ballpoint pen. Fountain pens or pencils will not be used. If corrections need to be made, we will cross the error out once with a straight line, enter the correct information next to it, and note the date and/or reason for correction. Comments will be made if data fields cannot be filled in because of missing information. The forms will be filled in as soon as possible and submitted to the checker for review, signed, dated, and forwarded to the study management team.

The original versions of all key trial documents, including the documentation sheets, will be kept at the trial headquarters (ie, the sponsor responsible for the trial) for a minimum of 10 years after the final report.

The principal investigator/head of the trial center will keep all administrative documents (ie, written correspondence with the ethics committee, regulatory authorities, trial management, and trial headquarters), the patient identification list, the signed informed consent forms, copies of the documentation sheets, and general trial documentation (ie, protocol and amendments) for the aforementioned time period. Original patient data will also be kept for the length of time stipulated for the trial centers but not for less than 10 years.

Clinical on-site monitoring at the German sites will be conducted according to good clinical practices and written standard operating procedures to ensure the patients' rights and safety are upheld, along with the reliability of the trial results. For initiation, trial sites will be visited onsite by a clinical research associate. During the trial, sites will be visited at regular intervals depending on the recruitment rate and data quality. Informed consent and defined key data will be checked for all patients. Medical files will be screened for adverse and serious adverse events. Patients' questionnaires will be checked. All trial-specific monitoring activities will be defined before starting the trial and documented in writing (monitoring manual). The sites in other countries will be monitored according to the corresponding national regulations in their own responsibility. No regular audits are planned. However, to ensure the correct execution of the study, audits may be conducted if necessary. Because this study is not linked to the German Medicinal Products Act, no inspections of higher federal authorities are scheduled. A data monitoring committee is not required since patients in this trial will receive standard treatment.

Results

This phase 2 trial investigates the number of radiation fractions with bladder volumes <200 ml in a prospective cohort of patients using a reminder app. In addition, this study evaluates whether the use of the app leads to a significant reduction of the proportion of fractions with bladder volumes <200 ml when compared to a historical control group without app support. The reminder app was developed by the professional company Nextlabel OHG from Lübeck, Germany. It reminds the patients to drink 300 ml of water 45 minutes prior to each radiation session. The time to be reminded can be set by the patients for each radiation session to consider potential changes in schedule (eg, due to maintenance of the linear accelerator). The patients must confirm their water intake and receive a puzzle piece as a reward. Prior to its use in the REFILL-PAC (Reminder App to Optimize Bladder Filling During Radiotherapy for Patients With Prostate Cancer) trial, the app was tested by 30 healthy volunteers to assess its functionality and practicability and to identify and solve relevant issues prior to the start of the trial. Recruitment for this trial will start in March 2025 and is planned to be completed in October 2026. Termination of the entire study (28 patients) is scheduled for December 2026. The expected results will be available at the beginning of 2027. The REFILL-PAC trial did not receive any specific funding. It is part of the Interreg Deutschland-Danmark project Health Advancing Technologies for the Elderly (HeAT) funded by the European Regional Development Fund (01-1-23 2).

Discussion

Expected Results

It is expected that the use of the reminder app will reduce the mean number of radiation fractions with bladder volumes <200

ml by approximately 30% from 26.7 (of 35 fractions) found in the historical control group to 18.7 fractions in patients with a bladder volume <200 ml at CT simulation [8]. A sample size of 25 patients is required for the phase 2 cohort to achieve a power of 90% for statistical significance and a 5% significance level.

Study Limitations

Although appropriate matching will be conducted based on 7 patient- and tumor-related characteristics, the risk of a hidden selection bias cannot be entirely excluded due to the retrospective nature of the data obtained from the control group. Moreover, the fact that patients in the phase 2 cohort must possess a smartphone and be able to use the app may lead to a selection bias. These limitations must be considered when the results of the comparative part of this study will be available and distributed.

Comparison With Prior Work

Radiotherapy for prostate cancer may be associated with significant urinary toxicity such as cystitis, particularly if the volume of the urinary bladder is <200 ml at the time of irradiation. Findings from 3 previous studies highlight the importance of patients drinking a sufficient amount of water each day before irradiation to achieve a bladder volume of <180 ml or, preferably, ≥200 ml [3-5]. To ensure appropriate bladder filling, protocols asking the patients to drink water before CT simulation and/or each radiation fraction have been investigated [5,6,8-17]. In the corresponding studies, the amount of water ranged between 200 and 600 ml, with a waiting period of 30 to 60 minutes before CT simulation or the radiation. However, bladder volumes during the radiotherapy course varied considerably, and adherence to the drinking protocols was suboptimal. This raises the question of whether an app reminding patients before each radiation session of the required water intake could improve adherence to the prescribed drinking protocol.

Dissemination Plan

The coordinating principal investigator will work toward a comprehensive internal and external dissemination of the study results. The coordinating principal investigator, biostatisticians, and staff members of the center will prepare a report regardless of whether the study concludes as planned or is terminated early.

The scientific results will be published in an international, peer-reviewed journal. Additionally, the results will be presented at meetings and symposia. Reports and publications related to the study must be coordinated with the statistician to avoid misinterpretations. Conclusions must be statistically validated and approved by the statistician. The study acronym REFILL-PAC will be used in all publications.

Conclusion

This phase 2 trial is the first study that investigates the impact of a reminder app on the number of radiation fractions with bladder volumes less than 200 ml in patients treated with normo-fractionated radiotherapy alone for localized prostate cancer. The hypothesis is that using the app will significantly reduce the number of fractions below 200 ml compared to a historical control group of patients who underwent normo-fractionated radiotherapy without app support. If the reminder app proves effective, it may contribute to a decrease in urinary toxicity.

Acknowledgments

The REFILL-PAC (Reminder App to Optimize Bladder Filling During Radiotherapy for Patients With Prostate Cancer) trial is part of the Interreg Deutschland-Danmark project Health Advancing Technologies for the Elderly (HeAT), which is funded by the European Regional Development Fund (01-1-23 2). The trial sponsor is the University Medical Center Schleswig-Holstein, Germany. Neither the funding body nor the sponsor has any role in the study conception, data handling, or article writing.

Data Availability

Further information regarding the REFILL-PAC (Reminder App to Optimize Bladder Filling During Radiotherapy for Patients With Prostate Cancer) trial is available at Clinicaltrials.gov (NCT06653751).

Conflicts of Interest

None declared.

Multimedia Appendix 1
SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) checklist.
[PDF File (Adobe PDF File), 247 KB - resprot_v14i1e68179_app1.pdf]

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Abbreviations

CBCT: cone beam computed tomography
CT: computed tomography
CTCAE: Common Terminology Criteria for Adverse Events
EBRT: external beam radiotherapy
HeAT: Health Advancing Technologies for the Elderly
REFILL-PAC: Reminder App to Optimize Bladder Filling During Radiotherapy for Patients With Prostate Cancer
VMAT: volumetric-modulated arc therapy

Edited by A Schwartz; submitted 30.10.24; peer-reviewed by BK Neilsen; comments to author 22.01.25; revised version received 03.02.25; accepted 27.02.25; published 08.04.25.

Please cite as:
Rades D, Küter JD, von Staden M, Al-Salool A, Janssen S, Timke C, Duma MN, Bartscht T, Vestergård Madsen C, Kristiansen C, Cremers F
A Reminder App to Optimize Bladder Filling During Radiotherapy for Patients With Prostate Cancer (REFILL-PAC): Protocol for a Prospective Trial
JMIR Res Protoc 2025;14:e68179
URL: https://www.researchprotocols.org/2025/1/e68179
doi:10.2196/68179
PMID:

Protocol

Designing eHealth Interventions for Pediatric Emergency Departments: Protocol for a Usability Testing Study With Youth, Parent, and Clinician Participants

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Abstract

Background: Usability tests provide important insight into user preferences, functional issues, and differences between target groups for health interventions and products. However, there is limited guidance on how to adapt the usability testing approach for a youth audience, especially for digital health interventions.

Objective: This protocol paper outlines a novel approach for conducting usability tests with a diverse audience of youth, parents, and clinicians in the development of 2 digital health tools for the pediatric emergency department (ED) setting.

Methods: This paper outlines a protocol for usability testing as part of a broader study aimed at co-designing ED discharge communication tools with youth, parents, and clinicians. The broader study involved co-designing 2 digital tools: one for asthma and one for concussions. A multimethods approach to usability testing was used to assess the functionality of these tools through 2 rounds of testing. A mix of youth, parents, and ED clinicians were invited to participate in each round of usability testing. Participants were asked to provide feedback on the tools through quantitative surveys and open-ended qualitative questions. The usability testing approach was adapted to suit each target group, such as including a youth in the data collection process, to enhance the quality of the data. The severity of usability problems was analyzed following the first round of testing, and each tool was refined based on this feedback. The second round of usability tests involved collecting both qualitative and quantitative feedback on the revised tools.

Results: All usability data have been collected and are being analyzed. Outcomes will be disseminated through a subsequent publication. Results will include demographic characteristics from each user group from both rounds of testing, severity of usability scores, qualitative and quantitative feedback, and differences in test outcomes between each target group.

Conclusions: This paper provides novel guidance for conducting usability tests with youth participants when designing digital health tools. By using a comprehensive co-design and usability testing approach, we anticipate that final tools will be highly relevant to the end users and will lead to better uptake and patient outcomes when pilot-tested in future studies. The outlined approach may be adapted to different health care contexts for other youth participants. Further research should continue to explore ways to design usability tests that are suitable for youth audiences, as there is still a significant gap in the literature around this topic.

International Registered Report Identifier (IRRID): DERR1-10.2196/64350

(JMIR Res Protoc 2025;14:e64350) doi:10.2196/64350

KEYWORDS

eHealth intervention; emergency department; usability testing; youth; health services; parents; pediatric; digital health tools; mixed methods; quantitative surveys

Introduction

The International Organization for Standardization describes usability as "the extent to which a system, product or service can be used by specified users to achieve specified goals with effectiveness, efficiency and satisfaction in a specified context of use" [1]. Usability testing is a method in which a product is evaluated by users as they perform tasks, and may include formative or summative testing [2]. Usability testing is considered a cornerstone of user-centered design, valuable for capturing user preferences, to identify any functional issues and determine differences between how certain demographic groups use a product or tool [3]. This information is helpful for both designers and researchers who want to ensure that a product suits the needs of the end user.

In the context of eHealth (ie, digital health tools and health information technologies), applying methods and approaches to usability testing could improve the design and implementation of new interventions. This includes digital tools such as mobile apps, kiosks, virtual care, and electronic health records [4]. The World Health Organization recognizes eHealth interventions as a global priority, as part of the 2020-2025 global strategy on digital health, to create more efficient and effective health care systems [5]. Despite this global health priority setting, it is unclear how often eHealth interventions undergo usability testing prior to implementation. One systematic review reported limited or poor-quality usability testing of electronic health records prior to implementation [6], while another review of 104 eHealth interventions reported that only 38% of them included an aspect of usability testing [4]. Often, eHealth researchers rely on industry-focused protocols, which may lack transferability to complex health care contexts. To evolve the rigor and field of usability testing in the development of eHealth interventions, more diverse testing protocols applied in specific health contexts (eg, emergency departments [EDs]), for specific populations (eg, youth, their caregivers, and clinicians), or for specific types of eHealth interventions (ie, websites versus kiosks) are needed.

Further, eHealth researchers should develop usability protocols that are developmentally appropriate for the target users (ie, age and condition) and relevant to the specific context (ie, hospital or outpatient clinic) where they may be deployed. A scoping review by Maramba et al [7] identified 133 studies where usability testing informed the development of eHealth interventions. However, no studies in the review reported on the usability testing of eHealth interventions in the ED setting, and despite 9 studies being related to child health [7], only 2 studies included youth (aged 14-21 years) as usability testing participants [8,9]. This represents a significant research-to-practice gap as youth and their parents (eg, parents, caregivers, and/or legal guardians) are typically early adopters of eHealth interventions, and their insights could benefit broader adoption. Health services researchers need guidance on how to conduct or adapt usability tests to ensure that end users are appropriately involved in design. The aim of this protocol paper is to describe a youth-, parent-, and clinician-focused approach to usability testing of 2 eHealth interventions for pediatric EDs. This paper will highlight key testing session logistics, considerations for test user eligibility, testing activities and scenarios, adaptations for youth test users, and approaches to synthesizing multimethods usability data.

Methods

Study Design

This protocol paper describes one component of the emergency department discharge communication strategies (EDUCATE) study, which aimed to evaluate a co-design method for discharge communication tools for use in the pediatric ED [10]. Based on methodological guidance from Barnum [2] and calls for a more comprehensive approach to usability testing, as reported in previous literature [6], a multimethods approach including quantitative (ie, surveys and severity scoring) and qualitative (ie, open-ended interviews) data was used. Using a multimethods approach allowed us to view usability data from different lenses, with count and frequency data from surveys and experiential data from qualitative sources. The protocol was designed to support remote synchronous usability testing. Remote, synchronous usability testing has previously been shown to be as effective as in-person usability testing for eHealth interventions among both adults and youth [11]. Formative usability testing was used, where tools were evaluated through 2 iterative cycles with a small number of participants [2] to identify any errors prior to implementation. The Template for Intervention Description and Replication (TIDieR) checklist was used to guide the reporting of this protocol paper [12] (Multimedia Appendix 1).

Ethical Considerations

The study received ethical approval from the institutional review board at IWK Health (#1024004). All participants provided written informed consent prior to each usability test. Additional consent was obtained from a research team member whose image is included in the study materials. Following each usability test, participants received a unique identifier, and their data remained anonymous and confidential. Upon completion of the usability test, all participants received a CAD $30 (US $20.96) gift voucher as a reimbursement for their time.

Tool Development

During the first phase of the EDUCATE study, 2 electronic discharge communication tools were co-designed by parents, youth, and ED clinicians (ie, nurses and physicians) [13]. A full description of the co-design process will be published in a future publication and is briefly described here. Two co-design teams were established, one for asthma and one for concussion, and met 8 times over a 2-year period between 2020 and 2022. Each co-design team worked together to develop an interactive web-based tool that would address a key discharge

communication issue for youth and families visiting the ED. One tool was co-designed to help parents and youth decide whether to visit the ED during an asthma attack, while the second tool was co-designed to help parents and youth navigate the postconcussion recovery journey after leaving the ED. Two user design experts integrated the co-design teams' ideas into 2 digital tools, which were then assessed for usability.

Usability Testing Steps

The usability testing process involved four steps, based on usability testing literature [2]: (1) defining the user profiles, (2) the think-aloud process, (3) task-based scenarios, and (4) refining and retesting. Each usability test was facilitated by a researcher trained in mixed and multimethods health services research (MS). Previous literature shows that usability tests often use one approach (ie, quantitative, qualitative, or heuristic methods) to collect usability data, but few use multiple methods [7]. Therefore, a combination of quantitative and qualitative methods was used to gather comprehensive usability data and to identify as many usability issues as possible. The usability tests included a combination of quantitative self-report survey questions, qualitative think-aloud processes, observations, and open-ended interview questions, and were planned to last approximately 60 minutes. This protocol paper focuses on the usability testing process, while more details on recruitment, study setting, and outcome data will be reported in a future publication. Table 1 and the following section describes each of the four usability steps in detail, including how each step was adapted for each target population (ie, youth, parents, and ED clinicians).

Table 1. Overview of the usability testing process including each step and corresponding component of the usability test.

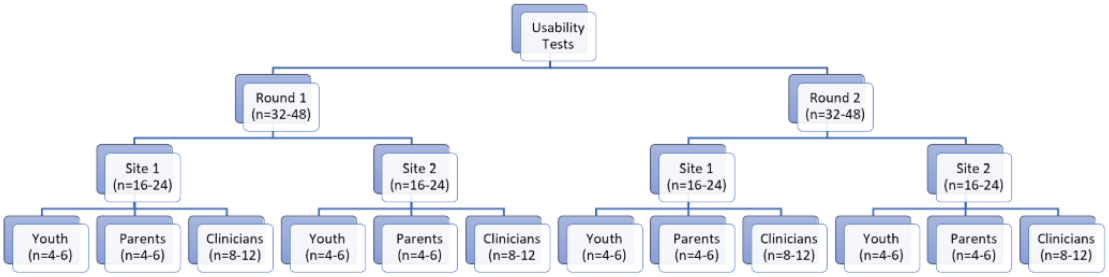
Step and item	Goal
Usability step 1: defining the user profiles	
Presession	
Screening questionnaire	• Determine eligibility for the usability test
Informed consent	• Gain written informed consent
Round 1 (total session time: 60 minutes)	
Opening script (5 minutes)	• Describe the study and provide an overview of tasks • Allow participants to ask questions
Demographic survey (5 minutes)	• Gather demographics, health care usage, and computer skills data
Usability step 2: think-aloud process—overview of the "think-aloud" process (5 minutes)	• Describe the think-aloud process • Go through 1 live example of the think-aloud process, using a familiar website (all participants) • Share a prerecorded video of the think-aloud process with a youth participant (youth participants only)
Usability step 3: task-based scenarios	
Task 1: first impressions (20 minutes)	• Gather initial thoughts about the tool • Complete a word desirability activity
Task 2: scenario-based activities (×2; 15 minutes)	• Gather qualitative and quantitative metrics related to specific tasks, designed to capture the main functions of the tool
Gibson survey (5 minutes)	• Gather additional quantitative usability testing data
Thank you and closing remarks (5 minutes)	• Thank participants for joining • Discuss compensation and next steps
Postsession	
Quantitative data analysis	• Gather time to complete tasks, number and frequency of errors, usability severity scores, and satisfaction data
Qualitative data analysis	• Gather qualitative feedback about usability issues and satisfaction with the tool
Usability step 4: refining and retesting	
Presession	
Screening questionnaire	• Determine eligibility for the usability test
Informed consent	• Gain digital e-consent
Round 2	
Demographic survey	• Gather demographic details about participants prior to testing
Posttask questionnaire	• Gather quantitative and qualitative usability and satisfaction data on a refined version of the tool through an asynchronous, remote usability test with a new group of end users

Step 1: Defining the User Profiles

Overview

Barnum [2] proposes that defining the user profile is an important first step in usability testing. As our tools were codeveloped by and for ED clinicians, parents, and youth, these 3 target groups were chosen as the user profiles. For this study, youth included any individual aged between 12 and 19 years who had visited the ED for either asthma or concussion in the past year. Parent users included any adult (>18 years) who visited the ED with their child for asthma or concussion presentations in the past year, and the clinician profile included any nurse or physician employed in a pediatric ED setting. Nielsen and Landauer [14] argue that 85% of usability issues could be identified with as few as 5 participants, and Barnum [2] proposes that formative usability testing is better suited to a smaller number of participants. Therefore, we aimed to include 2 to 3 participants from each user group (youth, parents, ED nurses, and ED physicians) for each tool across 2 study sites for a proposed sample of 16 to 24 participants from each site in each round of usability testing (Figure 1).

Figure 1. Overview of the expected number of usability testing participants to be recruited from each site for each round of testing for each tool.



Eligibility and Pretest Survey

To determine eligibility, a screening survey was administered to interested participants through the REDCap (Research Electronic Data Capture; Vanderbilt University) platform [15]. Since participants would be testing a digital tool, it was important to screen for health literacy level and access to a computer with audio/video capabilities. To assess health literacy level, the REDCap survey included branching so that parents would be directed to the METER health literacy test [16], which is shown to be a quick and valid measurement of health literacy level among adults. Youth were directed to the Health Literacy Assessment Tool 8 test [17], a quick, feasible and accurate health literacy assessment tool for youth [1]. Clinicians did not have to complete a health literacy test. The screening survey can be found in Multimedia Appendix 2. Participants provided written informed consent and agreed on a day and time to complete a test session with the facilitator (MS).

Test Session Setup

Participants joined the session remotely via the Zoom (Zoom Video Communications) using their own computer and webcam. The facilitator provided a brief overview of the study and allowed participants to ask questions to ensure that they understood the expectations of the usability test. The facilitator described that the aim of the usability test was to find problems with the tool and assured participants that their skills and abilities were not being evaluated. This was important to create a safe testing space, particularly for youth participants. Participants were then asked to complete a demographic questionnaire on REDCap prior to the start of the test. The facilitator shared a link to the survey and allowed the participant to complete the test in real time to ensure higher completion rate. Sessions were video recorded.

Step 2: the Think-Aloud Process

The think-aloud process involves participants talking through their thought process as they complete a task or solve a problem [18]. This approach is common in usability tests of eHealth interventions [6,7] and is valuable for understanding participants' decision-making processes rather than strictly observing their behaviors [19,20]. Following the completion of the demographic survey, and immediately prior to the start of the usability test, the facilitator explained to participants how to use a think-aloud approach during the usability test. A mock example was used, which involved navigating a popular Canadian departmental store's website so that test users could become familiar with the think-aloud process in a web-based environment they recognized. While it was important to demonstrate the think-aloud process with all participants, the co-design team suggested that a second think-aloud example featuring a youth should be modeled for youth participants prior to their usability test. Therefore, a youth member of the co-design team created a 1-minute video of themselves using the think-aloud process to find their way on a popular theme park's map (Figure 2). This was played for all youth participants prior to the start of the usability test. Examples of the think-aloud process were shared with the co-design teams and refined based on their feedback prior to starting the usability tests with participants.

Figure 2. A screen capture of the youth-led think-aloud example.

Step 3: Task-Based Scenarios

Overview

Once participants confirmed that they were comfortable with the think-aloud process, the facilitator started video-recording the usability testing session. The facilitator used a variety of techniques to fully evaluate the usability of the eHealth intervention by adapting traditional usability methods for the end user population (ie, youth, parents, or clinicians). Before sharing a link to the tool, the facilitator shared a link to a web-based Microsoft Word document to guide the user through tasks and included visual prompts to support the scenario-based exercises. This approach was used to eliminate the need for alternating screen sharing by the facilitator and participant and to reduce complexity in the remote testing environment [21]. Six documents were developed, based on the 6 unique user groups (ie, youth with asthma, their parents, and their clinicians; and youth with concussions, their parents, and their clinicians).

Task 1: First Impressions

The first task in the usability test was designed to gather participants' first impressions of the tool. This crucial step in usability testing can quickly determine whether users like or dislike a tool in about 80% of cases [2]. After opening the tool, users were invited to click around, using the think-aloud process to describe their initial reactions to the tool. The facilitator used open-ended prompts to encourage verbalizations of what the participant was thinking; these included the following: "What are your first impressions of the tool?" "What do you think the purpose of the tool is?" Participants were then asked to choose 5-10 words from an adapted list of 118 desirability reaction words of Benedeck and Miner [22]. For usability tests, the Nielsen Norman Group [23] suggests adapting the original list to include approximately 25 words that are appropriate for the user interface being evaluated, with at least 40% of chosen words having a negative connotation. This activity aimed to gather additional user satisfaction data while helping participants, particularly youth, feel more comfortable about sharing their honest thoughts about the tool. This approach has been successfully used in previous usability tests [24]. The list of desirability words can be found in Multimedia Appendix 3.

Task 2: Scenario-Based Questions

Next, participants were presented with a scenario relevant to their user identity (ie, youth, parent, or clinician) and medical condition (ie, asthma or concussion). Each scenario was designed by a research team member (MS) based on the user's persona, as outlined by Quesenbery and Brooks [25]. This involved crafting a situation with the user as the main character where they must achieve a specific goal by using the eHealth intervention being tested. The facilitator used a visual guide and a predetermined script to describe a scenario and then ask participants to complete 2 tasks. The tasks were designed to walk participants through key features of the tool so that additional navigation and usability errors could be easily identified. Participants were asked to use the think-aloud process to describe their thoughts and decisions as they completed each task. Participants were asked open-ended questions about the scenario-based activities, such as the following: "How did you find using the tool to complete that task?" "Is there anything you would change about the tool to make that task easier?" The user-specific tasks are outlined in Multimedia Appendix 4.

Global Feedback

Following the scenario-based tasks, participants were asked open-ended questions about the tool, such as the following: "Is there anything else you would change about the tool to make it better?" "On what device/format would you most likely use this tool if you were to use it in the future?" Quantitative data about

the functionality and satisfaction of the tool were captured through a REDCap survey, which was administered to participants at the end of the usability test. The facilitator shared a link to the survey using the chat feature of the web-based meeting platform and waited until participants completed the task in real time, to ensure a high completion rate. This posttest was adapted from a survey by Gibson et al [26], which is a validated tool for collecting patient and provider satisfaction data on educational resources. The survey by Gibson et al [26] aims to gather information on visual appeal, functionality, content, and intended use. Branching was used to direct participants to the correct survey in REDCap, as the youth survey also included a question to understand the impact of seeing a youth-led example of the think-aloud process. The posttest surveys adapted from Gibson et al [26] can be found in Multimedia Appendix 5 [26].

Step 4: Refining and Retesting

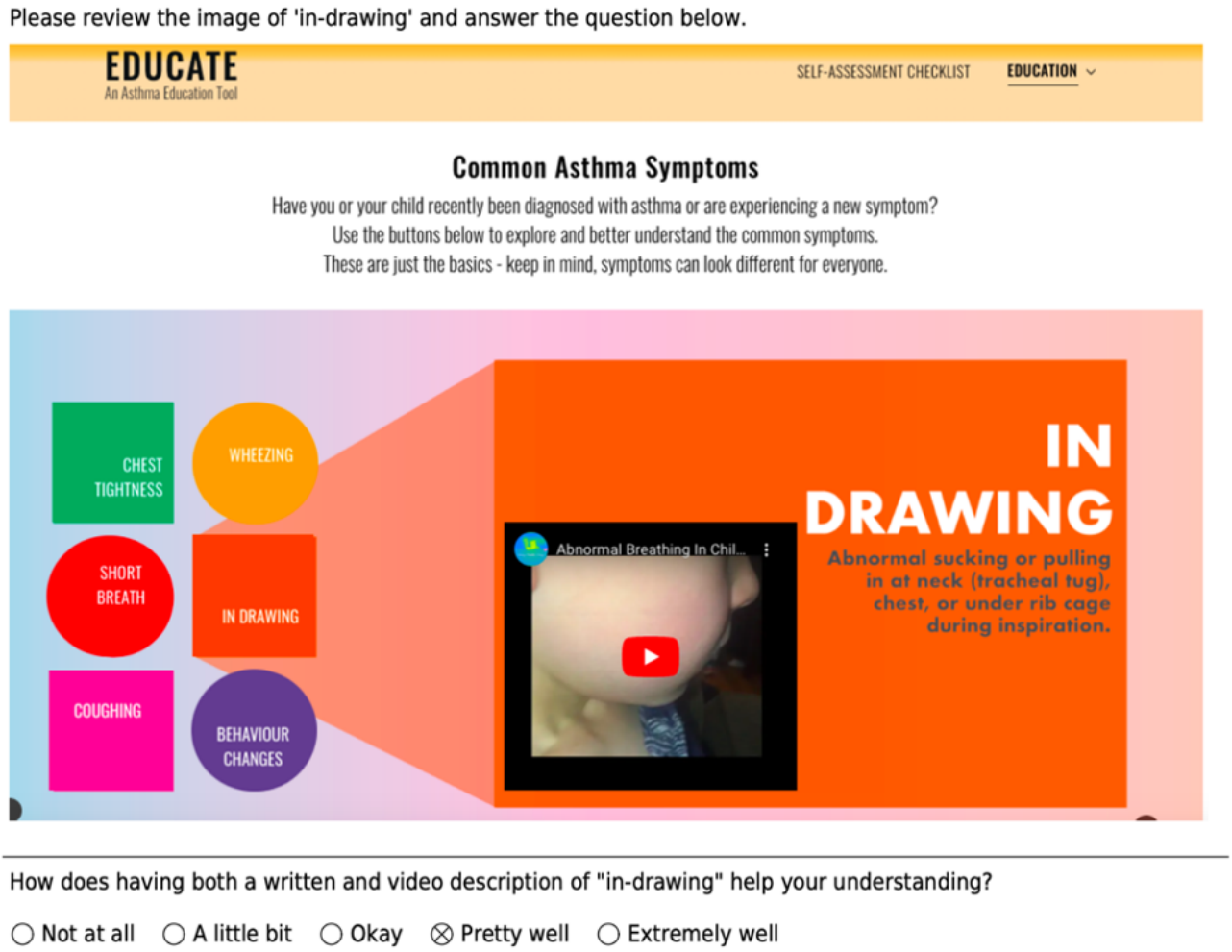
Following each usability testing session, the video recording was uploaded to a secure, password-protected internet server. Four coders (MS, JC, AG, LW) watched the videos and independently scored the usability issues using a combination of Nielsen's [27] scoring system and qualitative analysis. The Nielsen scoring system for severity of usability issues is based on a 5-point scale, ranging from 0 (no usability problem) to 4 (catastrophic usability problem) [27]. Nielsen [27] proposes 3 factors associated with a usability issue: frequency of the problem, impact of the problem, and persistence of the problem. If an eHealth intervention is evaluated to include only minor usability issues (score of 0-2), then the tool may be released without further refinement, while an eHealth intervention with major or catastrophic issues (score of 3-4) should undergo alterations before another round of testing and/or public release [27]. Each coder scored the recorded usability sessions using a deductive approach, following Nielson's [27] scoring system. A numerical value and descriptive details were entered into an Excel (Microsoft Corp) sheet to explain the reasoning underlying each score. Coders then met to discuss their scores and reach a consensus on final severity scores for each usability test.

In conjunction with Nielson's [27] severity scoring step, each reviewer made notes about users' open-ended responses or comments during the usability session. For example, if users described their dislike of a certain feature of the eHealth intervention, the reviewer documented this during the qualitative analysis. Directed content analysis was used to understand the qualitative data and identify the most reported user issues [28]. This type of qualitative analysis allows for a deeper interpretation of qualitative data, often informed by a theory or previous research, and allows for the quantification of the data [28]. In this study, the quantitative findings informed the qualitative data analysis and allowed researchers to calculate the number of user issues with additional context. Following qualitative analysis and severity scoring of each usability test, a description of the most severe usability issues and a list of proposed changes was sent to the design team. The developers then refined the tools by addressing severe usability issues and the most common cosmetic concerns.

The refined tools were brought to each co-design team for further input before undergoing a second round of usability testing with another sample of target users. As the first round aimed to identify catastrophic usability issues, the second round was intended to identify additional, minor issues. This second round of usability testing involved a modified, remote, asynchronous approach to capture any additional usability issues in the tools. As the first round aimed to identify catastrophic usability issues, the second round was intended to identify additional minor issues. Therefore, a modified approach was used to quickly gather usability information without placing unnecessary burden on participants. To capture remote usability data, images and video clips were embedded in a new REDCap survey to demonstrate the main functions and features of the tools (Figure 3). Participants then completed posttask questionnaires using a Likert scale, informed by Nielson's [27] methods, with additional free-text boxes to capture qualitative data. Basic demographic questions were also included in the survey.

The final version of each tool was then presented to the co-design team members for their thoughts. Each team made final decisions about what refinements should be incorporated into each tool, signaling the end of the usability testing process.

Figure 3. Example of an embedded video clip, along with posttask questions from the asthma tool.



Results

The first round of usability testing was conducted between December 2021 and July 2022, while the second round of testing was conducted between November 2022 and March 2023. Data analysis of round 1 took place in July and August 2022 and informed the second round of testing. The final results from both rounds of usability testing will be shared in a future publication. Outcome data will include an overview of severity of usability scores from round 1, qualitative feedback on tool usability and satisfaction from rounds 1 and 2 of testing, and demographic details about study participants. Details about the changes made between rounds 1 and 2 of usability testing will also be presented and may include changes such as button size or location, colors, and new navigation pathways. We will describe any observations related to user characteristics and feedback and identify opportunities for future usability testing and implementation.

Discussion

Anticipated Findings

This paper addresses an important gap in the academic usability literature by detailing a co-designed approach to usability testing that was adapted for youth, parents, and clinicians. In particular, this paper describes multiple adaptations that were made to the testing procedures to address developmental stages and comfort levels of youth participants. These adaptations included modeling the think-aloud technique by other youth, allowing for a test-and-try before initiating the recording, screening for the appropriate level of health literacy so participants would be able to complete tasks, using multiple methods for soliciting feedback (self-report survey, observation, and interviews) so participants had varied opportunities to express opinions and suggestions, keeping testing sessions brief and accessible offsite (ie, via Zoom), keeping the sessions short (<60 minutes), using branching logic in data collection methods so participants only accessed information relevant to them, and including less cognitively demanding activities (eg, word desirability activity) to solicit feedback. By applying these approaches to usability testing, it is anticipated that the feedback will be highly relevant, leading to a more user-centered product. We expect that the first round of usability testing will lead to several changes to the tools, while the second round may result in fewer or more minor changes. By using a co-design approach and bringing the usability feedback to each co-design team for further consideration, the next step of piloting the 2 tools in ED settings will lead to positive uptake and outcomes. Previous studies have indicated the benefits of using a co-design approach to engage more end users [29]. However, few usability studies tend to include the youth perspective, even when they are the target

audience [7]; hence, we expect this paper to be a significant and beneficial contribution to the usability literature.

Strengths and Limitations

While this paper provides a comprehensive overview of an approach to usability testing for youth, there are several limitations to consider. Due to the remote nature of the usability tests, participants require internet and computer access. Further, among individuals who do complete a remote usability test, the differences in home environments and technical equipment may affect the quality of the testing process [21]. Future work may focus on offering technical support or request a specific technology setup, as these concerns may have limited participation for some individuals, particularly those from lower socioeconomic backgrounds. Additionally, while it is not a requirement to speak English as a first language to participate in the study, the digital tools were only designed in English, and therefore non–English speakers may be unable to complete the usability tests. Although a small sample of participants is needed to identify most usability issues, a small sample may reduce the generalizability of the findings, which may be seen as a limitation. We have future research planned to mitigate both of these concerns by co-designing multilingual digital tools with broader populations to ensure that the specific needs of clinicians, parents, and youth from varied backgrounds are met. Finally, while the findings of the usability tests may not be generalizable to a non-ED health care context or for individuals presenting with medical conditions apart from concussion and asthma, the techniques used to engage youth may be applied to any usability testing setting.

Key Recommendations and Conclusion

Youth provide valuable perspectives into eHealth intervention designs and therefore should be included in the usability process; however, there is a significant gap in the literature around usability testing with youth in health services. Therefore, researchers may find the methods used in this paper helpful for guiding usability tests with youth participants in other health care contexts. Further outcome data are needed to determine what works well in youth-based usability studies, some of which will be shared through a future publication presenting the outcomes of the detailed approach.

Acknowledgments

We would like to acknowledge the members of each co-design team who designed the digital health tools assessed through usability testing.

Data Availability

The datasets generated during this study are not publicly available because the results have not yet been analyzed but are available from the corresponding author on reasonable request.

Conflicts of Interest

None declared.

Multimedia Appendix 1
TIDieR (Template for Intervention Description and Replication) reporting guidelines.
[DOCX File , 495 KB - resprot_v14i1e64350_app1.docx]

Multimedia Appendix 2
Screening survey for usability participants.
[DOCX File , 209 KB - resprot_v14i1e64350_app2.docx]

Multimedia Appendix 3
The list of desirability words.
[DOCX File , 14 KB - resprot_v14i1e64350_app3.docx]

Multimedia Appendix 4
An overview of the user-specific tasks.
[DOCX File , 20 KB - resprot_v14i1e64350_app4.docx]

Multimedia Appendix 5
Posttest surveys adapted from Gibson et al [27].
[DOCX File , 279 KB - resprot_v14i1e64350_app5.docx]

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Abbreviations

ED: emergency department
EDUCATE: emergency department discharge communication strategies
REDCap: Research Electronic Data Capture
TIDieR: Template for Intervention Description and Replication

Edited by A Schwartz; submitted 16.07.24; peer-reviewed by E Bai; comments to author 13.09.24; revised version received 08.11.24; accepted 27.02.25; published 14.04.25.

Please cite as:
Somerville M, Wozney L, Gallant A, Curran JA
Designing eHealth Interventions for Pediatric Emergency Departments: Protocol for a Usability Testing Study With Youth, Parent, and Clinician Participants
JMIR Res Protoc 2025;14:e64350
URL: https://www.researchprotocols.org/2025/1/e64350
doi:10.2196/64350
PMID:

Protocol

iCogCA to Promote Cognitive Health Through Digital Group Interventions for Individuals Living With a Schizophrenia Spectrum Disorder: Protocol for a Nonrandomized Concurrent Controlled Trial

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Abstract

Background: Cognitive impairments are a key aspect of schizophrenia spectrum disorders (SSDs), significantly affecting clinical and functional outcomes. The COVID-19 pandemic has heightened concerns about mental health services and cognitive stimulation opportunities. Despite evidence-based interventions like action-based cognitive remediation (ABCR) and metacognitive training (MCT), a research-to-practice gap exists in their application across mental health settings.

Objective: The iCogCA study aims to address this gap by implementing digital ABCR and MCT through a national Canadian collaborative effort using digital psychological interventions to enhance cognitive health in SSDs.

Methods: The study involves 5 Canadian sites, with mental health care practitioners trained digitally through the E-Cog platform, which was developed by our research group. Over 2.5 years, participants with SSDs will undergo pre- and postintervention assessments for clinical symptoms, cognition, and functioning. Each site will run groups annually for both ABCR and MCT, totaling ~390 participants. A nonrandomized concurrent controlled design will assess effectiveness design, in which one intervention (eg, ABCR) acts as the active control for the other (eg, MCT) and vice versa, comparing cognitive and clinical outcomes between the interventions using generalized linear mixed effect modeling. Implementation strategy evaluation will consider the digital

platform's efficacy for mental health care practitioners' training, contextual factors influencing implementation, and sustainability, using descriptive statistics for quantitative data and thematic analysis for qualitative data.

Results: A pilot pragmatic trial has been conducted previously at the Montreal site, evaluating 3 early implementation outcomes: acceptability, feasibility, and engagement. Patient and therapist acceptability was deemed as high and feasible (21/28, 75% of recruited service users completed therapy, rated feasible by therapists). Technology did not appear to significantly impede program participation. Therapist-rated levels of engagement were also satisfactory. In the ongoing study, recruitment is underway (114 participants recruited as of winter 2024), and intervention groups have been conducted at all sites, with therapists receiving training via the E-Cog learning platform (32 enrolled as of winter 2024).

Conclusions: At least 3 significant innovations will stem from this project. First, this national effort represents a catalyst for the use of digital technologies to increase the adoption of evidence-based interventions and will provide important results on the effectiveness of digitally delivered ABCR and MCT. Second, the results of the implementation component of this study will generate the expertise needed to inform the implementation of similar initiatives. Third, the proposed study will introduce and validate our platform to train and supervise mental health care practitioners to deliver these interventions, which will then be made accessible to the broader mental health community.

Trial Registration: ClinicalTrials.gov NCT05661448; https://clinicaltrials.gov/study/NCT05661448

International Registered Report Identifier (IRRID): DERR1-10.2196/63269

(JMIR Res Protoc 2025;14:e63269) doi:10.2196/63269

KEYWORDS

schizophrenia spectrum disorders; digital technology; cognitive health; cognitive remediation; metacognitive training; schizophrenia; digital group interventions

Introduction

Background

Schizophrenia and related psychoses present debilitating challenges, imposing an enormous burden on individuals, families, and communities [1,2] and are characterized by symptom recurrence, social deterioration, and cognitive impairments [3-8]. Most affected individuals experience persistent positive (eg, hallucinations and delusions) and negative symptoms (eg, amotivation, avolition, and reduced expressivity), alongside notable cognitive challenges like difficulties in verbal memory, executive functions, and attention. In addition to these impairments are cognitive distortions [9], affecting reasoning and information processing and, collectively, represent a core feature of schizophrenia, impacting clinical and functional recovery [10-13]. Thus, addressing overall cognitive health in schizophrenia is crucial. Over the past 25 years, advancements in psychological interventions, including cognitive remediation (CR) and metacognitive training (MCT), have shown promise for the treatment of schizophrenia spectrum disorders (SSDs). Both CR and MCT have been found to enhance cognitive functioning and decrease cognitive biases [14,15].

Cognitive Health Interventions in Schizophrenia: State of the Evidence and Delivery Format

Meta-analyses affirm the effectiveness of CR in enhancing cognition [14,16,17] and MCT in addressing cognitive biases [15,18]. Notably, various mental health practitioners with an understanding of cognitive processes can be trained to provide these interventions, providing flexibility in service delivery [19-21]. Delivered in a group format, these interventions enable practitioners to reach multiple service users simultaneously [20]. Research indicates the feasibility of using technology for remote cognitive assessment and psychological interventions, as individuals with psychosis express interest and willingness to engage with digital mental health services [22-24] and find this mode of communication more satisfying and less challenging than observed in the general population [25].

Preliminary Work on Remote Delivery of Cognitive Health Interventions

Our preliminary work investigated the remote delivery of action-based cognitive remediation (ABCR) and MCT [26]. ABCR is a distinct form of CR, which integrates the traditional cognitive training techniques of CR with simulated workplace scenarios and goal setting [27]. This work involved evaluating 3 crucial early implementation outcomes: acceptability, appropriateness, and feasibility for both patients and therapists. Across 6 cohorts (3 ABCR and 3 MCT) conducted within Montreal, patients expressed high acceptability, with overall satisfaction for expectations and perception of progress. The interventions demonstrated feasibility; 36 participants completed therapy, attending an average of 10 MCT sessions and 12 ABCR sessions.

Using recently developed measures [28], therapists also reported excellent acceptability, appropriateness, and feasibility of the interventions [26]. Several facilitators and barriers to delivering these digital interventions were also identified. Barriers comprised patients' clinical status (eg, more severe symptomatology and medication side effects), interaction issues (eg, lack of involvement and decreased accountability), technological challenges (eg, access to devices and the internet), program elements (eg, language options), and scheduling conflicts. On the other hand, facilitators included patients' motivation to learn, therapist characteristics (eg, warmth and proper training), financial support for internet connectivity, program support (eg, education on interventions and ice breakers), and logistical adjustments (eg, offering evening sessions and forming smaller groups).

Objectives

Having established the acceptability, appropriateness, and feasibility of our digital interventions that collectively represent the early stages of implementation, the next step is to examine how the proposed digital strategies promote the uptake of these interventions across mental health care settings. A major challenge with evidence-based psychosocial interventions is that very few are subsequently tested in effectiveness or implementation trials and thus have little impact on population health [29]. The field of implementation science has emerged over the last 20 years, promoting strategies to adopt and integrate evidence-based interventions and change practice patterns within specific settings. Implementation frameworks, such as the Consolidated Framework for Implementation Research (CFIR) [30], provide the roadmap and tools to achieve this. To test this implementation strategy, we propose a study spanning 5 different mental health care sites across Canada. In collaboration with partners and knowledge users, we will conduct a hybrid effectiveness-implementation trial and create a bilingual digital learning platform (English and French) to ensure the long-term use of these digital interventions nationwide. The first objective of this study is to investigate the clinical effectiveness of the digital modality of ABCR and MCT. The second objective of the study is to investigate the implementation strategy involving (1) the contextual factors influencing the digital delivery of cognitive health interventions [31], (2) the effectiveness of a digital learning platform (E-Cog) to train mental health practitioners, and (3) the sustainability of the maintenance of these interventions within current clinical settings.

Methods

Study Design

A hybrid effectiveness-implementation trial [32-34] relying on digital technology will be used. The effectiveness component involves assessing the outcomes of these interventions, while the implementation component focuses on conducting the research in a way that emulates the naturalistic clinical setting. This design is ideal for transferring evidence-based behavioral interventions into real care environments [32-35], as it confirms clinical effectiveness while targeting necessary procedures to deliver and sustain such interventions in real-world care settings. A nonrandomized concurrent controlled design will be used to assess clinical effectiveness where one intervention acts as the active control for the other. The nonrandomized concurrent controlled design was selected, as it eases access to the preferred intervention by service users, overcoming the challenges of randomizing participants in real care settings and facilitating recruitment.

Study Setting

This study takes place across 5 sites providing care to those with psychotic disorders across Canada. These sites include the Centre intégré universitaire de santé et de services sociaux (CIUSSS) de l'Ouest-de l'Ile de Montréal, Royal Ottawa Health Care Group, Kingston Health Sciences Centre, Ontario Shores Centre for Mental Health Sciences in Toronto, and Vancouver Coastal Health. We will recruit 390 service users across the 5 sites.

Selection Criteria

Inclusion criteria include 18 years of age or older; diagnosis of affective or nonaffective psychosis or related disorder; followed and treated by a clinician at one of the services mentioned earlier; considered symptomatically stable and capable of using the digital platforms and participating in intervention groups, as judged by their primary clinicians; access to a private space to ensure group confidentiality; and provision of emergency contact and consent to allow researchers to contact their clinician or emergency services in the event of an emergency during study procedures. Most criteria are present for the safety of the group and participants. Exclusion criteria include intellectual disability, hospitalization at the time of recruitment, inability to speak or read English or French, and high suicide risk as per evaluation. We will recruit 4-6 mental health practitioners per site who will complete training on the E-Cog training platform to deliver the 2 cognitive health interventions. Practitioners will be eligible if they have a background in psychology, social work, nursing, or any other health-related training.

Recruitment

Recruitment for this study uses a multimodal communication strategy designed to effectively reach potential participants. This strategy includes displaying informational flyers on hospital television screens, distributing email newsletters to health care employees, and presenting intervention details to case managers to facilitate referrals. Additionally, recruitment materials will be posted in clinic waiting rooms. n example of the recruitment pamphlet is provided in Multimedia Appendix 1. Health care team members can refer eligible participants or obtain consent for the research team to make direct contact. Participants are permitted to be engaged in other psychological or psychosocial interventions while participating in our study. Data on whether they are currently receiving other interventions will be collected.

Ethical Considerations

This study has been approved by the respective research ethics boards (REBs) of the 5 mental health sites and their partner institutions. The study will be conducted in Montreal (CIUSSS de l'Ouest-de l'Ile de Montréal; REB 2023-561) [36], Ottawa (Royal Ottawa Health Care Group; REB 2022034) [37], Kingston (Kingston Health Sciences Center; REB 6037321) [38], Toronto (Ontario Shores Centre for Mental Health Sciences; REB 38116) [39], and Vancouver (Vancouver Coastal Health; REB H22-02300) [40]. The research adheres to the principles outlined in the Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans and complies with Canadian legal requirements for scientific research involving human participants, including the Privacy Act and applicable clinical trial regulations [41]. Participants provide informed consent through a comprehensive process that includes a detailed explanation of the study's objectives, procedures, potential risks and benefits, and their rights as research participants, in accordance with the Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans guidelines. This process will involve both written documentation and verbal discussion, and participants will be informed of their right to withdraw from the study at any time without consequence to their ongoing care. Particular attention will be given to ensure

an understanding of these processes among individuals with SSDs. All collected data will be deidentified using unique participant codes, with personal identifiers stored separately in encrypted files accessible only to authorized research personnel. In terms of compensation, participants will receive monetary remuneration for each completed assessment measure, with a standardized gift card amount of US $18 per assessment session or focus group. This compensation structure ensures fair and consistent reimbursement for participants' time and effort while maintaining ethical standards for human participant research. The compensation details will be clearly communicated to participants during the informed consent process to ensure transparency and avoid undue influence on participation decisions.

Measures

To assess the effectiveness of the 2 digital cognitive health interventions (objective 1), primary outcomes will encompass quantitative measures of cognitive function for ABCR and cognitive biases for MCT. These outcomes were selected in alignment with the primary targets for each intervention and primary outcomes assessed in the past ABCR and MCT studies. To capture the full extent of these outcomes, both objective and self-report measures were selected. The collection of these primary outcomes will be prioritized. Secondary outcomes for both interventions will include clinical and functional measures. Propensity score matching will consider background characteristics such as sociodemographic variables, illness duration, medication dosage, length and nature of prior treatment, and subjective reports of cognitive capacity and biases. To promote data quality, research staff will partake in centralized interrater reliability sessions every 6 months. To evaluate the implementation strategy (objective 2), a combination of quantitative and qualitative data will be gathered. Refer to Table 1 for a breakdown of the data types to be collected, organized by objectives, time points, and stakeholders.

Table 1. Summary of the type of data to be collected as a function of objectives, time points, and stakeholders.

Objectives or data type and measures	Measurement time points	Stakeholder groups
1. Effectiveness (quantitative)		
Cognitive tests or tasks: • Brief version of the CANTAB[a] computerized battery (Intra-Extra Dimensional Set Shift, Stocking of Cambridge, and Spatial Working Memory)[b] [42] • Wechsler Memory Scale (Logical Memory Subscale)[b] [43] • Cognitive bias against disconfirmatory evidence story[b] [44] • Jumping to conclusions (Beads)[b] [45]	• Preintervention • Postintervention • 3-month follow-up	Service users
Subjective cognition: • Subjective Scale to Investigate Cognition in Schizophrenia (Brief)[b] [46] • Cognitive Motivation Scaleb [47] • Davos Assessment of Cognitive Biases Scale[b] [48]		
Symptoms: • Positive and Negative Syndrome Scale-6 [49] • Brief Negative Symptom Scale [50] • Psychotic Symptom Rating Scales [51]		
Psychosocial: • Self-Esteem Rating Scale—Short Form [52] • Overall Emotional and Social Loneliness Scale [53] • Short Warwick-Edinburg Mental Well-Being Scale [54] • Questionnaire About the Process of Recovery [55] • Basic Psychological Need Satisfaction and Frustration Scale [56] • Autonomous-Controlled Motivation for Intervention Questionnaire [57] • Personal and Social Performance [58]		
Intervention: • Health Care Climate Questionnaire [59] • Autonomous-Controlled Motivation for Intervention Questionnaire [57] • MMI[c] Cognitive Training Questionnaire [60] • Satisfaction With Therapy (STQ[d]) [61] • Time spent on cognitive drill exercises (ABCR[e]) • Last log in (iCog platform)	• Midintervention	Service users
2. Implementation (quantitative and qualitative)		
Evaluation of E-Cog platform: • Number of practitioners invited to participate in the E-Cog training • Number of practitioners agreeing to participate in E-Cog training • Reasons for nonparticipation or participation • Number of practitioners not agreeing to participate in E-Cog training • Total number of attendees participating in all of the training modules • Total number of attendees per session or module • Semistructured interview (health care practitioners)	• Preintervention • During intervention	Health care practitioners and service users
Evaluation of factors influencing the implementation of the 2 digital interventions: • E-Therapy Attitudes and Process Questionnaire—Therapist Version [62] • Semistructured interview (service users and health care practitioners)	• Postintervention (8-12 and 24-30 months after the 2 interventions are implemented)	Health care practitioners and service users
Sustainability: • Program Sustainability Assessment Tool [63] • Monitoring of the intervention offer after an effectiveness trial at each site	• Postintervention	Health care practitioners and service users

[a]CANTAB: Cambridge Neuropsychological Test Automated Battery.

[b]Denotes primary outcomes in the study.

[c]MMI: MUSIC Model of Academic Motivation Inventory.

[d]STQ: Satisfaction Therapy Questionnaire.

[e]ABCR: action-based cognitive remediation.

Cognitive Health Interventions

Interventions will be delivered through a secure videoconference platform. Network-connected tablets will be provided as necessary for the trial duration. ABCR [27,64] sessions consist of computer-based cognitive training activities (Brain Training Pro; 60%), teaching of problem-solving strategies (20%), and transfer activities (20%). Transfer activities include discussing and role-playing how cognitive skills are applied in everyday life and teaching potential strategies for overcoming cognitive challenges. ABCR targets include processing speed, attention, memory, executive functions, and social cognition, which are all commonly impaired in psychosis [12]. ABCR will be delivered in 16 sessions lasting 1.5 hours each over an 8-week period. MCT targets cognitive biases and errors in judgment underlying delusions using the theoretical foundations of cognitive behavioral therapy [65]. Sessions consist of discussions and activities aimed at increasing participants' awareness of distortions and expanding their current problem-solving strategies. MCT will be delivered in 12 sessions lasting 45-60 minutes each over 6 weeks.

Both interventions will be offered at all sites. Depending on the site, interventions will either be offered concurrently or in sequence. Intervention group allocation follows a personalized, participant-centered approach. Potential participants will meet individually with the research coordinator at their site, who will provide a comprehensive overview of both interventions. Together, they will collaboratively determine which intervention best aligns with the participant's personal goals and preferences. To maximize participant benefit and engagement, individuals will have the opportunity to complete the alternative intervention after finishing their initial chosen intervention. This flexible approach ensures that participants can potentially benefit from both interventions.

To improve adherence, participants will be contacted prior to each session with reminders. If participants miss several sessions in a row, therapists or a research assistant will contact them to confirm their interest in continuing the intervention and discuss any barriers to their participation. If any adverse reactions occur during the trial, participant involvement in our study may be discontinued after a discussion with the research team. Finally, to improve and track treatment adherence, sessions will be audio recorded, and 2 sessions from each of the ABCR and MCT groups will be randomly selected for review by 2 experienced facilitators using the treatment integrity assessment tool.

Training Platform

E-Cog training platform [66] is a digital platform providing training certifications for ABCR and MCT interventions developed by our group following the analyze, design, develop, implement, and evaluate model for the design of digital learning platforms [67]. Each training certification includes three training modules: (1) impact of cognitive impairments in psychosis and an introduction to remediation strategies (2 hours), (2) technological tools for digital mental health (1 hour), and (3) theoretical foundations and practical delivery of ABCR (~9 hours) or MCT (~12 hours). After obtaining the training certification, mental health practitioners participate in weekly supervision by a dedicated experienced trainer using a secure videoconferencing software. Screenshots from the training platform can be found in the multimedia appendices (Multimedia Appendices 2-4).

Involvement of Individuals With Lived Experience

Peer support workers have been involved at different stages of the project. The pilot study, which informed this study, involved 2 peer support workers in the project committee. In this study, our peer support worker has been providing continuous consultation, which has led to changes throughout the study (eg, adapting intervention materials). Our peer support worker will also be involved in the intervention groups and will be coconducting the service user qualitative interviews.

Statistical Analysis

Power

Monte Carlo simulations computed in R (R Foundation for Statistical Computing) were used to estimate the required sample size for our proposed models. Our analyses, based on simulated data, suggest that a total sample size of 300 provides enough statistical power (up to 90%) to detect anticipated effect sizes on primary outcomes of cognitive capacity and cognitive bias based on values from our group and those reported in the literature (CR: d=0.50 and MCT: g=0.27) [9,20,27,31]. The attrition rate for our digital groups has been approximately 20%; we will nonetheless conservatively adjust for an attrition rate of 30%. When considering the propensity score, this results in a requirement of 390 participants. Comparable studies using the same interventions and statistical methods in in-person settings have included similar sample sizes as those proposed at our individual sites [68,69]. Further, this sample size will allow us to detect anticipated effect sizes on secondary outcomes related to symptomatology (CR: d=0.28 and MCT: g=0.38) [70,71] and functioning (CR: d=0.36-0.51 and MCT: d=0.37) [31,71,72]. We also anticipate that the proposed sample size will be adequate to explore sex- and gender-related differences using subgroup analyses of 2 (male and female) and 4 (men, women, nonbinary, and other) groups, respectively.

Data Analysis

Data related to the analysis of objective 1, focusing on clinical effectiveness, will be compared between both interventions. Primary and secondary outcomes will be compared between the 2 interventions, using one as the active control for the other. First, propensity score matching will be used to identify a subset of participants who will comprise the active control group that is equivalent to the intervention group on background variables (sociodemographic variables, illness duration, medication dosage, length and nature of prior treatment as well as subjective reports of cognitive capacity and cognitive biases). Then, Z-standardized outcome data will be compared between the groups with generalized linear mixed effect modeling techniques using R software. Factors of interest will include fixed time (pre, post, and follow-up), fixed treatment (ABCR and MCT), fixed time and treatment interaction (time*treatment), random site (CIUSSS de l'Ouest-de l'Ile de Montréal, the Royal's Institute in Ottawa, Kingston Health Sciences Centre, Ontario Shores Centre for Mental Health Sciences in Toronto, and Vancouver Coastal Health), random intercepts (participants'

ID), and random slopes (participant*time). Age, illness duration, medication dosage, length, and nature of prior psychological treatment will also be included as fixed covariates. This procedure will be done twice, with the active control group subset using propensity score matching. This approach ensures that participants are not counted twice and is an integral part of the propensity score matching procedure. Statistically, performing the procedure twice helps to validate the robustness of the matching process without introducing bias, as each participant is only included once in each comparison. Specifically, the procedure will be as follows: (1) ABCR as the intervention and MCT as the active control and (2) MCT as the intervention and ABCR as the active control. Missing data pattern will be assessed for whether it is missing completely at random, missing at random, or not at random [73]. If data are missing at random, multiple imputation will be applied [74]; if data are missing not at random, then the robustness of the primary analyses will be evaluated through sensitivity analyses.

Analyses for all implementation objectives will be executed using descriptive statistics for quantitative data and thematic analysis for qualitative data, following Braun and Clarke's [75] interpretive descriptive approach. This method emphasizes the researcher's active role in the analytical process, allowing for a nuanced understanding of themes such as facilitators and barriers to implementation, identified from CFIR semistructured interviews. Investigator triangulation will be used, with 3 independent raters conducting iterative qualitative analyses until a consensus (≥80%) is reached. A convergent quantitative-qualitative mixed methods design [76] will facilitate a comprehensive comparison of results from quantitative and qualitative analyses, aiming to develop a holistic understanding of factors influencing implementation. Side-by-side comparison tables will support this analytical process and engage implementation teams in interpretation. To ensure reflexivity, member checks will be conducted with participants to validate findings, ensuring that their perspectives and interpretations are accurately represented and that any potential biases in the researcher's analysis are addressed. This methodological framework is designed to uphold rigorous standards in qualitative research while ensuring that the findings are credible, dependable, and relevant to broader contexts. All qualitative analyses will be done using NVivo (version 15; Lumivero).

Results

A pilot pragmatic trial [26] has been conducted previously at the Montreal site, where 6 cohorts (3 ABCR and 3 MCT) were run, evaluating 3 early implementation outcomes: acceptability, feasibility, and engagement. Of the 28 participants attending at least 1 session, 21 completed more than half of the sessions. All completers reported a positive experience with therapy, 2 of 3 were not bothered by the remote setting, and 16 trusted the confidentiality of the information shared. Technology did not appear to significantly impede program participation. Therapist-rated levels of engagement were also satisfactory [26].

This study was approved by the institutional review board by September 2023. From September 2022 to January 2023 staff training was conducted across all 5 sites. Intervention materials including intervention manuals and digital portals began in June 2022 and continued until November 2023. Therapist training began on the E-Cog learning platform in April 2023 and is ongoing. All sites began recruitment in 2023 and have run cohorts of MCT and ABCR in their respective regions. Quantitative data collection occurs prior to and following the intervention group and is ongoing, qualitative data collection for implementation assessment began in summer 2024 and is ongoing. As of winter 2024, a total of 114 participants have been recruited and 32 therapists are enrolled in the E-Cog training platform with 25 therapists having completed the training. The updated project timeline can be accessed for those who create free accounts on the iCogCA Hub web page [77].

Discussion

Overview

This study aims to address the crucial clinical needs of individuals with SSD by evaluating the feasibility and effectiveness of delivering cognitive health interventions through a digital platform. We hypothesize that these interventions will yield positive outcomes in terms of accessibility, engagement, symptom reduction, and cognitive functioning.

Principal Findings and Comparison to Prior Work

The objectives of this study are 2-fold, focusing on both service users and mental health care providers. The first objective aims to assess the effectiveness of digital cognitive health interventions in enhancing accessibility and engagement for individuals with SSD. If proven effective, these interventions may provide an evidence-based framework for other service providers providing care for individuals with psychotic disorders and could be adapted for other populations receiving mental health services where these interventions show similar efficacy (eg, mood disorders) [78,79]. Objective 2 aims to identify facilitators and barriers to digital delivery and a digital training platform for clinicians. We anticipate that this study will introduce and validate our platform to train and supervise mental health care practitioners to deliver these interventions, which will then be made accessible to the broader mental health community. Further, these findings will furnish crucial information for the implementation of digital health technologies to improve access to psychosocial therapies for optimized care. These findings will be used to guide the implementation of similar projects across Canada. Notably, New York State has already fully integrated CR into its psychiatric care systems [80], and parallel efforts are underway in Australia [81] and the United Kingdom [82]. Collaborating with a National Steering and Implementation Committee, we will test our set of tools based on the CFIR and make them accessible to the mental health community. Site-specific implementation committees, which include patient partners, will assist with the local implementation of our cognitive health interventions.

Strengths and Limitations

This proposed national collaborative effort serves as a catalyst for leveraging digital technology to enhance the adoption of evidence-based psychosocial interventions. This study has

several strengths. The first is the implementation across multiple Canadian sites, which enhances the generalizability of our findings. Second, we also aim to engage a broad pool of participants, both service users and mental health practitioners, by using digital technology to provide the intervention and training. Encouragingly, previous studies have demonstrated that a significant portion of those with severe mental illnesses appear to have the required technological access and ability to join, participate, and benefit from digital services [83,84]. We have also a planned comprehensive collection of quantitative and qualitative data. Our data collection plan involves service users and mental health practitioners at multiple time points, allowing us to answer our research questions in a multifaceted manner. Finally, we have engaged with diverse stakeholders throughout various stages of the study, including those with lived experiences, clinicians, researchers, and managers.

Some limitations of our study include the nonrandomized concurrent controlled design, which raises concerns about potential group differences. However, we will address this by statistically controlling for measurable background characteristics. Second, although we aim to engage a broader population by providing services using a digital format, we acknowledge that there could be variability to technology access. We have planned to provide tablets and internet to service users without access to technology. For service users or health care providers unfamiliar with technology, we will also offer orientation sessions to help them become comfortable with the digital format. Next, the recruitment of therapists within a research setting may not reflect therapists involved in nonresearch settings. In addition, although we have taken great care in selecting instruments that have been validated in our population and available in both English and French, some limitations may still exist with the instruments chosen. For instance, ceiling effects have been observed in the Cambridge Neuropsychological Test Automated Battery cognitive test. Finally, there may exist differences across 5 sites in training experiences and implementation fidelity. We plan to attend to this by standardizing training and fidelity checks conducted across all sites.

Conclusions

In summary, this project aims to address pressing clinical needs related to cognitive impairments and biases in SSDs. By leveraging digital technologies, it aims to facilitate the adoption of evidence-based interventions within clinical settings, support future implementation of similar initiatives, and validate an adaptable platform designed for widespread use.

Acknowledgments

The authors would like to thank the study staff, community and clinical partners, and study participants who support this work. SG and GS are supported by a Chercheur Boursier Junior 1 from the Fonds de Recherche du Québec en Santé. ML is supported by a James McGill Professorship from McGill University. ET receives postdoctoral fellowship funding from the Canadian Institutes of Health Research (#171198). The authors thank the following people for their support with this project: Shalini Lal, Michael Bodnar, Deji Ayonrinde, Alexandra Baines, Ridha Joober, Tania Lecomte, Jai Shah, Nicola Wright, David Attwood, Patricia Debergue, Alonso Montoya, Tim Pauley, and Phil Tibbo. This research was undertaken thanks in part to funding from the Canada First Research Excellence Fund awarded through the Healthy Brains, Healthy Lives initiative at McGill University and by a Canadian Institutes of Health Research Project (grant #180501).

Data Availability

The datasets generated or analyzed during this study are not publicly available due to ongoing data collection but are available from the corresponding author on reasonable request.

Authors' Contributions

CA-Y and HT were responsible for writing the original draft and conducting investigations. They will also handle future formal analysis. MB, SG, KML, ET, and GS developed the conceptual framework and methodologies and participated in writing and reviewing the manuscript. AES contributed to the visualization and also engaged in manuscript review and editing. CRB, MM, SM, MP, and TSW contributed to conceptualization and methodology, provided resources, and reviewed and edited the manuscript. ML played a multifaceted role including conceptualization, methodology development, drafting and reviewing the manuscript, as well as overseeing the project administration and securing funding. DR-C was involved in conceptualization, methodology development, writing the original draft, and reviewing the manuscript, in addition to supervising the entire project. All authors reviewed the final manuscript.

Conflicts of Interest

This project is carried out in collaboration with the company SBT, which provides licenses for the Happy Neuron platform. ML reports grants from Roche Canada, grants from Otsuka Lundbeck Alliance, and personal fees from Boehringer Ingelheim, Janssen, Lundbeck Canada, and Otsuka Canada outside the submitted work. SG has received financial compensation for consulting services from Boehringer Ingelheim outside the submitted work. MB has received consulting fees from Boehringer Ingelheim. KML reports consulting fees from Otsuka Canada, Lundbeck Canada, and Boehringer Ingelheim. SM has received consultant fees from

Boehringer and ROVI and is developer of metacognitive training. DR-C reports consultations fees from Otsuka Canada Pharmaceutical, outside the submitted work. All other authors declare no conflicts of interest.

Multimedia Appendix 1
Example of iCogCA recruitment pamphlet.
[PNG File , 1033 KB - resprot_v14i1e63269_app1.png]

Multimedia Appendix 2
E-Cog training platform home page.
[PNG File , 383 KB - resprot_v14i1e63269_app2.png]

Multimedia Appendix 3
E-Cog training platform action-based cognitive remediation introduction page.
[PNG File , 821 KB - resprot_v14i1e63269_app3.png]

Multimedia Appendix 4
E-Cog training platform metacognitive training introduction page.
[PNG File , 539 KB - resprot_v14i1e63269_app4.png]

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Abbreviations

ABCR: action-based cognitive remediation
CFIR: Consolidated Framework for Implementation Research
CIUSSS: Centre intégré universitaire de santé et de services sociaux
CR: cognitive remediation
MCT: metacognitive training
REB: research ethics board
SSD: schizophrenia spectrum disorder

Edited by A Schwartz, T Leung; submitted 14.06.24; peer-reviewed by T Wykes, P Harvey; comments to author 11.10.24; revised version received 02.12.24; accepted 26.02.25; published 15.04.25.

Please cite as:
Au-Yeung C, Thai H, Best M, Bowie CR, Guimond S, Lavigne KM, Menon M, Moritz S, Piat M, Sauvé G, Sousa AE, Thibaudeau E, Woodward TS, Lepage M, Raucher-Chéné D
iCogCA to Promote Cognitive Health Through Digital Group Interventions for Individuals Living With a Schizophrenia Spectrum Disorder: Protocol for a Nonrandomized Concurrent Controlled Trial
JMIR Res Protoc 2025;14:e63269
URL: https://www.researchprotocols.org/2025/1/e63269
doi:10.2196/63269
PMID:

Protocol

Evaluating a Web-Based Application to Facilitate Family-School-Health Care Collaboration for Children With Neurodevelopmental Disorders in Inclusive Settings: Protocol for a Nonrandomized Trial

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Abstract

Background: An individual education plan (IEP) is a key element in the support of the schooling of children with special educational needs or disabilities. The IEP process requires effective communication and strong partnership between families, school staff, and health care practitioners. However, these stakeholders often report their collaboration as limited and difficult to maintain, leading to difficulties in implementing and monitoring the child's IEP.

Objective: This paper aims to describe the study protocol used to evaluate a technological tool (CoEd application) aiming at fostering communication and collaboration between family, school, and health care in the context of inclusive education.

Methods: This protocol describes a longitudinal, nonrandomized controlled trial, with baseline, 3 month, and 6-month follow-up assessments. The intervention consisted of using the web-based CoEd application for 3 months to 6 months. This application is composed of a child's file in which stakeholders of the support team can share information about the child's profile, skills, aids and adaptations, and daily events. The control group is asked to function as usual to support the child in inclusive settings. To be eligible, a support team must be composed of at least two stakeholders, including at least one of the parents. Additionally, the pupil had to be aged between 10 years and 16 years, enrolled in secondary school, be taught in mainstream settings, and have an established or ongoing diagnosis of autism spectrum disorder, attention-deficit/hyperactivity disorder, or intellectual disability (IQ<70). Primary outcome measures cover stakeholders' relationships, self-efficacy, and attitudes toward inclusive education, while secondary outcome measures are related to stakeholders' burden and quality of life, as well as children's school well-being and quality of life. We plan to analyze data using ANCOVA to investigate pre-post and group effects, with a technological skills questionnaire as the covariate.

Results: After screening for eligibility, 157 participants were recruited in 37 support teams, composed of at least one parent and one professional (school, health care). In September 2023, after the baseline assessment, the remaining 127 participants were allocated to the CoEd intervention (13 teams; n=82) or control condition (11 teams; n=45).

Conclusions: We expect that the CoEd application will improve the quality of interpersonal relationships in children's IEP teams (research question [RQ]1), will show benefits for the child (RQ2), and improve the well-being of the child and the stakeholders (RQ3). Thanks to the participatory design, we also expect that the CoEd application will elicit a good user experience (RQ4). The results from this study could have several implications for educational technology research, as it is the first to investigate the impacts of a technological tool on co-educational processes.

International Registered Report Identifier (IRRID): DERR1-10.2196/63378

(JMIR Res Protoc 2025;14:e63378) doi:10.2196/63378

KEYWORDS

neurodevelopmental disorders; coeducation; whole-school approach; family-professional partnership; web application; inclusive education; family-school-health care

Introduction

Background

There is a growing body of literature on the benefits of using educational technologies to support children with special educational needs or disabilities (SEND) and, notably, those due to neurodevelopmental disorders (NDD; eg, [1-4]). Most of these technologies target students as their primary users, forgetting the social environment that has to work together to support the children in their educational project. This study aims to conduct a field study to assess the effectiveness of an interactive web application (namely, the CoEd application) for fostering collaboration between family, school, and health care practitioners.

In several countries, a key element in the support of the child's schooling is the individual education plan (IEP), which defines their needs and gathers information on aids and adaptations that can be implemented to help them attain their full potential. IEP structures differ by country, but the core process emphasizes a robust partnership among families, school staff, and health care professionals, with regular meetings and a deep understanding of the child's profile and progress [5,6]. Effective communication between teachers and parents is universally recognized as a cornerstone of a child's education [6,7]. The ability of parents to share pertinent information about their child's disabilities, strengths, and weaknesses significantly enhances educators' awareness and enables them to tailor their pedagogical approaches [8]. Furthermore, parental involvement in the educational process has far-reaching implications, encompassing the holistic development and well-being of children with SEND. It serves as the bedrock for fostering a culture of productive family-school collaboration and cultivating a supportive school environment [9,10]. For students grappling with complex disorders such as autism spectrum disorder (ASD), the synergy of collaboration between parents and educators paves the way for improved academic performance, smoother integration, and enhanced social adaptation [11]. In a broader context, collaboration between parents and educators emerges as a catalyst for positive outcomes, benefiting students across the spectrum of educational needs [12]. Despite all of this, studies on the IEP process consistently underscore the pronounced discord between stakeholders' aspirations for effective teamwork and the actual communication and collaboration practices in place [12-17]. This paradox is particularly evident in the experiences of parents, teachers, and educators who frequently encounter obstacles ranging from resource constraints to training deficits, communication impediments, intercoordination challenges, and intricate administrative processes [12,18-22]. These challenges are not unique to inclusive education of children with NDD and extend to other areas such as patient care [23,24].

Within the continuum of collaborative practices in inclusive education, 3 progressive levels can be delineated: cooperation, coordination, and collaboration [25]. As elucidated by Larivée et al [26], elevation in the school-family-community collaboration level correlates with mutual recognition of expertise, bidirectional communication, shared responsibilities, and the spirit of reciprocity.

Several theoretical models of collaborative practices within the framework of IEPs have been proposed. These models may pivot around the child, exemplified by the "Whole School, Whole Community, Whole Child" model [27,28], or emphasize the dynamics of partnerships between stakeholders, as exemplified by the Sunshine model [29]. Other models are grounded in the objectives of IEPs, as demonstrated by polycentric approaches based on the child's life project [30]. Additionally, some models embrace a multidimensional perspective typified by the Holistic School Care Coordination System Model [31,32].

The proliferation of these models underscores the pivotal role of educational systems in facilitating interactions between educators and families. This entails the provision of guidelines and recommendations for effective collaboration, alongside the allocation of critical resources encompassing time, physical infrastructure, and financial support [19,20]. Among the envisaged solutions, harnessing digital technologies emerges as a promising avenue to support continuous communication for efficient stakeholder collaboration [33,34].

Prior Work

Maintaining communication and collaboration within the extended team for IEPs is challenging due to various communication channels like emails and phone calls. Despite digital advancements, tools often prioritize one-to-one communication over team-based sharing. Additionally, the lack of trackability in one-to-one exchanges hampers information flow within the team. To the best of our knowledge, very few digital tools are designed to help stakeholders with team-based information sharing, communication, and collaboration in the follow-up of the IEP and of the child's schooling and development [35]. Many proposed devices in this field lack maturity, either due to an inadequate design that does not consider user needs, resulting in usability issues, or because participatory design methods were used without subsequent effectiveness studies conducted to standard methodological levels for producing evidence (for a review, see [35]). An example of that is illustrated by the CoEd application, which provides a web application with functionalities aiming at fostering information sharing, communication, and collaboration in IEP and with the support team [36]. Through participatory methods, the CoEd application was designed based on stakeholders' needs and iterative design steps for eliciting good

user experience, usability, and utility (see [36] for the design process).

Aims

We propose to conduct a field study aiming to evaluate the impact of using the CoEd web application on 3 outcomes. First, we hypothesized that the CoEd application will improve communication and relationships between stakeholders (family, school, and health care practitioners), as well as their attitudes toward school inclusion, and increase each stakeholder's perceived self-efficacy (research question [RQ]1). Second, we hypothesized a beneficial effect of using CoEd on the child in terms of behavioral or academic functioning (RQ2). Third, we expect that using CoEd results in a better quality of life for both the stakeholders and the children (RQ3). Finally, as it is crucial when evaluating technology to verify that it is both effective and usable [37], we added measures related to the user experience of participants. Thanks to the participatory design, we expected that the CoEd application will elicit a good user experience (RQ4).

The paper follows the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) guidelines for reporting study protocols [38]. The SPIRIT checklist for this paper is provided in Multimedia Appendix 1.

Methods

Ethical Considerations

The ethics committee (Comité Opérationnel d'Évaluation des Risques Légaux et Éthiques [COERLE]) of the French National Institute of Informatics and Mathematics (Inria) approved the study protocol (application number 2022-08).

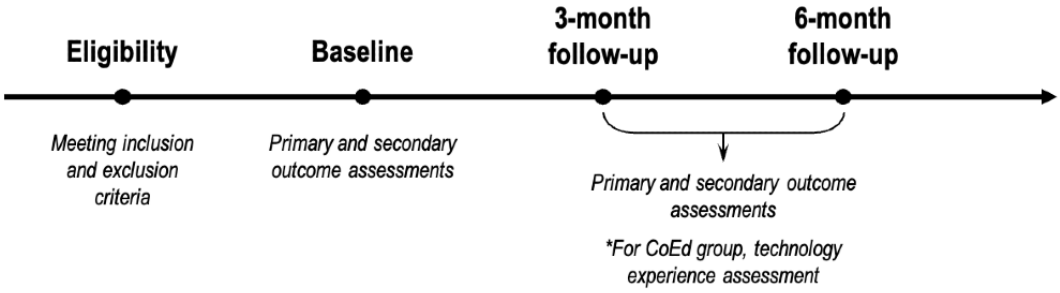
As the study protocol implies the management of health-related data, the CoEd app is hosted and managed on a secured server at Inria as if CoEd's data are medical data, in respect of the General Data Protection Regulation (GDPR). Additionally, the study protocol and data management processes were approved by the National Commission of Informatics and Liberty and by the Inria Security Homologation committee (application number 13953). All participants were informed about the study and gave written informed consent.

Study Overview

We designed a longitudinal, nonrandomized controlled trial to evaluate the impact of the CoEd application developed by our team [36]. We enrolled teams monitoring the school or social inclusion of secondary school pupils with NDD (between 10 years and 16 years old). These teams were recruited throughout France via email communication with schools, school districts, special education advisors, academic inspectors specializing in Special Education, and associations supporting families of children with NDD. Field partners of the project, namely the Nouvelle-Aquitaine academy, Autism Resources Center, and Association pour la Réadaptation et l'Intégration, were also engaged in the recruitment process and encouraged participation in their networks. We also put out calls for participants on digital social networks. Parents, teachers, and health care professionals were asked to complete a questionnaire to check the inclusion criteria. When the participant and child were eligible, all the members of the follow-up team were contacted, and the study was presented to them. Once participation was confirmed, individual participants received a consent form. They were given a week to return the completed form, with researchers available to address any questions during this period.

Whether they were in the control or experimental condition, they had to complete a baseline assessment and a 3-month follow-up assessment, and if they were willing to continue participating, they would complete a 6-month follow-up assessment (Figure 1).

Figure 1. Timeline of the field study according to the group conditions and the number of school terms (3 months for each term) for study participation.



Eligibility Criteria

To participate, a support team had to consist of at least two stakeholders, including at least one of the parents. Additionally, the pupil had to be aged between 10 years and 16 years, enrolled in secondary school, be taught in mainstream settings, and have a diagnosis of ASD, attention-deficit/hyperactivity disorder, or intellectual disability (IQ<70). The pupil needed either an established diagnosis or to be undergoing a multidisciplinary intervention for diagnosis.

Allocation and Blinding

In this quasi-experimental trial, the group allocation was not randomized. Group allocation was carried out as participants were recruited according to eligibility criteria, taking care to balance groups in terms of team size. A nonrandomized procedure was chosen because we recruited participants as volunteers arose who had a complete team. As the control group did not use the CoEd application and functioned as usual whereas the experimental group was asked to use the CoEd application and needed secure access to the web-based application, it was not possible to conduct a double-blind study.

Outcome Measures

Selection of Outcome Measures

Outcome measures were chosen from the researchers' hypotheses and participatory decision-making. In 2 focus groups, parents, teachers, and health care professionals discussed the CoEd application's potential impact and evaluation criteria (Multimedia Appendix 2). Participants reviewed preselected indicators and suggested new measures, especially concerning quality of life and caregiver burden, for the field study. As a result, the primary outcomes include 3 main dimensions (ie, stakeholders' relationships, perceived individual efficacy, and attitudes toward school inclusion). To this end, parents, teachers, and health care professionals completed a series of common or specific questionnaires (Table 1). The secondary outcomes include measures for stakeholders (burden and quality of life) and for the children (quality of life, school well-being, and school inclusion perception; Table 1). Additionally, a measurement of technology experience that covers technology skills and CoEd experience was included for the intervention group (Table 1). Although some questionnaires had a validated French version, others did not. In the latter case, as we are French native speakers, we translated them in collaboration with native English speakers. The scales used are presented in Table 1.

Table 1. Description of the assessment batteries to address the targeted (primary and secondary) outcomes and technology experience of participants.

Outcomes, dimension, and subdimension	Questionnaire	Respondent			
		Child	Parent	Teacher	Professionals
Primary outcomes (stakeholders)					
Relationship					
Parent-teacher	Parent-Teacher Relationship Scale II[a]	—[b]	X	X	—
Therapeutic or interprofessional	Helping Alliance Questionnaire	—	X	X	X
Perceived educational efficacy					
Self-efficacy	Basic Psychological Need: Satisfaction and Frustration scale	—	X	X	X
Achievement of educational goals	Goal Attainment Scale	—	X	X	X
Attitudes toward school inclusion					
Teachers	Multidimensional Attitudes Towards Inclusive Education Scale	—	—	X	—
Parents	Attitudes Toward Inclusion/Mainstream[a]	—	X	—	—
Secondary outcomes (stakeholders)					
Burden					
Family burden	Caregiver Strain Questionnaire	—	X	—	—
Adult burden	Zarit Inventory Short Form	—	—	X	X
Burnout	Maslach Burn-out Inventory[a]	—	X	X	X
Quality of life					
Adult	WHOQOL-Bref	—	X	X	X
Family	Beach Center Family Quality of Life (FQOL)	—	X	—	—
Secondary outcomes (children)					
School life					
Child's quality of life	Pediatric Quality of Life Inventory (PedsQL)	X	X	—	—
School well-being	Multidimensional Students' Life Satisfaction Scale (MSLSS)	X	—	—	—
School inclusion	Individual school perception	X	—	—	—
Technology experience[c]					
Technology skills					
Computer skills	Computer Usage Questionnaire	—	X	X	X
CoEd application experience					
Subjective user experience	User Experience Questionnaire, short version and Technology-based Experience of Need Satisfaction (TENS)[a]	—	X	X	X
Objective user experience	The uses and usages of the CoEd application are quantified with the following indicators across periods of 3 months or 6 months: (1) number of times the application is opened and (2) number of exchanged posts	—	X	X	X

[a]Translated in French by the authors.

[b]Not applicable.

[c]Intervention group only.

Primary Outcomes

Perception of Stakeholders' Relationships

Parents and teachers completed the Parent-Teacher Relationship Scale [39], which consists of a 24-item questionnaire measured on a 5-point Likert scale (1=strongly disagree to 5=strongly agree) assessing the 2 dimensions joining and communication-to-other, including their feeling of affiliation and support; the dependability and availability of both parties; shared expectations; and beliefs about the child and each other, their communication, and their sharing of information and emotions. To assess the relationship with medical-social professionals, the Helping Alliance Questionnaire [40] was completed by parents, teachers, and health care practitioners. The Helping Alliance Questionnaire initially evaluated the therapeutic alliance through the 2 dimensions perceived helpfulness and collaboration, but it was adapted to the purpose of the study. Two versions were used: a 13-item parent form and an 11-item professional form, both using a 6-point Likert scale (1=totally disagree to 5=totally agree).

Perceived Individual Efficacy

The feeling of self-determination was measured using the French version of the Basic Psychological Need Satisfaction and Frustration Scale [41], which assesses satisfaction and frustration with the 3 basic psychological needs: competence, affiliation, and autonomy. This 24-item scale using a 5-point Likert scale (1=Completely False to 5=Completely True) provides a proxy of general individual efficacy. A version of the Goal Attainment Scale [42] adapted by our team was proposed. Initially, parents and professionals were asked to independently specify 2 to 5 school, social, or behavioral goals for the young individual, along with their current level, desired level, difficulty, and importance. At the end of the experimentation, the goal was recalled, and the adults were asked to assess the level of goal attainment. This adapted version of the Goal Attainment Scale provides a probe of (individual) educational efficacy.

Attitudes Toward Inclusive Education

The parents' attitudes toward inclusive education was measured using the Attitudes Toward Inclusion/Mainstream scale [43]. This questionnaire, consisting of 18 items that are rated on a 5-point Likert scale (1=strongly agree to 5=strongly disagree), assesses the overall attitude of parents toward the inclusion of students with disabilities in mainstream schools, including 4 dimensions (benefits factor, satisfaction with special education, teacher ability and inclusion support, child rights). The Multidimensional Attitudes Towards Inclusive Education Scale [44] was selected to evaluate teachers' attitudes toward the inclusion of students with disabilities in mainstream schools. It consists of 18 items assessed using a 6-point Likert scale (1=strongly disagree to 6=strongly agree) and measuring 3 dimensions (cognitive, affective, behavioral).

Secondary Outcomes

Perception of Caregiver Burden

Parents and professionals completed the Zarit Burden Inventory Short Form [45,46], which consists of 12 items assessing the individual perception of their burden. Each item is scored between 1 point and 5 points (1=never to 5=almost always), and the total score is the sum of all item scores. The higher the score is, the higher the burden is, with the following cut-offs: no to mild burden (0-10), mild to moderate burden (10-20), and high burden (>20). For parents, the assessment was completed with the Caregiver Strain Questionnaire [47] to evaluate the familial burden through 21 items using a 5-point Likert scale (1=not at all to 5=very much) and 3 dimensions (objective burden, internalized subjective burden, and externalized subjective burden). The Caregiver Strain Questionnaire has been specifically validated with families of children with disabilities, including NDD or ASD. For professionals, the level of burnout was assessed using the French version of the Maslach Burnout Inventory [48], a 22-item scale using a 7-point Likert scale (1=never to 7=every day) that evaluates emotional exhaustion, depersonalization in relationships with others, and a sense of reduced personal accomplishment in one's work.

Stakeholders' Quality of Life

Parents and professionals completed the WHOQOL-BREF [49], a 26-item scale using a 5-point Likert scale (1=Very Low, Very Dissatisfied, Not at all, Very Difficult, Never to 5=Very High, Very Satisfied, Extremely, Very Easily, All the Time) recommended by the World Health Organization to assess individuals' quality of life based on 4 dimensions (physical health, psychological health, social relationships, environment). The quality of life of the family was assessed using the Beach Center Family Quality of Life scale [50], adapted into French by Rivard et al [51]. This scale, consisting of 25 items using a 5-point Likert scale (1=Slightly Important, Very Dissatisfied to 5=Very Important, Very Satisfied), measures 5 dimensions of family quality of life: family interactions, parenting, emotional well-being, physical and material well-being, and disability-related support.

Child's Quality of Life

The pupil's quality of life was assessed using the Pediatric Quality of Life Inventory [52]. The Pediatric Quality of Life Inventory is composed of 23 items using a 5-point Likert scale (0=never to 4=almost always) assessing children's physical, emotional, social, and school functioning through self-report (completed by children) and proxy report (completed by parents).

Child's Perception of School Life

The student's sense of school inclusion was evaluated using the single-item inclusion scale by Aron et al [53], which measures 7 levels of the sense of inclusion and has been adapted to assess the sense of inclusion in both the school and peer group contexts. School satisfaction was evaluated using an 8-item subscale that uses a 7-point Likert scale (1=strongly disagree to 7=strongly agree) derived from the French adaptation of the Multidimensional Students' Life Satisfaction Scale [54,55].

Measurement of Technology Experience (Experimental Group Only)

To assess the potential effect of prior technology skills on the use of CoEd, parents and professionals completed the Computer Usage Questionnaire [56] that consists of a self-reported measure of 18 questions asking for the frequency (5-point scale

ranging from never to very often) of different computer activities and software usage.

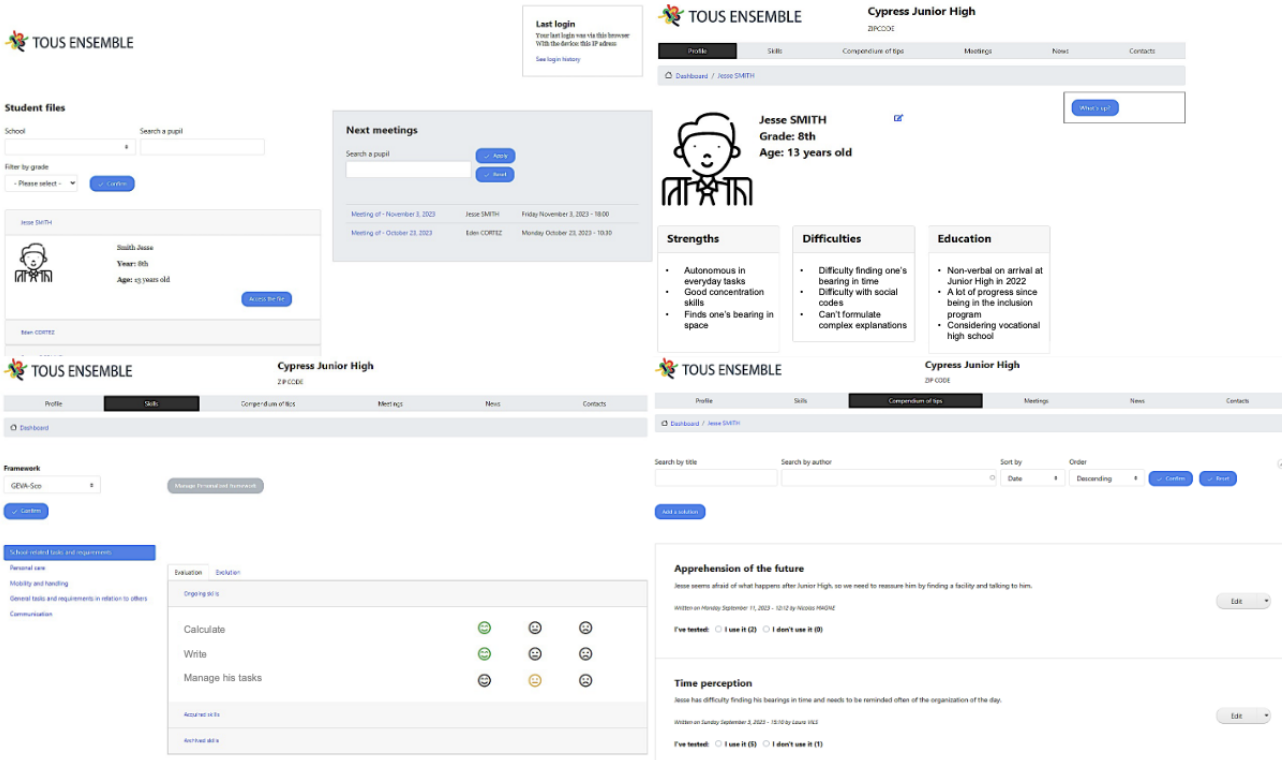
To address the specific user experience with the CoEd application, the User Experience Questionnaire short form [57] was selected as the measurement. It uses a 7-point Likert scale (–3=fully agree with negative term to +3=fully agree with positive term) of subjective perceptions of users in terms of both the hedonic and pragmatic dimensions toward a given product and according to a benchmark for digital products. The Technology-based Experience of Need Satisfaction-Interface [58] is related to the self-determination theory framework for assessment and uses a 5-point Likert scale (1=Do Not Agree to 5=Strongly Agree) to assess basic psychological need (autonomy, competence, relatedness) satisfaction through the interaction with the interface or system. Satisfaction of these needs is arguably associated with sustained engagement with a technology.

Complementary to the subjective measures, direct measures of CoEd use and usage are collected through active interactions (log data) with this web application, in particular the number of times the app was opened and the number of exchanged posts (Table 1).

Presentation of the CoEd Technology

Specific to the French school context, the CoEd application (Figure 2) is accessible through a web browser and allows users to view and edit one or multiple student files. Users need to be registered by the administrator and can log in with an email and password. Roles—parent, teacher, or external professional—are assigned during registration, offering equal file access rights. A designated moderator role, open to any team member by consensus, is suggested for content moderation.

Figure 2. Screenshots of different tabs from the CoEd app.



Once logged in, the user can access the student's file, which consists of 6 tabs: profile, skills, meetings, compendium of tips, news, contacts.

As an identity card, the profile provides key main information to know about the child. A “What’s up?” block allows users to be informed of new content in the folder.

The skills section allows users to review the child’s skill assessment. Two skill referentials are provided: (1) a formal IEP evaluation (ie, Geva-Sco scale for French IEP) and (2) a custom skill referential, where users can determine the categories and skills they wish to assess according to the child’s profile.

The meetings tab allows user awareness of past and upcoming meetings about the child. This section also provides an interface to automatically generate reports about past meetings in PDF format, which are accessible by all users.

On the compendium of tips tab, users can share tips, aids, and adjustments that they successfully used with the child in particular situations. They can receive feedback from the other team members.

The news section is dedicated to punctual and rapid information sharing, such as daily events or feedback and particular events.

On the contacts tab, all team members related to the child’s folder are identified, including their role in the team and contact information.

Procedure

When the participants were assigned to the CoEd intervention condition, the researchers created the child's page and the users' logins on the CoEd application. The participants may provide initial general information to be put on the child's page by the researchers. At the beginning of the study and after collecting baseline measures, the participants of the CoEd intervention condition received a user manual and video tutorials to help them handle the application, and additional training could be provided by the researchers if needed. Once the study began, the participants were asked to use the application at least once a week but were free to use it as often as they wanted.

The participants from the control group did not receive any intervention and were asked to function as usual.

All questionnaires were administered through online forms. Every participant received an identification number, which was used to anonymize the data collected. At the date of measurement (baseline, 3-month follow-up, 6-month follow-up), participants were instructed by mail to complete the questionnaires. The data collection was monitored by the researchers, and the participants who did not answer were reminded once a week by mail or phone. If participants remained unreachable for more than 6 weeks, they were labeled as "lost" and excluded from the trial.

The data collected through forms and the CoEd application were stored on a secure server at the Inria research center and anonymized using participants' identification numbers. Only researchers working on the project are authorized to consult the collected data.

Statistical Analysis

Power

We did not find previous studies assessing the impact of a digital device on IEP teams' relationships and communication in order to perform a power analysis. However, some behavioral interventions with the same target were published and reported moderate effect sizes. Thus, we based our power analysis on an effect size of d=0.600.

Planned Statistical Analyses

We plan to conduct pre-post mean comparison analysis on primary (RQ1) and secondary outcomes (RQ2 and RQ3) to assess within and between-team effects of the intervention. We will conduct within-team analyses using 1-way ANCOVA to compare pre and postintervention differences separately for each team's experimental and control groups. This approach helps identify specific changes within teams and assesses differential effects between groups. Additionally, a between-team analysis will treat all participants as a single population, using repeated-measures ANCOVAs or linear regression analyses to examine the overall intervention effect across teams. This global analysis disregards team distinctions to assess the intervention's overall impact. In addition, using ANCOVA will allow us to control for potential bias coming from the variability in technological skills (Computer Usage Questionnaire; see Table 1) as well as any variable that may compromise the homogeneity across groups. Missing data will result in the exclusion of related observations, and dropouts will be monitored to explore the reasons.

By combining these methods, we aim to provide a comprehensive evaluation of the psychological intervention's effectiveness, considering both within-team variation and overall effects.

To assess the user experience (RQ4), only the participants of the CoEd intervention condition answered the user experience questionnaire. These data will be analyzed through descriptive statistics and compared with questionnaire-related benchmarks.

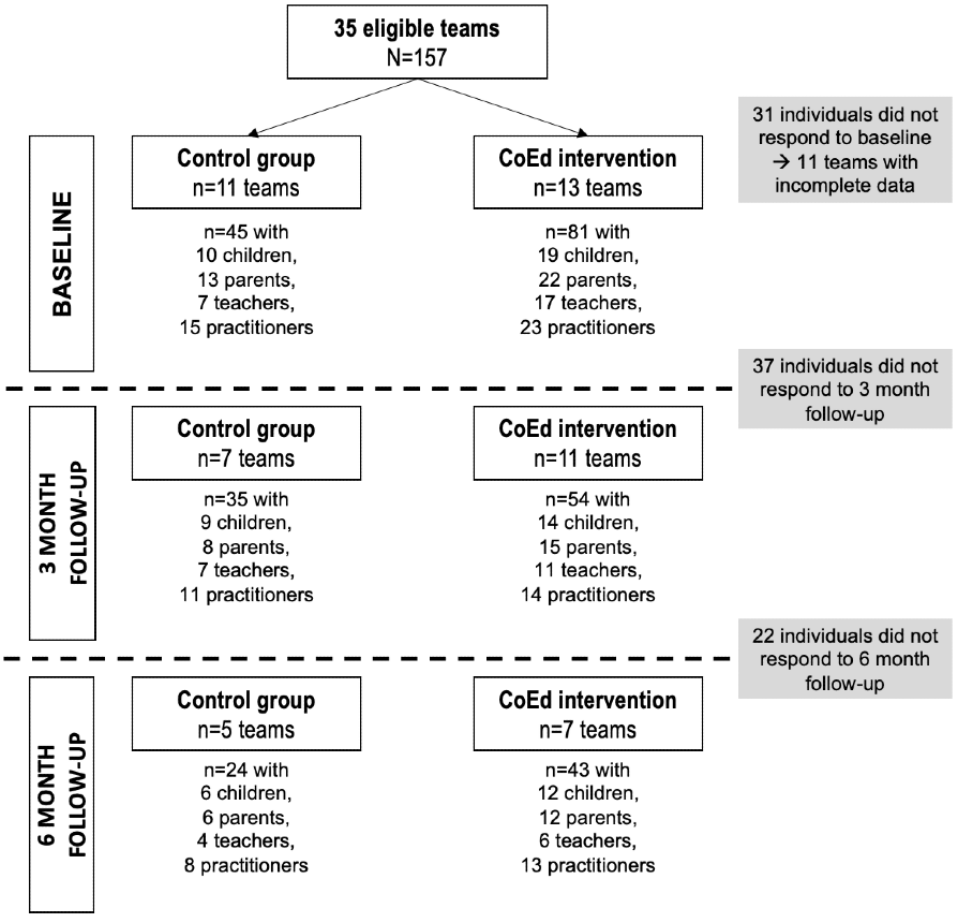
Results

The study was funded in 2021 with public funds from Conseil Régional d'Aquitaine and the Fondation International pour la Recherche Appliquée au Handicap (FIRAH), Klesia, and Comité National Coordination Action Handicap (CCAH).

Figure 3 shows the flowchart of the recruitment process. We initially recruited 37 eligible teams who were allocated to either the experimental or control group, which resulted in a sample size of 157 participants (2-7 people per team). At baseline, 31 individuals did not complete the questionnaires, leading to the exclusion of 11 teams due to incomplete data. In September 2023, the recruitment ended with 13 teams participating in the experimental condition (n=82) and 11 teams in the control condition (n=45). The experimental group is larger than the control group due to the nature of our action-research approach. Participants and partners expressed a strong preference for being included in the intervention to benefit from the CoEd app, viewing control group assignment negatively. To address this while maintaining rigorous assessment, we included more participants in the experimental group, ensuring sufficient data for analysis and respecting the ethical considerations of action research.

At the end of data collection (June 2024), a total of 59 individuals had dropped out: They stopped responding to the questionnaires and did not reply to our follow-up attempts. Consequently, there were 89 remaining participants at the 3-month follow-up and 67 participants at the 6-month follow-up. Data cleaning and analysis began in March 2025, and results are expected by June 2025. We anticipate that the findings may be ready for publication by the end of 2025, although this timeline remains provisional.

Figure 3. Flowchart of participant recruitment.



Discussion

Expected Results and Comparison With Prior Work

This research protocol was developed to empirically evaluate the impact of a digital technology solution on collaborative relationships among stakeholders in inclusive education. Conducting a field study with a quasi-experimental protocol will provide true empirical support of the technology's utility and effectiveness for fostering stakeholder collaboration. Through the targeted primary outcomes, we particularly expect an improvement in the quality of interpersonal relationships as well as more congruent cross-stakeholder attitudes toward school inclusion while empowering each stakeholder in their capabilities to achieve their own goals as educator and to support child in their IEP (RQ1). We also expect a beneficial effect of using the CoEd application on child-related outcomes (RQ2) and on the quality of life of stakeholders and children (RQ3).

Meyer et al [35] identified 6 digital projects and a strategy using an existing social network, all at different development stages. Of these projects, 3 used participatory design, 4 conducted needs analyses, and 3 were field-tested. However, none included a control group nor aimed to evaluate the impact on school inclusion, IEPs, stakeholder interactions, or health and well-being dimensions. From this review, it becomes evident that conducting quasi-experimental field studies and involving a substantial number of educational teams and various stakeholders will be an essential contribution. Building on this, our protocol seeks to provide robust evidence for a digital co-education tool designed with user-centered design methods and approaching a gold standard methodology.

Strengths and Limitations

The CoEd application has already completed all the design and user testing in order to reach the step of empirical evidence thanks to this study (see [36] for the design study). Furthermore, our field study included evaluations that cover more broadly other critical indicators for co-educators, such as their mental health using the burden and quality of life assessments. There is strong evidence of the great influence of perceived self-efficacy on a person's well-being [59,60]. Hence, we will be able to explore the links between the primary outcomes (interpersonal relationships, attitudes toward school inclusion, and self-efficacy) and some health measures. For the children, the collaboration benefits from technology could promote, by the bounds effect, their sense of school inclusion, school-life satisfaction, and overall well-being through an effect on parent-teacher relationships and collaboration between stakeholders [6,7,61-63]. This technology could also facilitate the implementation of IEPs by leveraging each stakeholder's expertise [6,8] and, as a result, increasing the educational achievement (academic and social objectives) for each child.

Additionally, the log data from the CoEd application will provide insights on its actual usage across time and the targeted primary outcomes. For instance, RQs could address the traditional dilemma between quality and quantity of exchanged

information, or content analyses could even document interpersonal tensions and their potential relation with a degraded partnership in the team and vice versa.

For the intervention group using the CoEd application, we are collecting data on usability, technology acceptance, and usage factors. This assessment is of great importance in studies examining the impacts of technology-based interventions, as usability and effectiveness are intrinsically related, and is part of most studies evaluating this kind of intervention [37].

These secondary indicators address the needs of project stakeholders (inclusive school policymakers, school organizations, teachers, practitioners, parents, and children with SEND) for successful participatory achievements and pave the way for innovative research, such as exploring relationships between CoEd acceptance and effectiveness in inclusive school environments. Most of the participants of this study are people who did not participate in the design steps of the project. Therefore, the bias from "being both designer and evaluator" is limited, and the results from this study will provide insight on the efficacy of using a citizen science approach in the domain of inclusive education. This study combines a traditional top-down approach (ie, expectations relative to specific primary criteria for a prescriptive purpose) with a bottom-up approach driven by the field expertise of the main stakeholders of school inclusion. As a reminder, the study outcomes have been cobuilt thanks to focus group methods involving actual stakeholders as well as researchers in the field (see Multimedia Appendix 2 for details about the focus group sessions). This citizen science approach (albeit risky) contributes to bridging science and practice, facilitating rapid societal impact, and emerging new research issues [64,65]. The results from this study could also contribute to documenting the effectiveness of citizen science and participatory design methods in designing innovative technologies tailored to the specific needs of people, especially in health and disability domains [24,65,66].

From our combined approaches, the study consortium encountered a few issues that reinforced the study-related challenges, especially with children with SEND and with a technology-based intervention. First, major challenges were related to the quasi-experimental study design in which the CoEd intervention condition is compared with a control condition where there are fewer teams. We paid great attention to matching the 2 groups with respect to the factors known for influencing the primary outcomes as well as possible. These factors include the size of the team, demographic factors, and the SEND of the child. Nonetheless, we are aware that such a matching method does not neutralize possible biases related to differences in the group size. We plan to explore the impact of any variable that is not matched between groups to investigate its impact on the intervention's effect. A second study challenge was the great variability in the participants' technological skills in the CoEd condition. Indeed, computer skills and prior experience with technology will necessarily influence the experience with using a digital tool and, in turn, modulate the intervention's effects. We set up a standardized training phase for the use of CoEd application according to training use scenarios and provided both written and video tutorials to help people handle the CoEd application. In addition, the questionnaire on technological skills will be used as a covariable to explore the impact of this interindividual variability on the intervention's effects. Another study challenge was associated with the increasing digitalization of schools, whether in teaching, student support, or parental involvement. Since the COVID-19 pandemic, this digitalization has significantly increased, especially in the field of education [67]. However, the extensive digitalization during the COVID-19 pandemic brought issues related to digital anxiety and data protection [68], increased screen time, and the effects on well-being and interpersonal relationships [69-71]. In this project, these themes were central during design and development steps, as it involved processing data concerning children with NDD. This point was addressed during the participatory design steps and proved to be a very important one for future users [36]. During the development steps, we made data security a priority, so that users can use the system with complete confidence (compliance with regulations, security certification). Finally, the last challenge our research had to confront was related to the context of digital development in France. The French government has introduced a new digital tool to bridge the gap between decision-making bodies for educational obligations and resources allocated for the implementation of an IEP and schools. This deployment has led teachers to increase digital data input on academic difficulties and IEP accommodations. However, this deployment has caused confusion with CoEd and could lead some teachers to limit their participation, as some data would need to be entered both in CoEd and the governmental digital tool. However, there are important differences between the CoEd application and the governmental tool: The latter is more oriented toward archiving aims and digitalization of the IEP, while the CoEd application promotes free sharing of experiential knowledge from each stakeholder, which indirectly contributes to IEP implementation and follow-up. In addition, the CoEd application allows stakeholders to communicate with each other about daily events, which is not covered by the governmental tool. In this context, the CoEd application can be viewed as an aid for following IEP objectives and to better support the use of the governmental app through complementary features.

Despite all these challenges, the outcomes of the CoEd study will yield significant insights on the benefits of a digital collaborative tool for teaching students with SEND. It will also yield some insights on the communication factors influencing the health of stakeholders and children. The study will also inform the feasibility of technology-based personalization of IEP and will likely teach some useful lessons for future technology-based field studies regarding empowering stakeholders to teach children with SEND.

Dissemination Plan

Results from our study will be disseminated via scientific publications and conferences. In addition, as we previously included decision-makers of the French public policy of inclusive schooling in the CoEd design phases, we made sure that the solution is ethically, technologically, and financially sustainable in the public services. This will provide a solid foundation for a business model in case there is a startup to market the technology.

A second perspective is to explore the feasibility of disseminating the CoEd application outside of the French frontiers, by scaling up in other countries. However, there are cultural and structural differences between countries, particularly regarding inclusive education. This international dissemination will necessitate an additional needs analysis and adaptations to the application for the specific context of other countries [72]. A first step will be to explore the feasibility of disseminating the application in French-speaking countries with a similar cultural background (eg, Belgium), thereafter moving to wider internationalization with other European countries. This internationalization strategy is certainly ambitious and will necessitate a new needs analysis and adaptations of the CoEd application.

Conclusion and Future Directions

Although further research is needed, the findings of the CoEd project will provide the first real evidence-based study in the field of educational technology for social environments supporting children with SEND with their IEPs.

To move the robustness of the evidence forward, it will be necessary to consider conducting a trial using strict randomized controlled trial methods. In the same vein, the question of a large-scale intervention exists. As also mentioned, our ecosystemic and participatory approach has led us to work directly with the key stakeholders in inclusive education in order to both design an upstream CoEd application and evaluate it downstream. Consequently, a scaling up in other countries for the evaluation of the CoEd application will be required for better proof of the interest for an interactive web application for a co-education process.

Acknowledgments

We would like to thank all the members of this project: first, the participants and second, all the professionals linked to the project (eg, engineers, technicians, techno-clinicians) as well as the structures and organizations that allowed the project to be conducted (French School Academy of Bordeaux-New Aquitania in France) and Aurélien Dumez, Computer Security Officer and Engineer at the Inria (National French Institute of Informatics and Mathematics) center of the University of Bordeaux who supervised all the computer development required for the CoEd solution and notably its conformity to General Data Protection Regulation (GDPR) and European standards for ethical research with a digital tool.

The study benefited from several funding sources, primarily the Inria, public funds of Conseil Régional d'Aquitaine (grant number: AAPR2021-2020-11922210; principal investigators [PIs]: HS and CM), Fondation international pour la Recherche appliquée au Handicap (FIRAH; PI: HS), Klesia, and Comité national Coordination Action Handica (CCAH). These funding sources had no role in the design of this study and will not have any role during its execution, analyses, interpretation of the data, or decision to submit results**.**

Data Availability

Upon study completion, the data sets generated during or analyzed during this study will be available from the corresponding author on reasonable request.

Conflicts of Interest

None declared.

Multimedia Appendix 1
SPIRIT checklist for this study.
[DOC File , 120 KB - resprot_v14i1e63378_app1.doc]

Multimedia Appendix 2
Description of Focus group for selecting study outcomes.
[DOCX File , 23 KB - resprot_v14i1e63378_app2.docx]

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Abbreviations

ASD: autism spectrum disorder
CCAH: Comité National Coordination Action Handicap
COERLE: Comité Opérationnel d'Évaluation des Risques Légaux et Éthiques
FIRAH: Fondation Internationale pour la Recherche Appliquée au Handicap
GDPR: General Data Protection Regulation
IEP: individual education plan
Inria: French National Institute of Informatics and Mathematics
NDD: neurodevelopmental disorders
RQ: research question
SEND: special educational needs or disabilities
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials

Edited by A Schwartz, T Leung; submitted 18.06.24; peer-reviewed by S Ashraf, F Regalado; comments to author 04.10.24; revised version received 22.12.24; accepted 26.02.25; published 17.04.25.

Please cite as:
Meyer E, Sauzéon H, Saint-Supery I, Mazon C
Evaluating a Web-Based Application to Facilitate Family-School-Health Care Collaboration for Children With Neurodevelopmental Disorders in Inclusive Settings: Protocol for a Nonrandomized Trial
JMIR Res Protoc 2025;14:e63378
URL: https://www.researchprotocols.org/2025/1/e63378
doi:10.2196/63378
PMID:

Protocol

Locomotive Syndrome Digital Therapeutics Provided via a Smartphone App: Protocol for a Single-Group Trial

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Abstract

Background: Locomotive syndrome (LS) is a condition in which muscle weakness and reduced motor function due to musculoskeletal disorders cause reduced mobility and physical function. In Japan, musculoskeletal disorders are the most frequent reason for requiring home support or nursing care, and the prevention and amelioration of LS are thus being emphasized. However, it is difficult for older people to make a habit of exercise therapy, which is the mainstay of LS treatment. We investigated whether digital therapy could (1) lead to behavioral change in older people and (2) prevent or improve LS in older people.

Objective: We sought to determine whether digital therapeutics (DTx) are useful for the prevention and amelioration of LS in older people, and we assessed the effects of DTx on the participants' exercise awareness and motor function.

Methods: We conducted a multicenter, prospective, longitudinal, nonrandomized, single-group study of Japanese adults aged ≥40 years who were eligible for LS checks. Each participant underwent an 8-week locomotion training (LT) intervention, and their subjective and objective motor abilities and motor awareness were objectively assessed at the following time points: baseline (before the start of the DTx), interim (4 weeks after the start of the DTx), and end (8 weeks after the start of the DTx). We evaluated the participants' objective motor function using the timed up and go (TUG) test, and we compare the results using a 3-way ANOVA with the TUG test at the 3 evaluation time points as the dependent variable. The results of the 25-question Geriatric Locomotive Function Scale, which is a subjective measure of motor function, and the results of the Behavioural Regulation in Exercise Questionnaire 3, which assesses motor awareness, were also evaluated using an ANOVA in the same way as the TUG test. The significance level was set at .05 / 3 = .0167 after Bonferroni correction.

Results: As of April 2025, this study had enrolled 47 participants, and complete data had been gathered from 45 participants for the proposed analysis. Study participation was ongoing as of April 2025.

Conclusions: The study cohort will be used as a basis for further observational and intervention studies. This research could lead to more efficient use of medical resources and a reduction in financial and medical burdens on individuals and the economy, and it could support the prevention and amelioration of LS and the establishment of exercise habits among older people.

Trial Registration: University Hospital Medical Information Network Clinical Trials Registry UMIN000053922; https://center6.umin.ac.jp/cgi-open-bin/ctr_e/ctr_view.cgi?recptno=R000061550

International Registered Report Identifier (IRRID): DERR1-10.2196/70163

(JMIR Res Protoc 2025;14:e70163) doi:10.2196/70163

KEYWORDS

locomotive syndrome; locomotion training; digital therapeutic; TUG; 25-Geriatric Locomotive Function Scale; BREQ-3; behavioral change; support application

Introduction

Background and Rationale

The Japanese Orthopaedic Association (JOA) issued its first guidelines regarding locomotive syndrome (LS) in 2007 [1]. Locomotive syndrome refers to a condition in which a musculoskeletal disorder results in muscle weakness and motor weakness, leading to reduced mobility and physical function [1]. The development of LS causes a decline in healthy life expectancy and can lead to individuals becoming bedridden and requiring long-term care [2]. In Japan, motor system disorders are the most frequent reason for requiring assistance at home or nursing care, accounting for 24.8% of all cases [3]. The JOA recommends the early detection of motor function decline by conducting LS checks (LSCs), in part to prevent the future need for assistance or care [4]. The JOA also advocates locomotion training (LT), which involves standing on one leg and squatting, to prevent and ameliorate LS [5].

Guidelines for assessing the risk of LS were developed in 2015 [6]; these defined stage 1 LS as the early stage of motor decline and stage 2 LS as advanced motor decline. In 2020, stage 3 LS was added, defined as a state of progressive decline in mobility and difficulty in social participation [7]. The risk of developing LS is assessed based on three items: (1) a stand-up test, (2) a 2-step test, and (3) the 25-question Geriatric Locomotive Function Scale (GLFS-25) [5].

Japan has one of the world's most prominent aging populations, and the burden of health care for the oldest segment of Japan's population on the country's insurance system continues to increase [8]. It is also necessary to consider how to make the most effective use of limited medical resources. The prevention and amelioration of LS are considered important as countermeasures against motor system disorders. Exercises such as LT are effective for preventing and ameliorating LS [5], but it is difficult for many older adults to start or continue an exercise routine. As one solution, we advocate an approach to the prevention and improvement of LS in older people based on using technological devices to promote behavioral change.

Technology is used in the medical field for electronic medical records, telemedicine, and surgical robots; in addition to this, mobile devices are used for medical procedures and support, which is called mobile health (mHealth) [9]. Digital therapeutics (DTx) are an area of mHealth that is receiving particular attention [10]. A variety of apps have been approved by insurance as DTx, including diabetes and hypertension self-management apps and smoking cessation support apps [11-13]. However, DTx for musculoskeletal diseases have not been approved for insurance coverage. Although some apps have functions such as step counting and exercise management, they are not scientifically supported. We have created a smartphone app for older people who have no exercise habits and whose physical functions have declined. The smartphone app has functions that support the implementation of 2 types of LT, using video and audio, and when participants carry out LT, the implementation status is recorded not only on the target person's smartphone, but also on the health care provider's smartphone. The advantage of this system is that health care providers can check the progress of LT remotely, and the patient can feel that they are exercising with the support of health care providers. We are conducting this study to determine whether the use of DTx can lead to behavioral change in older people and prevent or improve LS.

Objectives

The study's primary aim is to determine whether the use of a smartphone app (ie, DTx) can prevent or ameliorate LS in older people: the outcomes are exercise awareness as assessed by the Behavioural Regulation in Exercise Questionnaire 3 (BREQ-3) and motor function as assessed by the GLFS-25 and timed up and go (TUG) test. In this study, participants who were unable to perform the stand-up test or 2-step test due to hip or knee pain were excluded from the measurement items. The research questions are as follows: (1) Can older people use DTx to proactively change their exercise habits with the help of their health care providers? (2) Are changes in exercise habits in older people associated with changes in motor awareness and function?

Our main and secondary study hypotheses are that (1) continued LT with DTx will prevent or improve LS in older adults and (2) well-established exercise habits will improve these individuals' motor awareness and function.

Methods

Participants and Study Setting

We plan to recruit a minimum of 50 participants aged ≥40 years who are eligible for LSCs [14] at any of 3 general hospitals (Bange-Kosei General Hospital, Southern Tohoku General Hospital, and Minami-Soma City General Hospital) that perform orthopedic surgery. The target minimum numbers of participants is 25 at Bange-Kosei General Hospital, 15 at Southern Tohoku General Hospital, and 10 at Minami-Soma City General Hospital. The overall recruitment target is based on the minimum sample size necessary to complete the intended analysis, taking omissions into account.

The study's inclusion criteria are as follows: participants aged ≥40 years who generally have lower-extremity muscle weakness [15] and who have visited 1 of the 3 abovementioned hospitals for an LSC, which are scored as follows: 1 point if the individual cannot put on a sock on one foot; 2 points if they stumble in their house; 3 points if they need a handrail to climb stairs; 4 points if they have difficulty using a vacuum cleaner at home; 5 points if they have difficulty carrying parcels weighing >2 kg; 6 points if they have difficulty walking continuously for >15 minutes; and 7 points if they cannot cross a crosswalk with a green light. Additional inclusion criteria are scoring ≥3 points on the Mini-Cog cognitive functional assessment [16,17], having access to the smartphone app, and being able to provide informed consent for study participation. The exclusion criterion was difficulty using smartphone apps due to cognitive decline or visual or hearing impairment.

Study Design

This trial is a multicenter, prospective, longitudinal, nonrandomized, single-group study of Japanese adults aged ≥40

years with applicable LSC results. The design includes 3 evaluation time points: baseline (0 weeks, ie, before the initiation of DTx), an interim evaluation (4 weeks after DTx initiation), and a final evaluation (8 weeks after DTx initiation).

An investigation of DTx that was designed to reduce anxiety about recurrence in postoperative breast cancer patients included a baseline assessment before the DTx intervention, an interim assessment after 4 weeks of intervention, and a final assessment after 8 weeks of intervention [18]. Previous studies have shown that 6 weeks of balance exercise intervention and 2 months of body weight–bearing exercise can improve lower limb muscle strength, balance ability, and walking speed in older people [19,20]. We and other research groups thus consider 4-week and 8-week postintervention assessment time points as appropriate for this type of study.

We registered the trial with the University Hospital Medical Information Network Clinical Trials Registry (UMIN000053922; receipt number R000061550). The date of approval was March 22, 2024.

Procedures

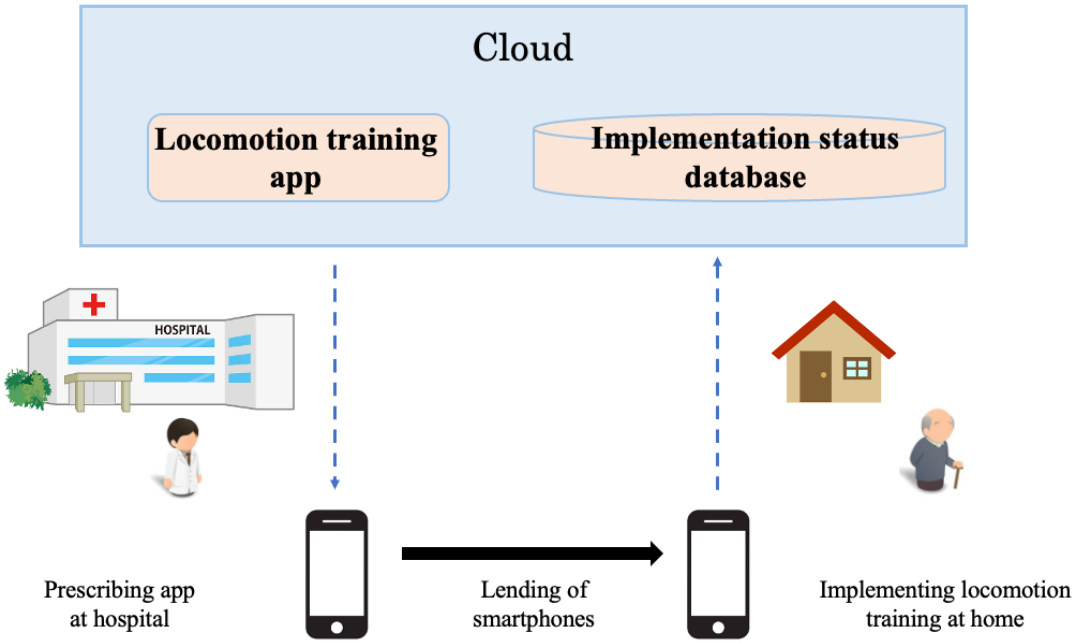
Recruitment

Participants will be recruited from among patients attending the collaborating hospitals. All 3 recruitment sites follow the same recruitment plan. Recruitment will continue until the target number of cases is achieved, with a 1-year time limit. At the end of a regular outpatient clinic session, a participant who meets all of the eligibility criteria and wishes to participate in the study will be provided with a description of the study, a questionnaire, and an evaluation sheet, and they will be asked to give their written informed consent to participate in the study. The need for follow-up and written consent for future contact will also be explained. The candidate participants are also informed that they can withdraw their consent or participation at any time if they so desire.

Intervention

The smartphone app used in this study is a newly prototyped app developed for this research study. We will provide smartphones equipped with a communication environment and downloaded apps in advance, which will be lent to the participants (Figure 1). The participants will be instructed to refrain from using the smartphone for any purpose other than use of the relevant smartphone app.

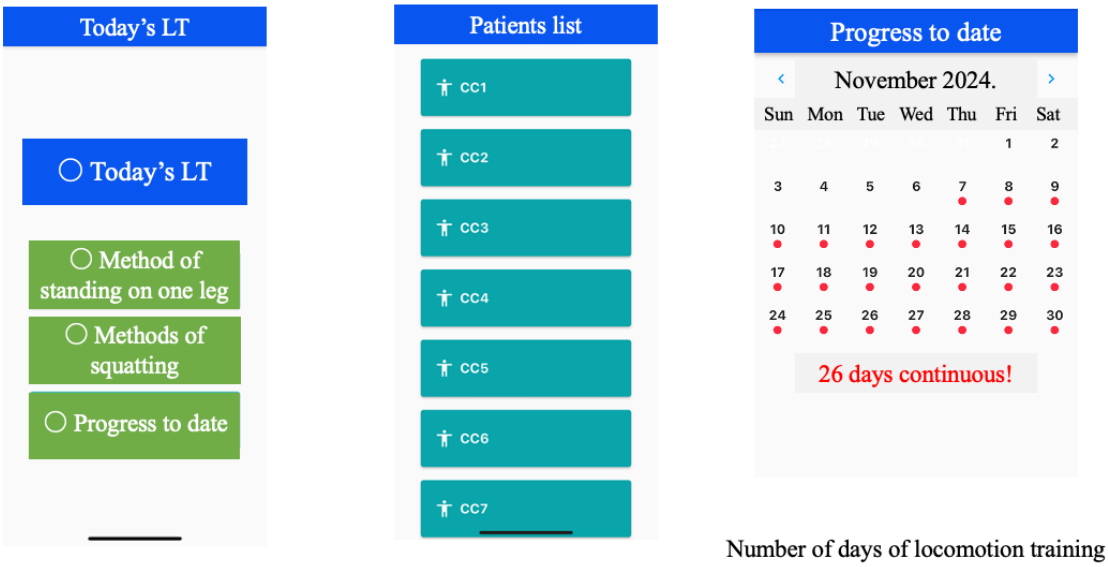
Figure 1. Implementation schema for the locomotive training (LT) app used in this study. The physician in charge will provide a smartphone onto which the LT app has been downloaded to the patient. The patients perform the LT at home, and the app's implementation data are stored in the database and saved in the cloud. Through the cloud, the physician can check the participant's LT implementation remotely.



Each participant will be scheduled for LT intervention every day for 8 weeks. The LT application is simple to use and is set up so that by touching the screen, a voice announcement is played and the user can perform 2 LT programs: the 1-leg stand program and the squat program. A single LT session consists of a program of 60 seconds of standing on one leg and 5 squats, with each exercise repeated 3 times. For participants with weak legs and backs who find it difficult to do the regular LT, it is recommended that they stand on one leg while supporting their body with their hands and fingers on a desk, or that they sit on a chair and stand up by putting their hands on a desk instead of doing squats. In addition, for participants with particularly weak legs and backs, each LT repetition could also be reduced to 1 time instead of 3 times [5]. Sustainable goals are set for each

individual for LT continuity. After completion of the LT, the participant touches the screen to check the record of the LT, not only on the participant's but also on his or her physician's smartphone (Figure 2).

Figure 2. Screenshots of the app used in this study. The app for patients has a simple design to help them perform the locomotive training (LT). The app for physicians allows them to check a patient's LT status based on the ID for that patient. The number of days with LT is displayed on the same screen for both the patient and the physician.



Outcomes

Timeline

The timetable of enrollment, interventions, and assessments is displayed in Table 1, including the quantitative self-reported outcomes and TUG results at the baseline, interim, and final evaluations. Demographic and clinical information will be obtained from the participants' electronic medical records at baseline and will include their date of birth, gender, BMI, medical history, and disease or diseases causing LS.

Table 1. Timetable and evaluation items.

Item	Baseline	4 weeks after DTx[a] initiation	8 weeks after DTx initiation
Patient consent	✓		
Patient background	✓		
Timed up and go test	✓	✓	✓
25-question Geriatric Locomotive Function Scale	✓	✓	✓
Behavioural Regulation in Exercise Questionnaire 3	✓	✓	✓
Days with locomotion training		✓	✓

[a]DTx: digital therapeutics.

Primary Outcome

The primary outcome is TUG test values before and after the DTx intervention. The TUG test is widely used in clinical practice as an outcome measure to assess mobility, fall risk, and dynamic balance in adults, and it can assess objective mobility [21,22]. Furthermore, previous research has shown that patients with LS have significantly longer TUG times than control groups [23]. In patients with rheumatoid arthritis, TUG values are significantly shortened and physical function is improved by continuing LT [24]. We determined that TUG is a useful indicator of the effects of LT for participants with LS.

Secondary Outcomes

Secondary outcomes are the participants' GFLS-25 and BREQ-3 scores. The GFLS-25 is a self-report questionnaire used to assess difficulties and impairments in daily activities related to LS and can be used to assess subjective mobility [5-7]. The BREQ-3 assesses motivation for exercise with 18 questions in 6 areas: intrinsic motivation, integrative adjustment, identification adjustment, incorporative adjustment, external adjustment, and demotivation [25]. The BREQ-3 is used in this study to assess changes in attitudes toward exercise before and after the DTx intervention.

Other Clinical Outcomes

We will evaluate the numbers of days LT was performed at 4 weeks and 8 weeks after the intervention, as recorded in the smartphone app.

Statistical Methods and Sample Size

The primary outcome of this study, TUG test values, will be measured repeatedly in the same participants at 0 weeks before the DTx intervention and 4 and 8 weeks after the intervention. These data will be compared with an ANOVA, with the TUG score as the dependent variable. The secondary outcomes, GLFS-25 and BREQ-3 scores obtained at the 3 time points, will also be compared with an ANOVA. The significance level will be set at .05 / 3 = .0167 with Bonferroni correction.

The minimal clinically important difference in the TUG test for patients with degenerative disc disease has been reported to be 3.4 (SD 5.0) [26]. Considering this finding, we set the minimal clinically important difference at 3 for this investigation. The required sample size was calculated using G*power (Heinrich-Heine-Universität Düsseldorf) [27]. We selected the corresponding *t* test, and we calculated the effect size as 0.6 based on a mean difference of 3.0 and an SD of difference of 5.0. Assuming that α is .05 and power $(1 - \beta)$ is .80, the required sample size was estimated to be 24. We set the target number of cases for this study at 50, taking into account that the SD might be smaller than in previous studies, some participants might drop out, and other factors.

Randomization and Blinding

This is a nonrandomized (unblinded) study and will use a single group. All participants will serve as their own controls; data from all participants before the DTx intervention will be used and compared with the data from after the DTx intervention. The planned statistical methods will add strength to the study's conclusions.

Data Monitoring and Adverse Event Reporting

The risk of adverse events from participation in DTx is very low. We are thus not establishing a data monitoring committee, and no interim analyses are planned to identify risks.

The principal investigator will (1) report the progress of the study without delay to the ethics review committee on an annual basis, (2) monitor adverse events related to the procedures and group program, and (3) discuss any necessary protocol amendments. If a member of the research team becomes aware of the occurrence of a serious adverse event, they will promptly report it to the research director, who will promptly report it to the principal investigator. If the principal investigator determines that the serious adverse event was unanticipated and is unable to be ruled out as being causally related to this study, he will promptly report it to the head of the research institution.

Ethical Considerations

The Fukushima Medical University Ethics Review Committee provided ethical approval for this study (REC 2023-196). All study methods follow the relevant guidelines and regulations, and written informed consent will be obtained from participants. The study's main results will be published in a peer-reviewed scientific journal and submitted for presentation at clinical and scientific meetings and conferences. The principal investigator will oversee the publication and presentation of the study results, including the determination of authorship. Participants will be asked if they would like to be informed about the study's main results, and those who express interest and provide contact information will be provided this information as soon as it becomes available. Data will be deidentified and participant information will be protected. Although no monetary rewards or other compensation will be provided to those participating in the research, in the event of an adverse event, we will respond promptly and provide compensation while consulting with the ethics committee.

Participants' data will be entered into a password-protected electronic file that will be kept on a secure computer by the principal investigator. Coding sheets with identifiable participant information will be stored on a secure computer as password-protected electronic files. Hard copies of consent forms and research documents will be stored in a locked filing cabinet at the research site.

Results

Trial enrollment began in April 2024 and will initially continue until at least April 2025. As of April 2025, 47 had participants agreed to be evaluated, 47 participants had completed the interim evaluation, and there were complete data sets from 45 participants for the proposed analysis. The data analysis has not yet been conducted.

Discussion

To our knowledge, this is the first trial to evaluate the effectiveness of DTx in preventing and ameliorating LS and changing the exercise behavior of older people. Although it is limited by its single-group design, the study has the strength that it evaluates the effectiveness of DTx in routine practice. External validity is also strengthened by the that fact that the practice sites are spread across 3 general hospitals and target communities with different sociodemographic characteristics.

A randomized design was not feasible, as the intervention is offered in routine practice [28], thus limiting causal conclusions. However, a randomized control study of approximately 200 participants per group in collaboration with local authorities has been proposed to strengthen this study. This is intended to improve the quality of the study by assessing in greater detail the impact of DTx on behavioral change and the prevention and amelioration of LS in older adults.

We are concerned that participants with low exercise awareness and low technology literacy may have difficulty participating in this study. However, for patients who are highly conscious of exercise but find it difficult to continue exercising on their own, or who are anxious about the content of the exercise, an advantage of the study is that they can exercise according to a set protocol with the cooperation of health care providers.

Notably, DTx enables the online assessment of the participants' engagement in LT and facilitates feedback in routine practice.

DTx is less burdensome for medical practitioners and more motivating for the participants as it creates an environment in which the participant is continuously supported by a physician. This research promises not only to lead to more efficient use of health care resources and reduced human and financial burdens, it may also lay the groundwork for more rapid implementation of DTx in real-world clinical practice, depending on the results. Nevertheless, a randomized controlled study based on our results will be required in order for DTx to gain insurance coverage in Japan, which calls for adequate funding and the cooperation of local authorities. If successful, the study will support the prevention and amelioration of LS and the establishment of better exercise habits among older adults.

Acknowledgments

We thank the hospital department heads for collecting the patient data and the study participants for their time and effort. This study is funded by a grant from the Japanese Orthopaedic Association (JOA-Subsidized Science Project Research 2022-1).

Data Availability

The datasets generated during and analyzed in this study will be made available from the corresponding author on reasonable request.

Authors' Contributions

TS and YM developed the evaluation method, participated in the study’s conception and design, obtained ethical approval, and wrote the manuscript. Both authors read and approved the final manuscript.

Conflicts of Interest

None declared.

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Abbreviations

BREQ-3: Behavioural Regulation in Exercise Questionnaire 3
DTx: digital therapeutics
GLFS-25: the 25-question Geriatric Locomotive Function Scale
JOA: Japanese Orthopaedic Association
LS: locomotive syndrome
LSC: locomotive syndrome check
LT: locomotion training
mHealth: mobile health
TUG: timed up and go

Edited by A Schwartz, J Sarvestan; submitted 16.12.24; peer-reviewed by S Osuka, H Namba; comments to author 25.02.25; revised version received 28.02.25; accepted 24.03.25; published 17.04.25.

Please cite as:
Sonobe T, Matsumoto Y
Locomotive Syndrome Digital Therapeutics Provided via a Smartphone App: Protocol for a Single-Group Trial
JMIR Res Protoc 2025;14:e70163
URL: https://www.researchprotocols.org/2025/1/e70163
doi:10.2196/70163
PMID:

Protocol

Impact of Psychosocial and Palliative Care Training on Nurses' Competences and Care of Patients With Cancer in Cameroon: Protocol for Quasi-Experimental Study

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Abstract

Background: Cancer is a leading cause of global mortality, accounting for nearly 10 million deaths in 2020. This is projected to increase by more than 60% by 2040, particularly in low- and middle-income countries. Yet, palliative and psychosocial oncology care is very limited in these countries.

Objective: This study describes a protocol for the development, implementation, and evaluation of a psychosocial oncology and palliative care course on Cameroonian practicing nurses' knowledge, self-perceived competence, and confidence in palliative and psychosocial oncology care provision for patients with cancer.

Methods: A single group pre-posttest design, incorporating both quantitative and qualitative methods will be used. First, a psychosocial oncology and palliative care course for practicing nurses in Cameroon will be developed. This course will then be implemented with 50 practicing nurses purposefully selected from 2 oncology units in the Littoral region and 4 hospitals in the Southwest region of Cameroon. Finally, to assess the impact of the training program we will undertake a pre and posttest survey of nurses' palliative and psychosocial oncology competences, a pre and post training audit of patients' nursing records to examine nurses' practice of palliative and psychosocial oncology care and undertake a critical-incident interview of nurses' transfer of learning to practice. Descriptive and inferential statistics will be used to analysis quantitative data, while qualitative data will be analyzed using the framework approach.

Results: This study was funded in September 2023. The training program development was initiated in March 2024 and completed in June 2024. Baseline data collection commenced in May 2024 and as of September 2024, we had collected data from 300 patient record. Training implementation is planned for October-December 2024, and post intervention data will be started in October 2024 and continue till April 2025. Data analysis will commence in October 2024 and we aim to publish study findings in peer review journals by November 2025.

Conclusions: This study will improve our understanding of Cameroonian nurses' palliative and psychosocial oncology competency gaps. It will result in the development of a palliative care and psychosocial oncology course and in the training of 50 nurses in psychosocial oncology and palliative care in Cameroon. This study will inform strategies for future psychosocial oncology and palliative care training initiatives in Cameroon and other low- and middle-income countries.

International Registered Report Identifier (IRRID): DERR1-10.2196/64871

(JMIR Res Protoc 2025;14:e64871) doi:10.2196/64871

KEYWORDS

palliative care; psychosocial nursing; oncology nursing; nurses; quality improvement; training; competencies

Introduction

The global need for palliative and psychosocial oncology care continues to grow with the increasing prevalence of life-limiting conditions such as cancer [1,2]. In 2020, there were 19.3 million new cancer diagnoses and close to 10 million cancer-related deaths worldwide. As high as 1.9 million of these deaths occurred in low- and middle-income countries (LMICs) [3]. The number of people requiring palliative care globally has increased significantly in the last 2 decades, from 20 million in 2014 [4] to 56.8 million in 2020 [5]. Unfortunately, LMICs, especially those in sub-Saharan Africa, who have little or no psychosocial oncology and palliative care services harbor up to 80% of this global need [1,6-8]. The limited palliative and psychosocial oncology services in these countries has been associated with barriers such as the lack of competent health care providers with palliative and psychosocial oncology skills, the nonintegration of palliative and psychosocial care in the existing health care system [7,8], the lack of policies to support effective palliative and psychosocial care provision [7,9], and the presence of legislation that limits opioid prescription resulting in poor pain relief, among others [10]. There is therefore a need for strategies to overcome these barriers and facilitate the integration of palliative and psychosocial oncology care into the national health care systems in LMICs [7,11]. Providing educational opportunities to enhance the skills of health care providers in palliative and psychosocial oncology care is one important strategy to ensure that patients have early access to these essential health care services [5,6,12].

Patients and their families who receive a cancer diagnosis experience a high prevalence of pain, emotional, spiritual, and psychosocial distress [9]. The provision of palliative and psychosocial oncology care to these patients and their families will help prevent and relieve these problems [1,6,9] and is cost effective [13]. This is therefore priceless in LMICs where there are limited health care resources, and the cost of care is mostly borne by patients and their families who lack the needed financial resources [13].

With the increasing incidence of cancer in Africa, oncology capacity building opportunities are needed to enhance health care provider's competences and possibly ensure adequate management of patients and their families [14]. Palliative and psychosocial care are important components of quality cancer care that reduces distress, anxiety, and depression and improves patients' quality of life and survival [6]. However, it requires close monitoring and presence, which may not be feasible for an already overloaded oncologists [15]. Thus, nurses are in an ideal position to provide palliative and psychosocial care to patients with cancer, particularly in Africa, with huge shortage of oncologists and physicians [16]. Nurse-led palliative and psychosocial have been shown to improve access to palliative and psychosocial care for patients with cancer in resource limited settings [15,17].

The Need for Palliative and Psychosocial Oncology Care in Cameroon

In Cameroon, there is an upsurge of noncommunicable chronic disease morbidity and mortality [18]. Although cancer is likely underreported, there were approximately 19,564 new cancer diagnoses and 12,798 cancer deaths in Cameroon in 2022 [19]. Similar to most sub-Saharan African countries access to cancer care in Cameroon is limited, although cancer is a leading cause of premature death in the country [20]. There are 3 main cancer centers situated in 2 regions of the country, serving patients from all 10 regions of the national territory [21-23]. The majority of patients visiting these centers present with advanced cancer diagnoses due to delays in access to screening, diagnosis, and treatment [23]. With the limited number of oncology centers and specialists in the country, patients with cancer are often admitted in secondary level hospitals found in each of the 10 regions. Thus, patients with cancer are often cared for by nononcology professionals, particularly nurses. The Cameroon ministry of Public Health has developed a national cancer control plan to increase the number of cancer cases detected and treated early [23]. Thus, the need for strategies to promote early and timely access to psychosocial and palliative care. A study in Cameroon on psychosocial distress and quality of life of patients with cancer [22] found that majority of patients (n=83, 69.2%) presented with clinically significant distress. Financial difficulties, fatigue, transportation issues, and difficulties with work or school were the most reported problems. Up to half of the participants had moderate to severe anxiety and depression symptoms. The quality of life was fair, and there was a statistically significant negative relationship between psychosocial distress and quality of life of patients. These patients however lack access to much needed palliative and psychosocial care.

Palliative care was started in Cameroon in 2003 by the Cameroon Baptist Convention Health Services [24]. The literature reports the lack of a palliative care policy framework in the national cancer control plan [8,23], and limited accessibility to palliative care drugs, especially morphine [25]. These represent a huge gap in access to cancer care and is therefore a significant burden on the population. Training nurses to provide palliative and psychosocial oncology care to patients with cancer in Cameroon can improve access to care, patient experiences and quality of life. A few studies in Cameroon suggested that nurses lack knowledge about palliative care and have negative attitudes toward care of the dying [26,27]. However, there has not been any palliative and psychosocial oncology care training targeting practicing nurses in Cameroon.

Study Aim

The overall aim of this proposed study is to develop, implement, and evaluate the impact of a psychosocial oncology and palliative care course on Cameroonian practicing nurses' knowledge, and self-perceived competence and confidence in palliative and psychosocial oncology care provision for patients with cancer, using Kirkpatrick's framework [28] for training

program evaluation. Our specific aims are to develop a psychosocial oncology and palliative care training program for nurses in Cameroon, to implement the training program with 50 nurses who provide care to patients with cancer in selected health care facilities in the Littoral and South-West regions of Cameroon, to assess the impact of the training program on nurses' psychosocial oncology and palliative care knowledge and self-perceived competence and confidence in psychosocial and palliative care provision for patients with cancer after program completion, to assess the strengths and weaknesses of this training program and identify possible implementation challenges to inform future psychosocial oncology and palliative care curriculum initiatives in Cameroon, and to assess nurses' transfer of their learning from this training program in the care of patients with cancer and perceived impact on patient outcome.

Methods

Design and Methods

A single group pre-posttest intervention design will be used in this study and will incorporate both quantitative and qualitative methods of data collection and analysis. The study will be conducted in 3 phases: course development; course implementation, and course evaluation (Table 1). The Kirkpatrick's framework for training program evaluation will be used to evaluate the psychosocial oncology and palliative care training program. The Kirkpatrick's framework is selected for its unique focus on evaluating the outcomes of interventions beyond learners' satisfaction. It consists of four hierarchical evaluation levels including reaction, learning, behavior, and results. Patients and the public will not be involved in the design, or conduct, or reporting, or dissemination plans of the research.

Table 1. Summary of the phases of the study.

Study phase and objective	Activities
Phase 1: Develop a psychosocial oncology and palliative care course for nurses	• Engage nurse educators, palliative care experts and oncologist as course development team • Develop course through Delphi method • Inform course development with content from the psychosocial care competencies framework for nurses in Africa [6], the international psycho-oncology society's core curriculum [29] and a palliative care course for preregistration nurse training in Cameroon [26]
Phase 2: Course implementation	• Recruit nurses who care for patients with cancer in 6 hospitals from 2 Cameroonian regions • Deliver the course to 50 nurses over a 4 days duration through theoretical lessons and a practical session
Phase 3: Course evaluation	• Undertake a pre- and post-training assessment of nurses' palliative care knowledge, self-perceived competence and confidence in palliative care provision, and nurses' psychosocial oncology care competencies • Conduct a pretraining audit of nursing records of 300 hospitalized patients with cancer to assess nurses' baseline practice of palliative and psychosocial oncology care • Administer an end of course survey to evaluate the strengths and weaknesses of the course • After 6 months of training, undertake a posttraining audit of nursing records of 300 hospitalized patients with cancer nursing records to assess change in nurses' practice • After 6 months of training, conduct critical incident interviews with 18 nurses to assess transfer of their learning to practice

Settings and Sample

The study will be conducted in 6 health care facilities in the South-West and Littoral regions. This will include 2 oncology units in Douala in the Littoral region and 4 health care facilities in Fako in the South-West region. Patients in the Southwest region of Cameroon who receive a suspected diagnosis of cancer are referred to an oncology center in Douala, the neighboring town in the Littoral region. Thus, they travel long distances to access oncology care. Secondary level hospitals located in the Southwest region provide some consultation by a visiting oncologist. There are few health care providers in the Southwest region with palliative care training [30] and we do not know of any training in psychosocial oncology for nurses in Cameroon. A purposive sample of 50 nurses who work in hospital units that provide care to patients with cancer in the study hospitals from the oncology, medical, surgical, and intensive care units will be recruited, 9 nurses from each study site in the Southwest region and 7 nurses each from the oncology units in the 2 sites in the Littoral region. In a similar study in this setting [31], a power calculation showed that using a P value of .05 to determine a statistically significant result, 50 participants were required to give 98% power to find a significant difference in palliative care knowledge. In Cameroon, we have an estimate of 1 nurse per 1000 population [32]. In most secondary and tertiary level hospitals, there are about 10 nurses working in each of the targeted units. Thus, 50 nurses will be selected from an approximate population of about 220 nurses. Nurses who have worked in either the oncology, medical, surgical, or intensive care unit for at least 6 months will included in the study. We consider that 6 months of work in any of these units will allow the nurse to have encountered several patients with cancer and gathered relevant knowledge of their needs from which we can learn during the course and to which they can compare their post training competencies. The nurses have to provide consent and agree to participate during the entire training duration.

Participant Recruitment Strategy

Permission to conduct the study has been obtained from the directors and supervisors of nursing services of the study hospitals. We are requesting assistance from the general supervisors of nursing services in each study site to identify nurses who meet the inclusion criteria of the study. Interested nurses will register for the training by completing an application form. Selected participants will be contacted to complete the course registration process and consent. All participants will provide consent to participate. Personal identifiers, will only be collected to match pretest and post questionnaires. The questionnaires will be anonymized by coding and removal of any personal identifiers.

Data Collection

All data collection activities will be undertaken by trained research assistants (RAs), under the supervision of the principal investigators. We will train the RAs on how to use the survey instruments and how to conduct the individual critical incident interviews. We will undertake a mock data collection and role play of interviews with the RAs during the training, to ascertain they can undertake the exercise. The principal investigators will undertake validation checks of the data to ensure that data is precise, accurate and complete.

Study Activities and Data Collection Methods by Aim

Study Aim 1: Develop a Psychosocial Oncology and Palliative Care Training Program

We will develop a psychosocial oncology and palliative care training program for Cameroonian practicing nurses using the psychosocial care competencies framework for nurses in Africa [6], the International Psycho-Oncology Society's (IPOS) core curriculum [29] and the palliative care course developed for preregistration nurse training in Cameroon [26,27]. At the outset of the study, we will establish a curriculum development committee consisting of 3 members including an oncologists, a palliative care nurse, and psycho-oncologist. The research team will work with the curriculum committee to contextualize the competency framework and IPOS core curriculum for use in the training of nurses in Cameroon. This will be done in collaboration with the psychosocial oncology society of Ghana [7]. We will work virtually via email exchanges, using the Delphi strategy [33] and will organize 2 Zoom (Zoom Video Communications) meetings to finalize and validate the training program.

Study Aim 2: Implement the Training With Nurses

The training will be organized at the conference room of participating hospitals to facilitate nurses' participation. Thus, 6 training sessions will be implemented with participants in the 6 study sites. Each training session will last 4 days. Day 1 and 2 will entail classroom training sessions; day 3 will be clinical case studies and scenarios through role playing under the supervision of a palliative care nurse, oncologist, and clinical psychologist and day 4 will be experience sharing, action plan development, and training evaluation. The classroom sessions will include interactive lectures assisted by PowerPoint (Microsoft) presentations, pictures and videos, presentation of case studies, sharing of personal experiences and group discussions of concepts and experiences. An international facilitator will be invited to take part in the training and give an opportunity for others to present virtually during the training. For the clinical case studies and scenarios, participants will be shared in groups of 5 to work on different clinical case studies and scenarios followed by sharing feedback with the entire team. A similar approach has been used and shown to be an effective strategy in the training of nurses in psychosocial oncology [34]. Participants will be provided with printed copies of the palliative care toolkit by Lavy and Woodridge [35]. In addition, they will be provided with links to online resources including the free online resources by IPOS.

Aim 3: Assess the Impact of the Training Program on Nurses' Psychosocial Oncology and Palliative Care Competences

A pretest and posttest survey will be used to assess the impact of the course on nurses' psychosocial oncology and palliative care knowledge and self-perceived competence and confidence in psychosocial and palliative care provision. An advantage of a pretest and posttest assessment is that it can be used to enhance understanding of what change, particularly in factual knowledge or skill sets that could be credited to a training program. All 50 study participants will receive a paper-based pretest evaluation to determine their baseline psychosocial oncology and palliative care knowledge, and self-perceived competence and confidence in psychosocial and palliative care provision. The paper-based assessment will take place at the hospital on the first day of training. Posttest data will be collected on the last day of the training. A questionnaire has been collated and comprises of 3 subscales to collect the pretest and posttest data. These subscales include a researcher developed demographic information subscale, the Palliative Care Quiz for Nursing [36], Perceived Palliative Care Self-efficacy Questionnaire [37], and the psychosocial oncology knowledge subscales [34]. The demographic questionnaire will collect information on participants' characteristics including nurses' qualification, hospital and unit of work, gender, religious affiliation, and previous education about palliative care and psychosocial oncology. The validated Palliative Care Quiz for Nursing will be used to assess change in nurses' palliative care knowledge, the Perceived Palliative Care Self-efficacy Questionnaire will be used to assess self-perceived competence and confidence in palliative care provision. These instruments have adequate psychometric property and have been used to assess student nurses' palliative care competencies in the study setting. For the assessment of psychosocial oncology competences, we have adapted the instruments used in the study by Mahendran et al [34] in Singapore.

Aim 4: Assess the Strengths and Weaknesses of This Training Program

A course evaluation survey will be administered to participants to explore their experiences of the course, their perspective of its strengths and weaknesses, and their plans for transfer of their knowledge and skills from this course to practice, in the care of patients with cancer. This will include both close-ended and open-ended questions to give nurses the opportunity to expand

on their responses and provide all relevant information as they deem necessary. This survey instrument is under development by the team and will be administered by research assistants on the last day of each training session.

Aim 5: Assess Nurses' Transfer of Their Learning From This Training in the Care of Patients With Cancer

Individual critical incident in-depth interviews will be conducted with nurses to explore the transfer of their learning to practice, its perceived benefits to patients and implementation challenges. A random sampling technique will be used to invite 3 nurses from each study site for this interview. Thus, a total of 18 nurses will be interviewed. These interviews will be organized at month 6 following completion of the training for each hospital. An interview guide will be used and it is envisaged that the interviews will last for 1 hour and will be tape recorded. In addition, a pre- and posttraining audit of patient files will be carried out to assess the number of patients with cancer that nurses assessed for psychosocial distress and coping, depression, anxiety, and palliative care, the number they plan psychosocial nursing and palliative care interventions (cognitive behavioral therapy) for and the number that nurses referred or suggest referral to specialist mental health and palliative care services or psycho-oncologists. The pretraining audit will be conducted at baseline, using a checklist. We will select files of the 50 most recently discharged patients with cancer or patients who died during hospitalization from each study site. Thus, a total of 300 hospital files will be studied from the 6 sites. Six months after training implementation in each site, we will undertake the posttraining audit. We will randomly select 50 files of patients with cancer currently receiving or who received nursing care from trained nurses. In total we will study 600 files, 300 from baseline and 300 post training.

Data Analysis

We will evaluate changes in mean scores from pretest to posttest to assess the impact of the course on nurses' psychosocial oncology and palliative care knowledge, and self-perceived competence and confidence in psychosocial oncology and palliative care provision. A paired *t* test, will be used to calculate the change in nurses' psychosocial oncology and palliative care knowledge from pretest scores to posttest scores, and to examine the significance of this change. The between and within group variations of the pretest and the posttest scores in psychosocial oncology and palliative care knowledge before and after the training program will be assessed using ANOVA. The McNemars test will be used to assess changes from the pretest to the posttest in nurses' self-perceived competence and confidence in psychosocial and palliative care provision. Descriptive statistics (close ended responses) and content analysis strategy (open-ended responses) will be used to analyze data on nurses' evaluation of the benefits of the course on their psychosocial oncology and palliative care competencies, their experiences of the course and its strengths and weaknesses, and how they were able to use them in practice.

A framework analysis [38] will be used to analyze critical incidents where nurses implemented their learning in practice and their perspective of how that benefited the patients with cancer in their care. Themes will be used to describe these experiences. Finally, a content analysis of the change in nurses' practice in terms of the number and content of patients' assessment for psychosocial distress, depression, anxiety, and palliative care, the number of patients with psychosocial and palliative care nursing care plans and the number that were referred to specialist mental health or palliative care services by nurses before and after the training. All project team members, RAs, and program coordinator will be involved in data collection and analysis.

Ethical Considerations

Ethical approval for this study has been obtained through the University of Buea institutional review board (Ref-2023/2165-10/UB/SG/IRB/FHS). Participants will receive an information sheet regarding the study and will provide written consent for the study. Participation in the study will be voluntary and participants will also have the freedom to leave the study at any time without giving a reason to the study team. Data will be anonymized to ensure and no identifiable information will be stored. No compensation will be provided to research participants.

Results

This study was funded in September 2023. The training program development was initiated in March 2024 and completed in June 2024. We engaged 12 cancer care, psychosocial oncology and palliative care experts, and nurse educators in Cameroon (n=7), the United Kingdom (n=2), Ghana (n=1), Indonesia (n=1), and the United States (n=1) in a 3-round Delphi process for the development of a bespoke palliative care and psychosocial oncology training program. As of August 30, 2024, we had obtained administrative authorization from all participating hospitals. The collection of baseline data on nurses' practice of psychosocial oncology and palliative care as documented in the nursing records of patients with cancer was commenced in May 2024. As of September 19, 2024, we had completed an audit of the records of 300 hospitalized patients with cancer from all study sites. The implementation of the training program is planned for October-December 2024. Following course implementation, posttest data will be started in October 2024 and continue till April 2025. Data analysis will commence in October 2024 and will continue until June 2025. We aim to present study findings at national and international palliative care and psychosocial oncology conferences and publish papers in peer review journals by November 2025.

Discussion

Expected Project Outcomes

This protocol provides details of the steps for the development, implementation and assessment of the impact of a psychosocial oncology, and palliative care training program on Cameroonian nurses' palliative care and psychosocial oncology knowledge, self-perceived competencies, and practice. In this study, we are developing a palliative and psychosocial oncology course for nurses in Cameroon. We will pilot it with 50 nurses working in 6 hospitals in the southwest and littoral regions of Cameroon. We envisage that this training program will improve

participating nurses' palliative care knowledge and self-perceived competence and confidence in psychosocial and palliative care provision for patients with cancer. The implementation of this training program will enhance our understanding of the components and strategies for an effective palliative care and psychosocial oncology training program for nurses in Cameroon. We also hope that study findings will support future psychosocial oncology and palliative care training initiatives in Cameroon and similar contexts.

The field of psychosocial oncology is still developing in Africa [39] and therefore, initiatives to enhance health care providers' competences in this practice area are crucial especially in sub-Saharan Africa. Given the limited numbers of oncologist, psycho-oncologist, mental health experts and palliative care physicians and nurses in Cameroon, it is important to train registered nurses, who make the most of the health care workforce in Cameroon to provide palliative and psychosocial oncology care to patients with cancer and their families. This project builds on previously successful educational initiatives in palliative care for nursing students in Cameroon to enhance care of patients with life-limiting illnesses including patients with cancer [26,27]. Training nurses in palliative care and psychosocial oncology in other contexts have yielded positive impacts in terms of improvements in their knowledge and skills in palliative and psychosocial oncology care provision, with positive patient outcomes [15,34,40,41]. Similar outcomes are anticipated for this training in Cameroon.

Similar to this study, most studies have used both validated instruments such as the Palliative Care Quiz for nurses, and nonvalidated self-reported tools to evaluate the effective of training programs [15,40,41]. However, the use of self-reported tools is limited, with the possibility of recall bias, and social desirability bias [42]. Participating nurses may not recall past practices and may also tend to please the researcher and answer questions in ways they consider right rather than giving a true self-assessment of their competencies. Furthermore, nurses could overrate or underrate their competencies, resulting in a response shift bias [43].

The Kirkpatrick's model of training program evaluation used in this study provides us with a logical structure and process to measure participants' learning, satisfaction and transfer of learning to practice. It will provide us with an understanding of the specific areas for improvement within this training program, based on its strengths and weakness, thus informing program enhancement [44]. We aim to disseminate our study's findings in a peer reviewed journal and local and international conferences. In addition, during program implementation we will engagement with general supervisors of nursing services, nurse educators, and other health care professions education stakeholders in Cameroon. This has the potential to inform nursing education reforms and drive the long-term goal of curriculum revision to include palliative care and psychosocial oncology in the training programs of health professionals in Cameroon.

Acknowledgments

We thank the participating study sites for granting access to the institution for this study. This work was supported with grant funding from Pfizer Global Medical Grants (76387581).

Data Availability

The datasets generated during and/or analyzed during this study are available from the corresponding author on reasonable request.

Authors' Contributions

All authors contributed to the conceptualization, writing-review and editing, and approval of the submitted manuscript and will be accountable for its contents. NB and TN performed supervision. NB, TN, and BA performed data curation. NB, TN, BA, EVA, EME, NE, and ASA performed investigation and methodology. NB, TN, and BA handled project administration, managed resource and software and conducted validation. NB wrote the original draft.

Conflicts of Interest

None declared.

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Abbreviations

IPOS: International Psycho-Oncology Society
LMIC: low- and middle-income country
RA: research assistant

Edited by T Leung; submitted 01.08.24; this is a non–peer-reviewed article;accepted 26.10.24; published 03.01.25.

Please cite as:
Bassah N, Tendongfor N, Ebob-Anya BA, Eta VAE, Esembeson M, Ngah NE, Abdul-Rahim SA
Impact of Psychosocial and Palliative Care Training on Nurses' Competences and Care of Patients With Cancer in Cameroon: Protocol for Quasi-Experimental Study
JMIR Res Protoc 2025;14:e64871
URL: https://www.researchprotocols.org/2025/1/e64871
doi:10.2196/64871
PMID:

Protocol

Mixed Comparative Evaluation of a Training Program Dedicated to Cystic Fibrosis Reference Centers: Protocol for the Pilot Implementation of Shared Decision-Making in the Treatment of Diabetes in Adult Patients With Cystic Fibrosis

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Abstract

Background: Diabetes affects half of the patients with cystic fibrosis who are aged 30 years and older. Diabetes progresses asymptomatically over a long period of time. Two treatment options are possible: start insulin as soon as cystic fibrosis diagnosis is made with the additional constraints of cystic fibrosis or wait while monitoring the patient's clinical condition and start insulin when diabetes symptoms develop and therefore later. This situation is particularly well suited to shared decision-making (SDM) between the physician (health care team) and patient/relatives.

Objective: The aim of this study was to perform qualitative and quantitative analyses for evaluating the outcomes and experience of SDM implementation between the physician/health care team trained for SDM and patients/their relatives for cystic fibrosis–related diabetes.

Methods: A quasi-experimental with a comparison study will be developed. Three cystic fibrosis reference centers (CFRCs) will be trained in SDM by using a web-based training, including a validated decision aid and coaching for physicians and the medical team. Two control CFRCs will maintain their usual practices. A qualitative analysis through observation of consultations, individual semistructured interviews with patients, and focus groups in CFRCs will be conducted based on a thematic content analysis. Questionnaires related to decision-making and experience of decision-making with and without SDM implementation will be administered to patients and physicians.

Results: Forty patients will be included (8 patients in each center), that is, 60 consultation observations (2 consultations per patient in the intervention groups given the modalities of the SDM process) will be conducted in 2025. Eight focus groups will be conducted in the 5 centers (2 groups in each intervention CFRC and 1 group in each control CFRC). This qualitative corpus plus responses to the patient and physician questionnaires will make it possible to know whether the practice of SDM in CFRCs is increased by an implementation strategy and to analyze the experience of patients and their relatives regarding decision-making modalities. Analysis of the outcomes and experience of the implementation of SDM are of importance to identify the facilitators and barriers to SDM from patients' and CFRCs' point of views.

Conclusions: Our study will give us keys to adapt, improve, and disseminate SDM more widely in the context of cystic fibrosis therapy. SDM could thus be used in routine clinical practice in CFRCs at the national level.

Trial Registration: ClinicalTrials.gov NCT04891159; https://clinicaltrials.gov/study/NCT04891159?id=NCT04891159

International Registered Report Identifier (IRRID): PRR1-10.2196/62931

(JMIR Res Protoc 2025;14:e62931) doi:10.2196/62931

KEYWORDS

shared decision-making; implementation; training; decision aid; cystic fibrosis

Introduction

Background

Many patients want to play an active role in their own care [1], and many health care professionals want the same for their patients [2]. Shared decision-making (SDM) in the physician-patient encounter is one way of meeting this wish. In SDM, "the information exchange is 2 ways […]. The defining characteristic of deliberation […] is its interactional nature (ie, between the physician and the patient or potential others), and both parties work toward reaching an agreement and both parties have an investment in the ultimate decision made" [3].

SDM often relies on information and decision support tools (decision aids), which provide written support for exchanges. Decision aids are increasingly digitalized and adapted to patients' health literacy levels [4]. They present management options with their benefits and risks, informing patients and enabling them to participate in the decision-making process if they wish so. They can be used both during and outside the consultation. For several years now, national and international health care policies have been encouraging the implementation of SDM for reasons ranging from ethical imperatives [5] to the reduction of unjustified variations in clinical practice [6]. However, despite the legal framework encouraging SDM in several countries (France [7], Germany [8], United Kingdom [9], United States [10]), the implementation of SDM in clinical practice is not yet widespread [11]. SDM research has focused on physician- or patient-mediated interventions to promote SDM [12]. Légaré et al [13] in their Cochrane review showed that a combination of both physician- and patient-mediated interventions is more likely to be successful. With regard to physician-mediated interventions, SDM training can teach health care professionals to involve patients in the decision-making process. A number of studies have shown the positive effects of training programs, such as improving physicians' SDM skills and increasing patient participation and satisfaction [14,15]. Joseph-Williams et al [16] in their systematic review also showed that patients want to be informed so that they can play an active role in decision-making. Patient-initiated interventions can also enhance the patient's ability to participate in the decision-making process. Patients who have learned to use tools that encourage them to ask questions to health care professionals participate more actively [17,18]. Finally, decision aids are a means of increasing SDM. The Cochrane systematic review by Stacey et al [4] based on 105 randomized controlled trials showed the beneficial effects of decision aids in improving doctor-patient communication (without increasing patient anxiety), improving patient knowledge, respecting patient rights, increasing physician and patient satisfaction, improving the quality of care, as well as reducing the decision-making conflict.

In 2017, we developed a decision aid based on the Ottawa Personal Decision Aid Guide [19] and the International Patient Decision Aid Standards Collaboration criteria [20] on the theme of cystic fibrosis–related diabetes treatment. Psychometric tests performed at the cystic fibrosis reference center (CFRC) in Lyon showed that the tool was valid and reliable [21]. In recent years, initiatives have been developing to implement SDM in routine clinical practice. Elwyn et al [22] in their systematic review of studies of decision support interventions concluded that the majority of studies do not base their design on an implementation theory or model. Although their review focused on the routine implementation of decision support interventions to promote SDM, there are other strategies for implementing SDM. For example, a large-scale, multicomponent SDM implementation program involving training of health care professionals in SDM and decision aids has been performed within the National Health Service in the United Kingdom (Making Good Decisions in Collaboration [MAGIC] Program). It showed that successful implementation of SDM in routine clinical practice (primary care, urology, obstetrics, oncology) was based on considering stakeholder attitudes, involving all stakeholders at an early stage and analyzing barriers and facilitators [23]. Such an approach is in line with the recommendations for implementation research developed by Grol and Grimshaw [24].

According to us, SDM seems to be particularly relevant in cystic fibrosis, where there are complex treatment options with variable short, medium, and long-term side effects, and where the disease and its treatments have a high impact on the patient's quality of life. This genetic disease affects almost 7000 people in France [25] and requires lifelong multidisciplinary care. From the moment of diagnosis, patients are regularly monitored in CFRCs. As a result, the doctor, the multidisciplinary team, and the patient/relatives have often known each other for a long time, forging a strong relationship based on mutual understanding and confidence.

A patient's quality of life is severely impaired by pulmonary exacerbations and regular digestive disorders. The patient's care load is considerable, combining daily respiratory physiotherapy, daily aerosol therapy, and multi-daily drug treatments. The social constraints (follow-up appointments every 3 months, daily medication intake, diet) associated with the disease and its treatment are considerable [26]. In addition, complications arise during the course of the disease such as diabetes. After the age of 30 years, half of all patients develop diabetes [27,28].

Diabetes adds significant morbidity [28,29]. Cystic fibrosis–related diabetes is quite specific, differing from type 1 diabetes and type 2 diabetes. It has the particularity of being asymptomatic for a long time, with normal fasting blood glucose levels. For this reason, international recommendations suggest annual screening for diabetes from the age of 10 years, with an oral glucose tolerance test [30]. If diabetes is confirmed by the results of the oral glucose tolerance test, the question arises of how to treat it with insulin. If the patient's clinical condition is stable and the fasting blood glucose level is normal, there are 2 possible treatment options: start insulin as soon as the diagnosis is made or defer initiation of insulin therapy and reserve it for cases where the patient is experiencing impaired respiratory function, increased frequency of exacerbations, or weight loss. Each of these options is complemented by the appropriate dietary and exercise measures generally recommended for all patients with cystic fibrosis. To our knowledge, very little work has been done on SDM in cystic fibrosis [31] and none on SDM for the treatment of cystic fibrosis–related diabetes.

Research Assumption

We hypothesize that the practice of SDM by CFRC health care teams for the decision to treat cystic fibrosis–related diabetes will be favored by the implementation of an SDM intervention based on e-learning training integrating an information and decision support tool and coaching for physicians and the medical team.

Aims

Primary Objective

The primary objective is to evaluate the pilot implementation of an SDM intervention, that is, the adoption of SDM between the health care professional and the patient with cystic fibrosis–related diabetes among patients managed in centers receiving the intervention compared with patients managed according to the usual decision-making practice in control centers. SDM is a decision-making process in which the health care professional (plus medical team) and the patient (plus his/her relatives) exchange information on treatment options and then reach a common agreement on the decision to take. It is based on an information and decision support tool used during the consultation. The SDM intervention evaluated comprises 5 components.

1. Web-based SDM training (e-learning) for the entire CFRC medical team
2. Individual coaching for physicians and medical team
3. SDM implementation: (1) consultation 1, including patient activation and delivery of the information and decision support tool to the patient; (2) consultation 2 on discussion and decision-making; and (3) between the 2 consultations, the patient has a cooling-off period of 8-15 days, wherein the physician discusses the content of the consultation with the CFRC team
4. Link with institutional patient engagement initiatives
5. Integration of SDM into CFRC multidisciplinary concertation meetings

Secondary Objectives

The secondary objectives were to evaluate the effects of SDM on patients' level of knowledge of management options with benefits and risks, anxiety, and decisional conflict compared with patients managed in centers without intervention and to evaluate the effects of SDM on the physician-patient relationship in terms of information and decision-making.

In Intervention Centers

The objectives were as follows.

1. To evaluate the implementation of the SDM approach.
2. To evaluate the experience of the implementation of SDM regarding the treatment of diabetes in patients with cystic fibrosis. For patients: observations of SDM consultations, individual semistructured interviews based on an interview guide containing key items relating to information and participation in decision-making (barriers, helps) based on our previous work in the field, and questionnaires (9-item Shared Decision-Making Questionnaire [SDM-Q-9], CollaboRATE, knowledge, State-Trait Anxiety Inventory, SURE [Sure of myself, Understand information, Risk-benefit ratio, Encouragement] questionnaire). For health care professionals: focus groups with CFRC teams held at the start of the intervention and afterwards in each CFRC in the intervention group.
3. To identify the individual and organizational factors that influence the implementation of SDM in the treatment of diabetes in patients with cystic fibrosis by health care professionals: focus groups with CFRC teams, semistructured interviews with patients, and exchanges with institutional decision makers such as quality services.

In Control Centers

The objective is to describe the process and experience of making decisions about diabetes treatment. For patients with cystic fibrosis, in usual practice, the objective is to conduct observations of consultations dedicated to the discussion of insulin therapy, individual semistructured interviews, and questionnaires. For CFRC health care professionals, the objective is to conduct focus groups with teams from each CFRC (focus groups held once in each CFRC during the course of the study).

Methods

Ethics Approval

This study has been approved by the Scientific and Ethical Committee of the Hospices Civils de Lyon University Hospital on the data study (outside the Jardé law; MR004-ID 21_356).

Design and Setting of the Study

Based on our previous work on SDM in cystic fibrosis [21] and the Consolidated Framework for Implementation Research of Damschroder et al [32], this quasi-experimental here-elsewhere study compares the populations of 3 centers receiving the intervention with those of 2 centers not receiving it (controls). The 5 centers will be studied simultaneously to reduce the risk of contamination of the control group. The evaluation will

follow a mixed methods approach, combining qualitative methods (consultations observations, individual semistructured interviews with patients, and focus groups with health care professionals) with quantitative methods (self-administered questionnaires). A convergent mixed methods approach will be used, with concomitant data collection, separate analysis, and subsequent linking of results. This study conforms to the StaRi (Standards for Reporting Implementation Studies) checklist (Multimedia Appendix 1).

Characteristics of the Participants

Patient Inclusion Criteria

The patient inclusion criteria were as follows: (1) older than 18 years, with cystic fibrosis, followed up in one of the 5 CFRCs; (2) be able to understand French; (3) have an oral glucose tolerance test at the stage of diabetes or with a blood glucose Holter considered by the clinician to be pathological, justifying possible insulin initiation; (4) have normal fasting blood sugar levels; (5) stable clinical pulmonary and nutritional status, enabling the 2 treatment options to be considered; and (6) having received the information and not exercised their right to object.

Patient Exclusion Criteria

Patients who had undergone a transplant and those receiving insulin therapy were excluded.

Inclusion Criteria for Health Care Professionals

Medical and paramedical professionals working in the adult CFRC (physicians, nurses, dietitians, psychologists, physiotherapists, etc) who have not exercised their right to object were included.

Description of Intervention and Comparisons

SDM Implementation Program

This program was divided into several parts and as already mentioned, theoretically based on the Consolidated Framework for Implementation Research [21] and on existing literature on the implementation of SDM [13], structured into 5 components (A to E) focusing on health care professionals and patients.

Component A: Health Care Professionals' SDM Training in the 3 CFRCs

A 2-hour e-learning course will be the common core of the training. It comprises 7 modules: (1) training objectives; (2) review of national and international literature on SDM; (3) understanding SDM; (4) cystic fibrosis–related diabetes; (5) developing an information and decision support tool; (6) communicate benefits and risks to the patient; and (7) encourage active patient participation by means of a video of 2 simulated consultations with a doctor from the CFRC in Lyon and a patient who volunteered to take part in the project since its inception: one consultation leading to a shared decision to start insulin now and the other to start later. The e-learning will be supplemented by a presentation by one of the researchers specialized in SDM at the 3 CFRCs to answer questions/comments from the teams.

Component B: Individual Coaching for Physicians and Medical Team After e-Learning

This will be performed by the SDM methodologist to improve physicians' adoption of SDM practice. In line with research on this method [33], coaching will be provided verbally. The SDM methodologist will observe 1 or 2 consultations in each of the CFRCs, providing both oral and written feedback. Her feedback will be standardized across the 3 CFRCs on the 3 essential components of SDM (bilateral information/deliberation/common agreement on the decision taken).

Component C: Implementing SDM in 6 Steps

The 6 steps are as follows.

1. Initial consultation with the patient to discuss diabetes treatment options, detailing the benefits and risks of each option. The physician and patient inform each other, discuss throughout the consultation with the help of the information and decision support tool, elicit their preferences, and work toward reaching an agreement on the decision to take.
2. Patient activation strategy: this patient-mediated method is based on the "Ask 3 questions" tool used in international SDM implementation studies [20]. It consists of short questions that patients can ask their doctor to enable them to participate more fully in decision-making if they so wish (ask 3 questions: what are my options? what are the possible benefits and harms of those options? how likely are the benefits and harms of each option to occur?) [20]. This tool is displayed in the waiting room before the consultation.
3. The physician gives the patient a paper version of the information and decision support tool [21].
4. The physician presents the exchanges with the patient to the CFRC team trained in SDM to obtain their feedbacks.
5. A cooling-off period of 8-15 days is required before the second consultation. During this period, the patient can discuss with his or her family, general practitioner, or any other health care professional outside the CFRC as well as with the CFRC team, and can call, based on the information and decision support tool, if he or she so wishes.
6. A second consultation takes place after this period of reflection to make the decision (in this case, to take insulin now or later). Several attitudes are possible: clear patient preference for one option, patient decides alone, refusal by the patient to choose an option, or the physician decides on the basis of the therapeutic thesaurus. It should be noted, however, that this is not the paternalistic model, as far as it is the patient who, after being informed, asks the doctor to decide; thereafter, they come to a common agreement on the decision taken (decision taken together), resulting in SDM.

Component D: Link With Institutional Initiatives to Promote Patient Involvement

This will be performed by means of a short questionnaire describing the current situation on the topic. At the start of the study, this questionnaire will be supplemented by a phone interview with the hospital quality manager or referent. As CFRC teams are integrated into university hospitals that implement patient engagement initiatives, it will be important

to collaborate with their management teams to work together on integrating the SDM approach into these hospitals.

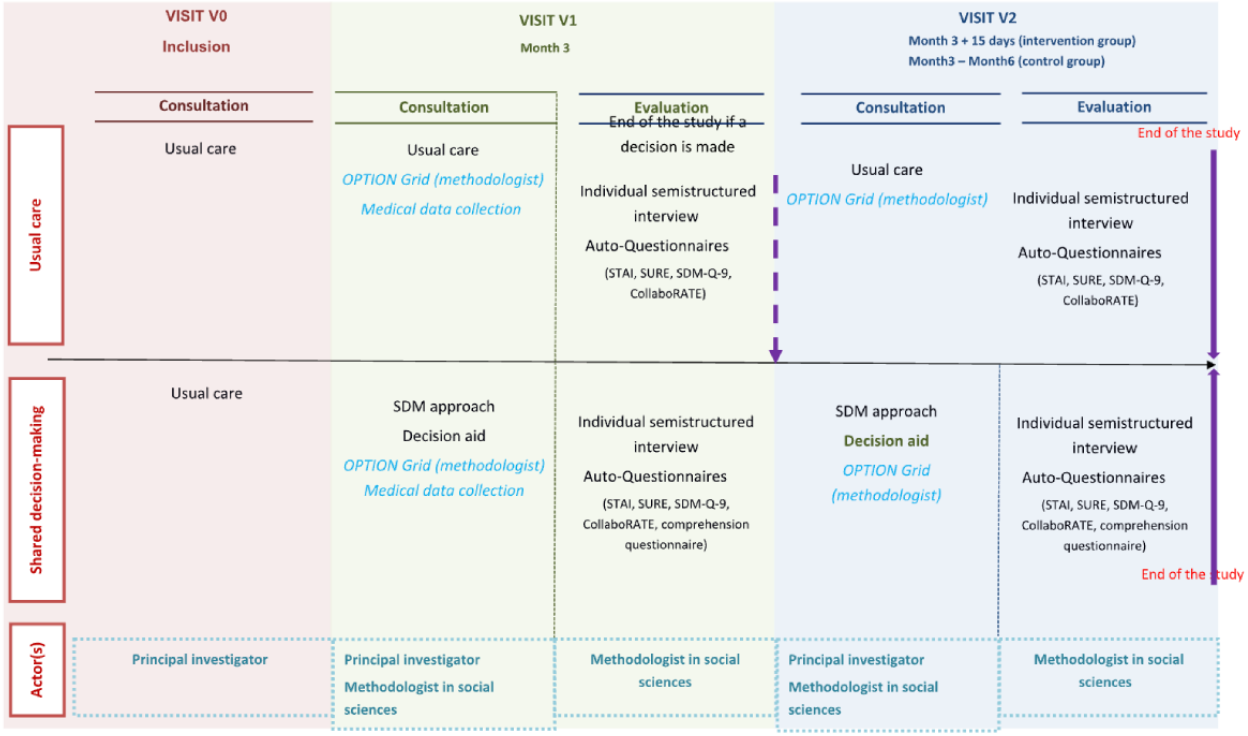
Component E: Integrating SDM Into CFRC Multidisciplinary Concertation Meetings

In order to best integrate SDM into the 3 CFRCs in the intervention group, we will organize in 2025 and in 2026 a meeting in each of the CFRCs to see how to integrate SDM into the recommendations for practice in multidisciplinary concertation meetings, and we will consider the organizational and practice specificities of each of these 3 CFRCs.

Standard Care

Insulin therapy decisions are made according to the usual practice defined in each CFRC, with decision-making procedures specific to each center and each CFRC physician/dietitian/nutritionist/team. The decision-making process generally involves 2 consultations (Figure 1).

Figure 1. FORAIDMUCO study protocol. SDM: shared decision-making; SDM-Q-9: 9-item Shared Decision-Making Questionnaire; STAI: State-Trait Anxiety Inventory; SURE: Sure of myself, Understand information, Risk-benefit ratio, Encouragement; OPTION: Observing Patient Involvement in Shared Decision Making.



Outcomes and Measures

The outcomes are measured using the following measures.

1. Adoption or nonadoption of SDM: SDM-Q-9 [34,35], CollaboRATE questionnaire [36], OPTION (Observing Patient Involvement in Shared Decision Making) questionnaire [37,38]
2. Level of patient knowledge: knowledge questionnaire developed by the authors on the basis of their previous work [39] and the literature since no validated knowledge questionnaire exists
3. Patient anxiety level: Spielberger State-Trait Anxiety Inventory [40]
4. Patients' level of decisional conflict: SURE questionnaire [41]
5. Patients' experience of information and decision-making procedures and more specifically of SDM implementation
6. Individual and organizational factors influencing SDM implementation

Inclusion Visit (V0)

When the patient comes to the CFRC following orally induced hyperglycemia, the physician will check the patient's eligibility criteria. During this visit, the physician will present the study and give the patient the information note. The physician will record the patient's nonopposition in the consultation report. The methodologist in social sciences must be informed of the patient's inclusion by sending an email containing the patient's first and last initials and the date of the V1 visit so that she can contact the investigating center to schedule her visit.

Visit V1

In the CFRCs of the control group, the physician will present the patient with information on diabetes management according to his or her usual practice. In the CFRCs in the intervention group, the physician will present the patient with information on diabetes management according to SDM (options, benefits, and risks) by using the information and decision support tool. The patient will be "activated" prior to the consultation, inviting him/her to ask questions using the "Ask 3 questions" tool. During the V1 visit for the control and intervention groups, the

investigator will fill in the patient's clinical data and SDM-Q-9 adapted to the physician immediately after the consultation. The patient fills in the questionnaires immediately after the consultation (the questionnaires are handed over by the methodologist or a member of the CFRC). The methodologist in social sciences will observe the physician-patient interaction during the consultation and complete the OPTION questionnaire; conduct an individual semistructured interview with the patient immediately after the consultation; ensure that the patient completes the SURE, CollaboRATE, SDM-Q-9, and Spielberger State-Trait Anxiety Inventory questionnaires (if the patient does not read French, the methodologist will read the questionnaires to the patient and fill them in with his/her agreement); and collect the patient's sociodemographic characteristics.

Decision-Making Visit (V2)

In the CFRC control group, insulin therapy decision-making will be performed according to the physician's usual practice. In the CFRCs of the intervention group, the decision-making visit will take place after a cooling-off period of 8 to 15 days following the V1 consultation. A discussion based on feedbacks from this period will take place between the physician and the patient, and either there is a common agreement on the decision taken (SDM) or the decision is taken by the patient or the decision is taken by the physician at the patient's demand. During this visit, the investigator will complete the SDM-Q-9 adapted to the physician immediately after the consultation. The patient fills in the questionnaires immediately after the consultation (the questionnaires are handed over by the methodologist in social sciences or a member of CFRC). The methodologist in social sciences will observe the physician-patient interaction during the consultation and complete the OPTION questionnaire, conduct an individual semistructured interview with the patient immediately after the consultation, and ensure that the patient completes SURE, CollaboRATE, SDM-Q-9, and the Spielberger State-Trait Anxiety Inventory. If the patient does not read French, the methodologist will read the questionnaires to the patient and fill them in with his/her agreement.

In the control and intervention groups, the methodologist in social sciences will attend the face-to-face consultation (possibly by videoconference if conditions require and allow) and will conduct the individual interview with the patient immediately after the consultation. If the patient is not available, the interview can take place up to V1+48 hours. The end of the research for patients in both groups is defined by the end of the individual interview at V2 or V1 for the control group if a decision is made following the consultation.

Health Care Professional Focus Groups

Two focus groups will be conducted in the intervention CFRCs (one at the start of the study and one at the end) and one in each of the 2 control centers by the methodologist in social sciences on the basis of a moderation guide containing the key items on which participants will be invited to discuss (barriers, facilitators of information and decision-making, dedicated time with and without SDM, information and decision support tool, etc). The discussion group will be made up of 4-8 health care professionals (physicians, nurses, physiotherapists, dietitians, psychologists, etc) depending on the center and will be as representative as possible of the CFRC's health care professional categories. In the intervention centers, the participating health care professionals will not necessarily have taken the e-learning training course. However, the group should be identical for both discussion groups unless a member is absent or leaves.

Data Collection and Analysis

Sample Size

As this is a pilot study, 40 patients will be included and interviewed over a 12-month period. The number of patients included corresponds to the active patient file of the 5 CFRCs over the 12-month inclusion period. Five physicians (1 in each center) will be involved in this study.

Analysis

All patients and health care professionals included in this study are in accordance with the inclusion and noninclusion criteria. The primary end point is the adoption or nonadoption of SDM from the patient's and health care professional's point of view. The secondary end points are patient knowledge; patient anxiety levels; patients' level of decisional conflict; patients' experience of information and decision-making procedures, and more specifically of SDM implementation; effect of SDM on the physician; and individual and organizational factors influencing SDM implementation.

Statistical Methods

Descriptive Analysis

A descriptive analysis of the characteristics of the patient population included (age, sex, history and severity of disease) and of the health care professionals on the CFRC teams (physicians, nurses, dietitians, psychologists, physiotherapists, etc, age, sex, profession, previous training in SDM) will be performed in the 2 study groups. Quantitative characteristics will be described by mean and standard deviation or by quartiles and minimum and maximum values depending on the shape of the distribution. Qualitative characteristics will be described by the numbers and percentages in each category. The comparability of the characteristics will be checked using the chi-square test for qualitative variables and the Wilcoxon test for quantitative variables. Data on the implementation of SDM in the intervention group will also be the subject of a descriptive analysis on the proportion of patients with at least one SDM consultation and the proportion of patients with 2 SDM consultations.

Analysis: Primary End Point

Adoption of SDM as perceived by the patient and measured using SDM-Q-9 will be analyzed in patients with no missing data on this criterion, although an approach to managing missing data may be considered. The frequency distribution of the 6 modalities of SDM-Q-9 will be described for each group in the patient unit. A total score will be obtained by summing the scores for each of the 9 questions. A transformation will be applied to obtain a total score between 0 and 100, with 0 indicating nonadoption of SDM as perceived by the patient and conversely 100 indicating adoption of SDM as perceived by

the patient. The total score will be described in each group by mean, standard deviation, median, quartiles, and range, and will be compared between the 2 groups with a nonparametric Wilcoxon test. For patients in the intervention group, the variation in the responses to each of the SDM-Q-9 questions between the 2 consultations will be tested using the McNemar test (test adapted to paired data). Total SDM-Q-9 scores between the 2 consultations will be compared using the Wilcoxon signed-rank test. The same analysis will be performed on the health care professional unit to compare the adoption of SDM as perceived by the health care professional. Discordances between patient and health care professional responses to each of the 9 questions on SDM-Q-9 will be described and tested using the McNemar test. The total SDM-Q-9 score obtained on the patient unit and the professional unit will be compared using the Wilcoxon signed-rank test.

Analysis: Secondary End Points

In accordance with the scoring rules of the OPTION grid, an OPTION score will be calculated for each patient-health care professional dyad if 100% of the 5 OPTION grid items have been completed. A total score between 0 and 20 will then be obtained by summing the answers to the 5 OPTION grid items between 0 and 4. The total score will be converted between 0 and 100, with high values indicating exemplary behavior by the dyad in adopting SDM. The OPTION score will be expressed as the mean and standard deviation for each group and will be compared using the Wilcoxon test.

In accordance with the scoring rules of the SURE questionnaire, a SURE score will be calculated for each patient if 100% of the 4 questionnaire items have been completed. A total score between 0 and 4 (a high value indicates a decisional conflict) will then be obtained by summing the binary responses of the 4 questionnaire items. The SURE score will be expressed as the mean and standard deviation for each group and will be compared using the Wilcoxon test. The percentage of patients whose SURE score is less than or equal to 3 (indicating a decisional conflict) will also be calculated in each group and compared using the chi-square test.

In accordance with the scoring rules of the CollaboRATE questionnaire, a CollaboRATE score will be calculated for each patient if 100% of the 3 questionnaire items have been completed. A total score between 0 and 9 (high values indicating a high level of SDM) will then be obtained by averaging the answers to the 3 questions between 0 and 9 on the questionnaire. The CollaboRATE score will be expressed as the mean and standard deviation for each group and will be compared using the Wilcoxon test.

A Spielberger State-Trait Anxiety Inventory score will be calculated for each patient if 100% of the 20 questionnaire items have been completed. A total score between 20 and 80 (high values indicating a high level of anxiety) will then be obtained by summing the scores associated with the 20 items. For questions 3, 4, 6, 7, 9, 12, 13, 14, 17, and 18, 1 point is awarded for not at all, 2 points for somewhat, 3 points for moderately, and 4 points for very much. For questions 1, 2, 5, 8, 10, 11, 15, 16, 19, and 20, the scoring will be reversed, that is, 4 points for not at all, 3 points for a little, 2 points for moderately, and 1 point for a lot. The Spielberger State-Trait Anxiety Inventory score will be expressed as the mean and standard deviation for each group and will be compared using the Wilcoxon test.

Semistructured individual interviews designed to assess the experience of information and decision-making procedures in the control and intervention groups and the effects of SDM on patients' and health care professionals' experience of care in the intervention groups only will be analyzed by means of a thematic content analysis conducted using NVivo 10 (QSR International) and 2 researchers participating in the study based on the interview guide developed and previously tested with patients at the CFRC in Lyon. The focus groups conducted in the control and intervention groups designed to analyze the individual and organizational factors influencing the implementation or nonimplementation of SDM will be transcribed on the basis of notes taken during the focus groups and will be analyzed on the basis of the interview guide developed.

Results

Forty patients will be included (8 patients in each center), that is, 60 consultation observations (2 consultations per patient in the intervention groups given the modalities of the SDM process) will be conducted in 2025. Eight focus groups will be conducted in the 5 centers (2 groups in each intervention CFRC and 1 group in each control CFRC) in 2025. This qualitative corpus plus responses to the patient and physician questionnaires will make it possible to know whether the practice of SDM in CFRCs is increased by an implementation strategy and to analyze the experience of patients and their relatives regarding decision-making modalities. Analysis of the outcomes and experience of the implementation of SDM are of importance to identify the facilitators and barriers to SDM from patients' and CFRCs' point of view.

Discussion

This is the first study protocol on cystic fibrosis treatment in France, which is designed to train health care professionals on SDM and implement and evaluate the outcomes of the SDM approach. Training materials and health care professionals trained in SDM could boost SDM implementation in cystic fibrosis therapy in French-speaking countries, where the so-called clinical champions in SDM are needed. Moreover, patients experiencing SDM could support and participate in the SDM acculturation process.

The aim of our study is also to propose an original study based on mixed methods combining quantitative and qualitative analyses by using validated evaluation tools (particularly in French) and to conduct the study with patients and health care professionals for whom the potential benefits are multiple: to support in decision-making concerning diabetes treatment; to improve communication between physicians, health care team, and patients; to improve the quality of experience of the decision-making steps; and to acculturate health care professionals to SDM and formalize their practice, thanks to SDM training.

The protocol and information and the decision support tool developed could serve as a basis for other situations in the field of cystic fibrosis, as in the case of lung transplantation, subject to the adaptations to be made. There are many opportunities for SDM in cystic fibrosis, but little is known about patients' experience of SDM [42]. The training materials and the teams already trained could prove to be the key to future success, with those trained becoming trainers for other centers. International comparisons could also be developed, notably within the framework of the La Collaboration Francophone sur la Prise de Décision Partagée FREeDOM (French collaboration on SDM), which brings together health care professionals, patients, researchers, and public decision makers, notably from Quebec, Switzerland, Belgium, and France, interested in adapting the approach developed to their countries/context.

Although this is the first French study to train health care professionals and implement and evaluate SDM in cystic fibrosis treatment, compared to the usual clinical practice, the number of CFRCs involved is limited, which will potentially limit the generalizability of the results obtained. This study will nonetheless be conducted at the national level. In addition, only a small number of patients with cystic fibrosis are concerned about the development of diabetes, which could impact the duration of our project in order to obtain the desired number of patients.

Acknowledgments

We would like to thank the patient partners and health care professionals of the 5 cystic fibrosis reference centers who participated in the development of this study and the Vaincre la Mucoviscidose Association for funding this study.

Data Availability

Datasets that will be generated and analyzed during this study will be available from the corresponding author on reasonable request.

Authors' Contributions

NM, SH, SP, CG, JH, ID, and QR developed the methodology. NM wrote the first draft of this paper. All authors read and approved the final manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
StaRi (Standards for Reporting Implementation Studies) checklist.
[PDF File (Adobe PDF File), 235 KB - resprot_v14i1e62931_app1.pdf]

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Abbreviations

CFRC: cystic fibrosis reference center
FREeDOM: French collaboration on shared decision-making
MAGIC: Making Good Decisions in Collaboration
OPTION: Observing Patient Involvement in Shared Decision Making
SDM: shared decision-making
SDM-Q-9: 9-item Shared Decision-Making Questionnaire
StaRi: Standards for Reporting Implementation Studies
SURE: Sure of myself, Understand information, Risk-benefit ratio, Encouragement

Edited by T Leung; submitted 05.06.24; this is a non–peer-reviewed article;accepted 26.10.24; published 28.01.25.

Please cite as:
Moumjid N, Gotte C, Hommey S, Poupon Bourdy S, Haesebaert J, Durieu I, Reynaud Q
Mixed Comparative Evaluation of a Training Program Dedicated to Cystic Fibrosis Reference Centers: Protocol for the Pilot Implementation of Shared Decision-Making in the Treatment of Diabetes in Adult Patients With Cystic Fibrosis
JMIR Res Protoc 2025;14:e62931
URL: https://www.researchprotocols.org/2025/1/e62931
doi:10.2196/62931
PMID:

Protocol

Complete Lifestyle Medicine Intervention Program–Ontario: Implementation Protocol for a Rural Study

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Abstract

Background: Sedentary lifestyles, poor nutritional choices, inadequate sleep, risky substance use, limited social connections, and high stress contribute to the growing prevalence of chronic diseases. Lifestyle medicine, emphasizing therapeutic lifestyle changes for prevention and treatment, has demonstrated effectiveness but remains underutilized in clinical settings. The Complete Lifestyle Medicine Intervention Program–Ontario (CLIP-ON) was developed to educate the rural population of Northern Ontario in lifestyle medicine to improve health outcomes and engagement.

Objective: This study evaluates the implementation and effectiveness of the CLIP-ON program for patients with chronic diseases in the Parry Sound area, focusing on lifestyle behaviors, health outcomes, enrollment, retention rates, and interdisciplinary team engagement.

Methods: This observational cohort study guided by the RE-AIM framework (Reach, Effectiveness, Adoption, Implementation, and Maintenance) includes pre- and postintervention assessments from participants and health care providers. A hybrid type II mixed methods design evaluates the intervention's effectiveness and implementation process in real-world settings through quantitative and qualitative data collection. CLIP-ON is tailored to the residents of the Parry Sound catchment area in Northern Ontario. Participants (≥18 years old) with chronic conditions such as prediabetes, type II diabetes, systemic hypertension, cardiovascular vascular disease, dyslipidemia, or high BMI (≥25) will be recruited through self-referral or provider referral. Approximately 10 participants per cohort will be enrolled in the CLIP-ON program, consisting of 22 weeks of weekly group sessions and monthly individual consultations with physicians, health coaches, kinesiologists, and registered dieticians either in person or through a web-based platform. CLIP-ON will cover the 6 pillars of lifestyle medicine through 14 group sessions followed by an 8-week supervised exercise program. Anthropometric and cardiometabolic variables will be measured before and after the program. Participants will be surveyed on lifestyle habits, wellness, perceived barriers, and program satisfaction at 3 and 6 months. Focus groups and dropout interviews with participants (n=10 per cohort) and providers (n=6 per cohort) will guide program

adaptations. Quantitative and qualitative data collected at baseline and follow-up will assess the program's implementation and identify barriers and opportunities for improvement.

Results: This study was approved by the Laurentian University Research Ethics Board (6021397) on July 6, 2023. The first cohort was enrolled in late 2023 and is still under evaluation. The second cohort began in mid-2024, and data collection is currently underway. A mixed methods analysis will be used at enrollment, program completion (22 weeks), and follow-up (6 months after program completion). Focus groups assessing the program's effectiveness and implementation will take place after the 22-week intervention. Data will be analyzed in early 2025.

Conclusions: This protocol provides insights into the implementation of this lifestyle medicine program and its impact on participants' health. The findings will guide future advancements and establish a scalable model for other communities.

Trial Registration: ClinicalTrials.gov NCT06192251; https://clinicaltrials.gov/study/NCT06192251

International Registered Report Identifier (IRRID): DERR1-10.2196/59179

(JMIR Res Protoc 2024;13:e59179) doi:10.2196/59179

KEYWORDS

chronic disease; nutrition, exercise; sleep; relationships; stress reduction; self-compassion; risky substance use; holistic medicine; whole health; implementation; lifestyle medicine; rural medicine; web-based platform; substance use; feasibility; wellness; barriers; opportunities

Introduction

Background

Chronic diseases, also known as noncommunicable diseases (NCDs) such as cancer, cardiovascular disease, cerebrovascular disease, and diabetes, are among the leading causes of death in Canada, with their prevalence steadily rising [1]. Hypertension, the leading global risk factor for death and disability, remains uncontrolled in more than 50% of patients [2]. NCDs are responsible for over 74% of global deaths annually [2-4], significantly affecting vulnerable and low-income populations [5-7]. Despite clear benefits from improved lifestyle choices, including better nutrition, regular physical activity, and stress reduction, there remains limited research on the long-term sustainability of these changes and the role of physician intervention [5,7-9].

Sedentary lifestyles, poor nutritional choices, and increased stress play significant roles in chronic disease development [7,8,10], with type II diabetes affecting over 10% of the population worldwide [11]. Type II diabetes, primarily linked to cardiovascular disease, contributes to over 1 million deaths annually [7,12-14]. Chronic disease–related health care costs in Canada account for more than US $136 billion annually [15], emphasizing the need for lifestyle interventions to reduce this burden [1,14].

Lifestyle medicine is an interdisciplinary medical specialty that focuses on 6 key pillars such as dietary changes, regular physical activity, stress management, restorative sleep, positive social connection, and avoidance of risky substances such as alcohol and tobacco has been shown to improve outcomes in chronic conditions [16-18]. Moreover, with its patient-centered focus [6,19-21], lifestyle medicine addresses the root causes of disease, aligning with the P4 (Preventive, Predictive, Personalized, and Participatory) medicine approach [6,22,23]. Achieving optimal health through a maintained commitment to lifestyle medicine has been shown to reverse many stages of chronic disease, reduce hospitalization and hospital costs, improve chronic disease management, and promote better health outcomes [4,5,14,24-28].

Studies indicate that the adoption of evidence-based lifestyle medicine practices has gained traction, with numerous programs demonstrating effectiveness in improving health outcomes and promoting sustainable behavior change [9,29-31]. Other studies support the adoption of evidence-based lifestyle medicine practices across North America [9,20,32,33]. Such evidence highlights the potential for lifestyle medicine to be integrated into routine health care, paving the way for broader acceptance and implementation in various clinical environments.

However, despite these promising outcomes, effective implementation of lifestyle medicine in clinical settings remains challenging. A strong patient-provider collaborative relationship is essential for achieving adherence to treatment plans and informed health care decision-making [34]. The physician's role as a health coach is critical in this process, underscoring the importance of training clinicians in lifestyle medicine practices [5,12,16,35]. Yet, many physicians report a lack of confidence and skills in delivering lifestyle medicine effectively [20], especially in rural areas. During the COVID-19 pandemic, virtual and digital platforms, such as lifestyle management tools, were developed to support patients [10,36], which has proven to be crucial for equitable health care access [16,35]. These tools hold the potential to address barriers in underserved areas where health care resources are limited, particularly in rural settings.

In this context, it becomes essential to evaluate the real-world implementation of lifestyle medicine to identify both successes and challenges, ensuring that lifestyle medicine can be effectively integrated into routine health care. This is especially relevant in rural areas, where health care access is limited, and the burden of chronic disease is high. Parry Sound, a rural community in Northern Ontario with a population of 6879 and a catchment area of 42,824 (including 10% Indigenous residents) [26,29,36,37], experiences disproportionately high rates of diabetes (8%) and hypertension (20%) compared with the provincial average [27]. These factors make it an ideal location

for integrating lifestyle medicine into care. Incorporating traditional Indigenous teachings, which emphasize the interconnectedness of mind, body, spirit, and emotions, can bridge gaps between traditional Western medicine and Indigenous Healing Practices and improve population health outcomes [28,36,38].

Inspired by the New York Lifestyle Medicine program [36,38], in 2023 our medical and research team, in collaboration with the health care community in Parry Sound, developed an innovative and whole health program named the Complete Lifestyle medicine Intervention Program, Ontario (CLIP-ON). These comprehensive interdisciplinary aims are to educate participants on the 6 pillars of lifestyle medicine and inform them about their integration into daily life to mitigate chronic disease and enhance overall health. To facilitate the implementation of lifestyle medicine practices, various models and methodologies have been proposed [39]. Among these, the RE-AIM framework (Reach, Effectiveness, Adoption, Implementation, and Maintenance) serves as a valuable tool for evaluating the impact of lifestyle medicine interventions in diverse settings [40,41]. To the best of our knowledge, this is the first program in lifestyle medicine in a rural area in Ontario. Our overarching hypothesis is that the implementation of CLIP-ON will significantly improve lifestyle behavior, health outcomes, and participant engagement, with feedback from participants and health care providers informing real-time program improvements.

Primary Objective

To evaluate the implementation and effectiveness of the comprehensive web-based platform and in-person CLIP-ON program for patients with chronic disease in the Parry Sound area, focusing on its impact on lifestyle behaviors, health outcomes including cardiometabolic parameters, and participants' engagement.

Secondary Objectives

The secondary objectives of this study are (1) to assess the reach and adoption of the CLIP-ON program by evaluating participant enrollment, and retention rates and (2) to gather and analyze direct feedback from participants and health care providers to inform real-time program improvements and enhance the program's overall effectiveness.

Methods

Design

This protocol outlines an observational cohort study guided by the RE-AIM framework (Reach, Effectiveness, Adoption, Implementation, and Maintenance) and includes pre- and postintervention assessments from participants and health care providers (RE-AIM milestones Multimedia Appendix 1). A hybrid design type II mixed methods approach [42,43] will be used to simultaneously evaluate both the effectiveness of the CLIP-ON and its implementation process in a real-world setting. This will involve the collection and analysis of both quantitative and qualitative data.

The CLIP-ON program is an interdisciplinary lifestyle medicine intervention delivered both virtually and in person, specifically tailored for residents of the Parry Sound catchment area in Northern Ontario. Within this district are 3 First Nation Communities (Wasauksing, Moose Deer Point, and Shawanaga First Nations), each of which has requested access to CLIP-ON. The study design is summarized in Figure 1, and the participant's and health care providers' measurements are presented in Table 1. Following informed consent, each participant will have an initial appointment with a certified lifestyle medicine physician at West Parry Sound Health Centre before starting the CLIP-ON program. Participants will complete the Physical Activity Readiness Questionnaire (PAR-Q+) by the Canadian Society of Exercise Physiology [44] to identify risk factors during moderate physical activity. A Physical Activity Readiness Medical Examination (PARmed-X) [45] will also be completed for participants who had potential medical complications from exercise according to their response to the PAR-Q+. During this visit, they will undergo a medical review and physical examination. They will also receive a requisition for blood work to establish their baseline cardiometabolic data. Each participant will complete a baseline (intake Lifestyle and health) questionnaire on Google Forms with the assistance of a trained research staff member over the phone. This preprogram questionnaire will collect demographic and baseline information about their lifestyle according to the 6 pillars of lifestyle medicine. Cardiometabolic variables will be measured before and after the CLIP-ON intervention. Participants will be surveyed by phone at 3- and 6-months regarding lifestyle habits, wellness, perceived barriers, and program satisfaction. At the end of the program, web-based platform (through Zoom) focus groups with participants and health care providers will be conducted to discuss their experiences and provide feedback for program development. Focus groups and dropout interviews with patients (approximately 10 per cohort, anticipating a drop-out rate of 10% based on similar studies [29], and providers (approximately 6 per cohort) will provide iterative feedback, enabling program refinement. The 2 cohorts are planned, with potential for expansion based on the available funding. The study timeline is illustrated in Figure 2.

Figure 1. CLIP-ON protocol. The intake lifestyle and health progress questionnaire was inspired by the Lifestyle Assessment Short Form [46], the 36-Item Short Form Health Survey, and the Patient Health Questionnaire-9 [47,48]. The Physical Activity Readiness Questionnaire (PAR-Q+) [44] and PARmed-X [45] were used to measure physical activity readiness. The 6 pillars of health inspired by the American College of Lifestyle Medicine are nutrition, sleep, relationships, physical activity, risky substance use, and stress management [18]. Three- and 6-month health progress questionnaires were inspired by the questions used in the New York City Health [38,49,50], the Hospital lifestyle medicine program, and the Complete Health Improvement Program lifestyle medicine program at Vanderbilt University [51,52].

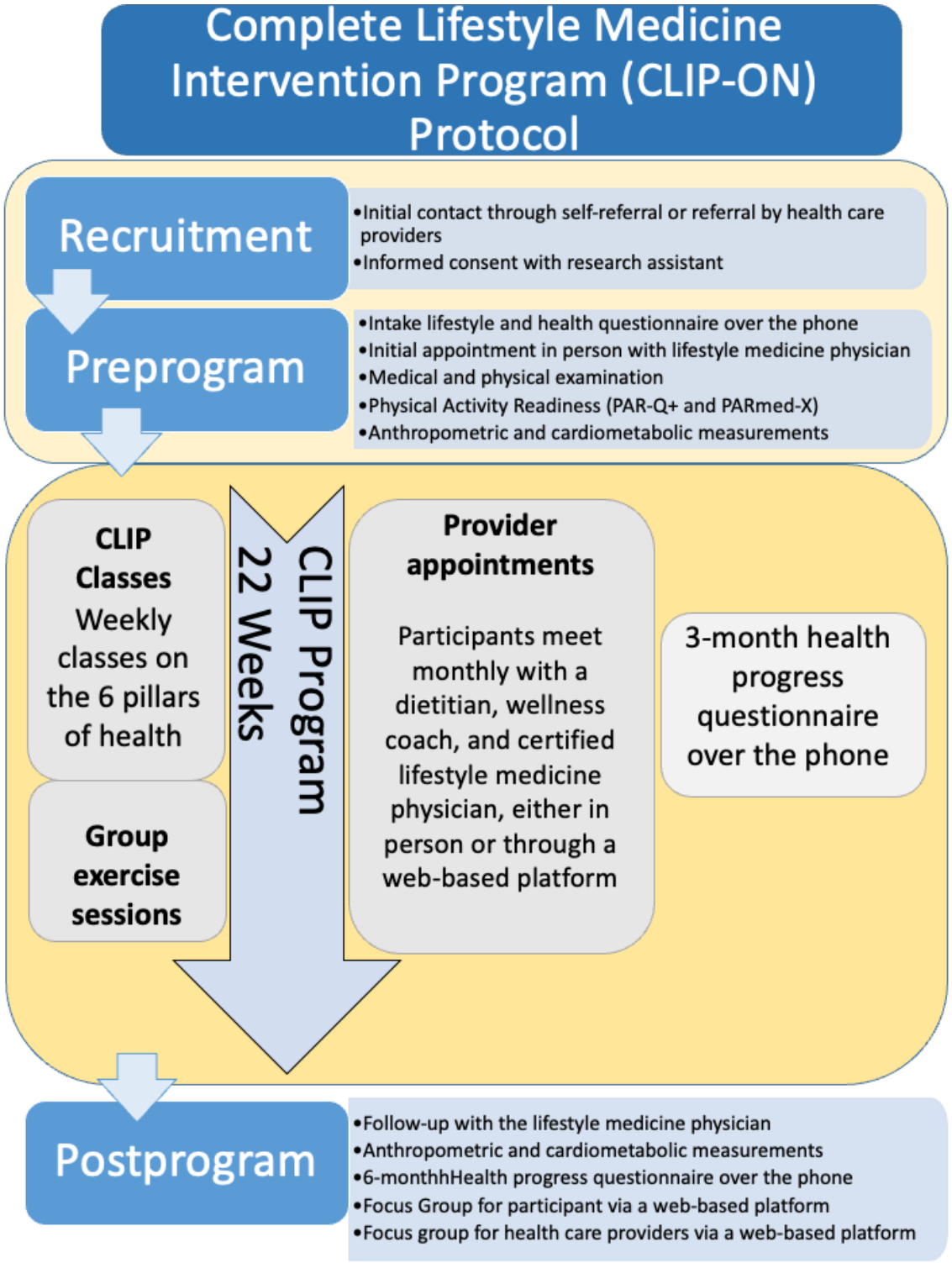

Table 1. Participants and health care providers measurements.

Measurement	Time	Variables	Details
Intake Lifestyle and Health Participants Questionnaire	Baseline, 6 months, and 12 months	Food consumption, motivation and confidence, neighborhood food environment, physical activity, media use and screen time, substance use, sleep, health, behavior, and well-being, and socio-demographics	Administered through phone or online, inspired by inspired by the Lifestyle Assessment Short Form [46], the short form survey instrument SF-36[a] and the PHQ-9[b] [47,48].
Health progress questionnaire[c]	3 months and 6 months	Similar to the intake questionnaire but includes additional questions on social support, satisfaction with the program	Conducted by phone with a research assistant
Anthropometric measurements	Pre- and postprogram	Health, weight, BMI, and waist circumference	Measurements taken by health care providers
Hemodynamic measurements	Pre- and postprogram	Blood pressure and heart rate	Measurements taken by health care providers
Cardiometabolic measurements	Pre- and postprogram	Hemoglobin, ions (calcium, magnesium, phosphate, sodium, potassium), Fasting blood glucose, Glycated Hemoglobin, cholesterol Lipid panels (total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, plasma, triglycerides) creatine glomerular filtration rate, Urine test: microalbumin, and albumin-creatine ratio	Blood and urine tests collected for analysis
Health care provider questionnaire	Preprogram	Provider social demographics, credentials, practice location	Completed before program involvement
Participants focus group	End of program	Experiences, benefits, challenges, program feedback, their thoughts on lifestyle medicine pillars addressed, and program continuation	Virtual focus group using a semistructured script led by an independent researcher or assistant
Health care provider focus	End of program	Feedback on recruitment strategies, their experiences, their thoughts on the content and materials provided, challenges encountered, future sustainability, suggestions for future program implementation cohort	Virtual focus group using a semistructured script led by an independent researcher or assistant

[a]SF-36: 36-item Short Form Survey.

[b]PHQ-9: Patient Health Questionnaire-9.

[c]These questionnaires include questions used in the Complete Health Improvement Program (CHIP) lifestyle medicine program at Linda Loma University and the New York City Health and Hospital lifestyle medicine program [38,49]. In addition, the Warwick, -Edinburgh Mental Well-Being scale guided the inclusion of questions pertaining to mental health [51,52]. Together, these existing surveys allow both quantitative and qualitative elements to be included in this study.

Figure 2. Timeline. It illustrates the key tasks throughout the study timeline. The first year focused on grant preparation, recruitment, preassessment, and intake questionnaires to prepare the first cohort. Year 2 emphasizes group sessions, individual appointments, end-of-program questionnaires, and postassessment for Cohort 1, while also initiating the same process for Cohort 2. Year 3 will primarily focus on data analysis and knowledge dissemination.

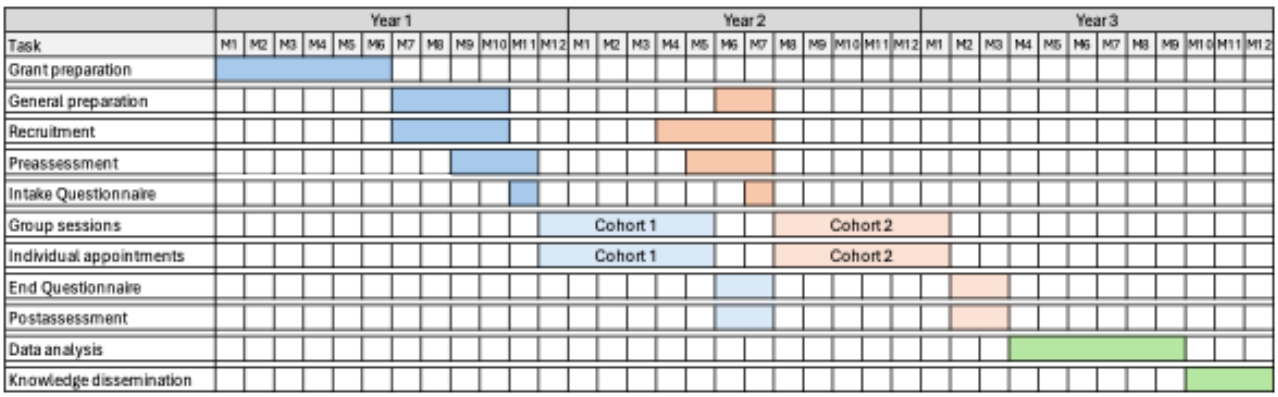

Figure 1 demonstrates participant flow throughout the CLIP-ON study, a hybrid lifestyle medicine program designed for rural Northern Ontario. The program addresses 6 pillars of health: healthy nutrition, regular physical activity, restorative sleep, stress management, avoiding risky substance use, and fostering positive relationships. Patients could meet health care providers in person or through a web-based platform. Group sessions and exercise classes during the 22-week program were available in 3 formats: in person, through a web-based platform, or as recorded sessions for later access. Intake lifestyle and health progress questionnaire inspired by the Lifestyle Assessment Short Form [46], the short form survey instrument SF-36 and the PHQ-9 [47,48]. Physical Activity Readiness Questionnaire: PAR-Q+ [44] and PARmed-X [45]. Three- and 6-Month Health Progress Questionnaire inspired by the questions used in the New York City Health [38,49,50] and Hospital Lifestyle Medicine program and the CHIP lifestyle medicine program at Vanderbilt University [51,52].

Participants

Inclusion Criteria

Adult participants (≥ 18 years) with chronic diseases such as prediabetes, type II diabetes mellitus, systemic hypertension, coronary heart disease, peripheral vascular disease, dyslipidemia, or health concerns related to excessive body weight (BMI≥25) will be recruited. Participants must reside in the Parry Sound, Ontario catchment area.

Exclusion Criteria

Participants with unstable medical conditions that prevent successful completion of program elements will be excluded. In addition, individuals who are unable to provide consent, do not meet the requirements of PARmed-X, and are unable to engage in a low-intensity, a professionally supervised exercise program will also be excluded.

Recruitment

Participants will be recruited through self-referral or referral by health care providers. Multiple avenues will be pursued to enhance recruitment efforts and reach a diverse population. Posters will be distributed throughout the Parry Sound community in high-traffic public locations such as grocery stores, coffee shops, libraries, and various departments within the Parry Sound Community Hospital. Pamphlets will be made available at health care provider clinics both within and outside of the hospital, including the Family Health Team and nurse-practitioner-led clinics. In addition, both posters and pamphlets will be distributed to local health care providers, who will be encouraged to share on social media (Facebook and Instagram [Meta]) in accordance with the ethical agreement to maximize outreach to the target population. These comprehensive recruitment strategies aim to ensure saturation of the rural environment and ensure equal opportunities for eligible participants to join the program.

Implementation Assessment

The CLIP-ON implementation assessment is guided by the RE-AIM framework which defines 5 dimensions: reach, effectiveness, adoption, implementation, and maintenance [40,41]. These dimensions will also help guide enhancements to the CLIP-ON program. Further details are provided in Multimedia Appendix 1.

Description of the CLIP-ON Program

Overview

The CLIP-ON program will consist of 22 weeks of weekly group sessions held at the local Parry Sound Bobby Orr Community Centre and monthly individual consultations, either in person at West Parry Sound Health Center or virtually, with an interdisciplinary team including physicians, a health coach, and registered dieticians. Participants will be encouraged to attend all 22 weekly classes and exercise sessions in person. However, a web-based platform option will be available for instances when they are unable to attend. Both the group class sessions and exercise sessions will be recorded for participants to access later. Each participant will receive a cookbook, exercise bands appropriate for their fitness level, and US $14.22 gift cards for local grocery stores as compensation for their time in completing program surveys and participating in focus groups.

Fundamentals of Lifestyle Medicine Group Class

CLIP-ON will cover the 6 pillars of lifestyle medicine through 12-14 group sessions on the Fundamentals of Lifestyle Medicine followed by an 8-week supervised exercise program developed and supervised by a kinesiologist. Table 2 outlines the topics covered in these group classes with a brief description of each. These classes will address the importance of the human microbiome and nutrition, fitness, positive relationship integration, stress and sleep management, and navigation of substance use toxicity and addiction. Concurrently, participants will discuss goal setting and planning with their lifestyle medicine physician, health coach, and dietician to incorporate knowledge and skills developed through the classes into their lives while motivating their success in the program.

Table 2. Topics and descriptions of each Fundamentals of Lifestyle Medicine group class.

Class topic	Class description	Providers
Introduction	An overview of what lifestyle medicine is and small group discussions for participants to meet each other.	Lifestyle medicine physician
Microbiome	Mostly focused on the gut microbiome, what it does, how every pillar can help build and maintain it, and what happens if we do not.	Lifestyle medicine physician
Nutrition	Two classes, one focused on explaining the recommendations of Canada's food guide, and another on discussing food preparation, practical cooking tips, and reading food labels.	Dietitian
Physical activity	Two Classes, one on the importance and benefits of physical activity and The Canadian Society of Exercise Physiologists' recommendations, and another class on how to move safely.	Kinesiologist
Sleep	Two classes, one on the benefits of sleep and what happens if we do not get enough sleep, another class on how to build our sleep hygiene, and an overview of insomnia and Cognitive Behavioral Therapy for insomnia.	Lifestyle medicine physician
Stress	Two classes, one on the impact of stress and the different ways it can manifest itself in our lives, and another class on stress management techniques.	Health coach
Social connections and positive psychology	One class on the impact of social isolation and the Positive Emotion, Engagement, relationships, Meaning, and Accomplishment (PERMA) [53,54] model of positive psychology for happiness and fulfillment.	Lifestyle medicine physician
Relationships with ourselves and others	One class on the concepts of Mindful Self-Compassion was developed by Kristin Neff and Christopher Germer, and Nonviolent Communication was developed by Marshall B. Rosenberg.	Lifestyle medicine and health coach
Risky substances and addictions	One class on the impact of addictions, the risk factors that can lead to addictive behaviors, and how to build our own resilience.	Lifestyle medicine physician
Conclusion	Discussion of takeaways and habit-building tips.	Lifestyle medicine physician

Exercise Group Class

An 8-week exercise program will be led by a registered kinesiologist and will follow the Fundamental Lifestyle Medicine group class session. The program will be structured yet adaptable to accommodate each participant's abilities and limitations. Before the exercise program, the kinesiologist will present the Education Sessions-Fitness Fundamentals, where they will explain why participants should exercise and how to be safe doing so. A booklet describing all activities will be shared with the participants that outline safe exercise guidelines, the rating of the Borg care of perceived exertion [44,55], when to stop exercising (symptoms and what to do), how to adapt the program, and exercises plan with picture of each exercise. The kinesiologist will then teach the entire exercise program in group sessions with the participants. Each session will last 1 hour and will follow this sequence warm-up, resistance training, cardio, flexibility, balance, core, and cool down. The exercise will use body weight resistance and a physiotherapy band appropriate for each person's capacity.

Enrollment

Participants will be screened according to the inclusion and exclusion criteria by the physician during their initial medical consultation. Eligible participants will be informed about the study's purpose, procedures, potential risks, and benefits during the informed consent process before enrolment. Participants will be made aware of their right to withdraw consent at any point during the study without any impact on their care.

Retention

The research staff and health care providers will strive to build strong rapport with participants encouraging them to attend the 22 weekly classes held in person at the local Parry Sound Bobby Orr Community Centre. If participants are unable to attend in person, a web-based platform option will be provided, along with access to recorded sessions. This approach ensured accessibility and adaptability to meet diverse patient needs. Attrition will be closely monitored, and for those who choose to leave the study, a structured exit interview with a research assistant will be conducted to gather feedback and identify potential areas for improving the program.

Ethical Considerations

This study received ethics approval from the Laurentian University Research Ethics Board (6021397) on July 6, 2023, and adheres to the guidelines stated in the Declaration of Helsinki. This study was registered at ClinicalTrials.gov (NCT06192251) in November 2023. Trained research staff informed participants of their right to withdraw themselves and the information collected on them up until the time of withdrawal, and informed consent was obtained. Patient data is available only to program health care providers and is segregated from research data. Participants are assigned a research code following the informed consent process, which links their research data through the study to allow appropriate analyses. Participant information is deidentified, and results will be published in this manner as well to ensure confidentiality.

Results

The first cohort of participants was enrolled in late 2023 and is still under evaluation. Data collection for the second cohort began in mid-2024 and is currently underway, with a projected end date in early 2025. A total of 16 participants have been recruited as of November 2024. Data analysis will be conducted in mid-2025, and we anticipate submitting the final manuscript by the end of 2025. A mixed method analysis [42,43] will be used to analyze the quantitative and qualitative data, collected individually at enrollment, program completion (22 weeks), and follow-up (6 months after program completion). Focus groups will be conducted after the 22-week intervention to assess the program's effectiveness and implementation.

Initial findings indicate that participants have gained knowledge about lifestyle changes, particularly in stress management and health behavior choices, and positively impacted their friends, family, and community by sharing their experiences. As more data is analyzed, it is anticipated that participants who commit to making changes will show improvement in their physical and mental well-being with the knowledge and practices learned from the classes and interdisciplinary health team.

In addition, initial participants included members of the local First Nation communities who raised concerns about accessibility for other First Nations such as challenges with significant travel and limited access to web-based platforms. In response to these concerns, there is confirmed interest in hosting a CLIP-ON cohort within these communities to ensure equitable access for all interested members.

Discussion

Expected Outcomes

We anticipate that these findings will support the long-term goal of establishing a lifestyle medicine program for rural Ontario communities that combines education, digital platforms, and interactions with an interdisciplinary health team. Its holistic, patient-centered approach to medicine strives to promote lifestyle changes that can prevent and treat chronic diseases, transform patient care in a manner that has been demonstrated to be successful in large urban centers and encourage its adoption and adaptation by health care providers across Canada. Our long-term goal is to demonstrate that CLIP-ON positively impacts community health and decreases health care use by reducing the impact of chronic illness.

Comparison to Previous Studies

CLIP-ON is the first lifestyle medicine program that will be conducted virtually and in-person in a rural Canadian community setting, while other Canadian lifestyle medicine interventions, such as Canadian Health Advanced Nutrition for Graded Exercise (CHANGE), have been implemented in large primary care settings in a physical format only [9,33]. This study will investigate the impact of incorporating all 6 pillars of lifestyle medicine as opposed to selected pillars [49-52,55-58]. It is also designed for patients with broad chronic diseases compared to other lifestyle medicine studies that focus on patients with specific chronic diseases [57,59-61]. Like the New York City lifestyle medicine program, CLIP-ON is built around all 6 pillars of health while providing individual support, goal setting, dietary recommendations, and monitoring support of an interdisciplinary health team [29,30,38]. However, Parry Sound's catchment area spans 9222 km^2 which is much larger than New York City's 790-km^2 urban setting [26,62]. The Parry Sound region includes 8 municipalities and townships and 4 First Nation communities housing over 42,000 residents who sometimes must travel long distances to access just primary care [26]. Therefore, understanding the unique challenges faced by rural Ontario communities will allow modifications to the program design that will be considerate of socioeconomic status, geographic and transportation barriers, preexisting patient-physician relationships, and cultural diversity.

The ability for participants to attend all programming virtually and in person was a core design to enhance program accessibility. This hybrid structure will also allow the onboarding of health care providers located throughout the province to engage in CLIP-ON more easily. Considering the vast catchment area of Parry Sound, limited transportation methods, and financial disparity within the region, it is understood that all participants may not have or have access to weekly transportation for classes. The research team will assist in identifying patient transport services to facilitate participant attendance at key program sessions wherever possible to enhance accessibility. A preexisting patient-physician relationship may result in discomfort for either participants or providers or introduce biased treatment towards some participants. Therefore, the research team will ensure that participants are matched with providers that they do not have an existing professional relationship with. Finally, special considerations will be incorporated for local Indigenous populations to be inclusive and respect their cultural requirements, including a land acknowledgment before every session and including providers with related experience and understanding of individual challenges and cultural differences.

These design elements distinctly position CLIP-ON as a whole health program designed to help all patients incorporate changes in various aspects of their lives in a setting where a lifestyle medicine program has yet to be introduced and piloted.

Strengths

CLIP-ON is the first lifestyle medicine program designed for rural communities in Ontario. This included extensive engagement with local health care providers and community members to understand their unique challenges and preferences. It incorporates specific design elements such as virtual programming, which increases program accessibility for patients facing geographic barriers so that they can attend classes, exercise sessions, and meetings with health care providers remotely. The hybrid delivery model provides flexibility, allowing patients to choose in-person or virtual participation, which is crucial for geographically isolated individuals. In addition, it enables the recruitment of remote health care providers, increasing the feasibility of building an interdisciplinary health team for the program. This flexibility offers CLIP-ON to be a sustainable, impactful, and scalable model of preventative health care.

The involvement of an interdisciplinary team of health care professionals, including physicians, dietitians, health coaches, and kinesiologists, provides a comprehensive care approach that addresses various facets of participants' health, enhancing the likelihood of sustainable health improvements. Furthermore, the program's use of the RE-AIM framework ensures that implementation is evaluated through a robust and credible scientific approach, facilitating future scalability and applicability to other regions.

Initial observations have noted that the group structure and interactions during lifestyle medicine classes and exercise sessions facilitate social connectedness within the first cohort. The program's focus on peer support and social interaction has led to increased participant accountability, as individuals share challenges and strategies within the group setting. Research shows that this peer support is often key to maintaining long-term behavior change [63]. Finally, the 2-cohort design of this study enables efficient incorporation of feedback from cohort one to enhance the program design for cohort two. The patient-centered approach, which integrates real-time feedback from participants and health care providers through focus groups and surveys, ensures continuous refinement of the program to meet participants' needs and further enhance satisfaction and engagement.

Limitations

This study has some limitations. Parry Sound's small core town population of 6879 combined with the geographic barriers associated with its vast catchment area and lack of public transit limited the initial recruitment to only 8 participants in the first cohort, as opposed to the anticipated 10-12 [25]. This small sample size may limit the statistical power of the study, making it difficult to establish significant findings that are generalizable to other rural communities. To mitigate this, we are actively exploring strategies such as broader outreach to health care providers within the catchment area and forming partnerships with community organizations to raise awareness of the program.

Initial feedback also suggests that some participants found the program duration of 6 months to be too short for achieving and maintaining meaningful lifestyle changes. Extending the program duration could allow participants more time to solidify lifestyle adjustments. In addition, longer follow-ups will support the long-term impact of lifestyle medicine on chronic disease management. To facilitate this, additional follow-up sessions and group support beyond the 6-month mark are being established to reinforce lifestyle habits. This could offer a more gradual transition toward self-management for participants.

The web-based platform, while increasing accessibility for most, may present technological barriers for older participants or those unfamiliar with using web-based platforms. This could potentially reduce engagement for certain segments of the population, especially if support for technology use is not adequately provided. To alleviate this, we have introduced a brief training session for participants on how to use the virtual platform, and technical support is now available throughout the program.

Future Directions and Dissemination Plan

We plan to conduct a follow-up assessment at 12 months and beyond to evaluate the sustainability of lifestyle changes and improvements in health outcomes among participants to provide valuable insights into the long-term impact of the CLIP-ON program. We will also explore the possibility of scaling the CLIP-ON program to other rural communities in Northern Ontario, considering adaptations based on the unique needs and cultural contexts of those populations. We will collaborate with local Indigenous communities to incorporate traditional health practices and teachings into the CLIP-ON program. This integration may enhance cultural relevance and improve health outcomes among Indigenous participants. We also plan to investigate the use of mobile health applications and web-based platforms to enhance participant engagement and accessibility such as tools for tracking progress, providing education resources, and facilitating communication with health care providers.

The results of this study will be shared locally through grand round presentations and with the hospital senior team and board members. There is a commitment from West Parry Sound Health Centre to support this study, and findings are regularly shared with senior leadership, the local education group executive, local primary care provider family health teams, and the Parry Sound Ontario Health Team. We will provide the results of the findings to each of these groups in an appropriate presentation at their request. In addition, we will share the results through publication and presentation within our Northern Ontario School of Medicine University and through presentation at the annual research conference.

Conclusion

This protocol paper will provide valuable insights into the implementation of a lifestyle medicine program, which will be evaluated for its impact on participants' health. The goal is to establish and disseminate an effective framework for secondary prevention, management, and in some cases reversal of common chronic diseases. By assessing the real-world implementation of this program, we aim to identify both successes and areas for improvement, ensuring the feasibility and sustainability of integrating lifestyle medicine into routine health care practices.

This comprehensive evaluation will not only guide future advancements in lifestyle medicine but also help establish a culturally inclusive and scalable model that can be adapted to benefit other communities, particularly those in resource-limited or rural settings.

Acknowledgments

The authors thank the health care providers, research administration team, patients, participants, and learners for their contributions and support to the CLIP-ON pilot implementation study. Very special thanks to the New York Lifestyle Medicine team, notably

Dr Michelle McMacken and Stephanie Albert who provided us with mentorship and direction regarding research tools and questionnaires. This program would also not be feasible without the incredible support from our entire local health care community. We would like to underline the support of Caitlin Champion, Connie Foster, Susan Garagan, Katie Hogue, Peter Istvan, Kathryn Knight, Karen Mills, John Neary, Natalie Pelto, Margaret Rundle, Kallie Stapleton, Heidi Stephenson, Ellen Walker, and Wil Smith. Special thanks to the West Parry Sound Health Centre Ambulatory Care and Emergency Department teams, Delores McKay, Melanie Sanford, and Magdalena Tarko from the Parry Sound Friendship Centre. Thanks to the Canadian Association for Lifestyle Medicine, formerly the Canadian Lifestyle Medicine Advocacy Group for their support and mentorship of Zahra Kassam, Sheila Lakhoo, Rikin Patel, Richa Agnihotri, and Tushar Mehta.

This study is funded through a Northern Ontario Academic Medicine Association Clinical Innovation Opportunity Grant. Providers are compensated at standard Ontario rates for their services (Health Coach, Dietician, Kinesiologist, Lifestyle Medicine Physician).

Funding for this study was supported by a Clinical Innovation Opportunity Grant from the Northern Ontario Academic Medicine Association (march 2023).

We confirm that no authors have potential competing interests, and all authors have equally contributed to each phase of the study, critically reviewed, and approved the manuscript.

Data Availability

The datasets generated during the study are available from the corresponding author upon reasonable request.

Authors' Contributions

MJ and CR are coprincipal investigators. All authors contributed substantially to the conception and design, data acquisition, data analysis and interpretation, drafting of the paper or critical revision for important intellectual content, and giving final approval of the submitted version. MJ, LA, and CR conceptualized the study. LA, MM, DF, NR, and JST provided administrative support. MJ, KB, MF, DF, SK, DL, CR, and EMC, participated in the development and teaching of the lifestyle medicine intervention. All authors contributed to the manuscript writing approval.

Conflicts of Interest

JST holds research grant funding from the Canadian Institute for Health Research, the Social Science and Humanities Research Council of Canada, and the Canadian Cancer Society. She was paid from the grant associated with this project to run the focus groups. All other authors declare no conflict of interest.

Multimedia Appendix 1
CLIP-ON (Complete Lifestyle medicine Intervention Program–Ontario): Phase I Program Evaluation Plan (RE-AIM Framework).
[DOCX File , 41 KB - resprot_v13i1e59179_app1.docx]

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Abbreviations

CHANGE: Canadian Health Advanced Nutrition for Graded Exercise
CHIP: Complete Health Improvement Program
CLIP-ON: Complete Lifestyle medicine Intervention Program–Ontario
NCD: noncommunicable disease
P4: Preventive, Predictive, Personalized, and Participatory
PARmed-X: A Physical Activity Readiness Medical Examination
PAR-Q +: Physical Activity Readiness Questionnaire for Everyone
RE-AIM: Reach, Effectiveness, Adoption, Implementation, and Maintenance

Edited by A Schwartz; submitted 05.04.24; peer-reviewed by RJ Marker, H Al-Jabr; comments to author 10.06.24; revised version received 03.08.24; accepted 30.10.24; published 31.12.24.

Please cite as:
Patel K, Allen L, Boucher K, Fedele M, Fong D, Kumar S, Lavigne D, Marin-Couture E, Partyka-Sitnik M, Rietze N, Smith-Turchyn J, Juneau M, Rhéaume C
Complete Lifestyle Medicine Intervention Program–Ontario: Implementation Protocol for a Rural Study
JMIR Res Protoc 2024;13:e59179
URL: https://www.researchprotocols.org/2024/1/e59179
doi:10.2196/59179
PMID:

Protocol

Cultural Adaptation of an Aboriginal and Torres Strait Islanders Maternal and Child mHealth Intervention: Protocol for a Co-Design and Adaptation Research Study

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Abstract

Background: There is limited evidence of high-quality, accessible, culturally safe, and effective digital health interventions for Indigenous mothers and babies. Like any other intervention, the feasibility and efficacy of digital health interventions depend on how well they are co-designed with Indigenous communities and their adaptability to intracultural diversity.

Objective: This study aims to adapt an existing co-designed mobile health (mHealth) intervention app with health professionals and Aboriginal and/or Torres Strait Islander mothers living in South Australia.

Methods: Potential participants include Aboriginal and/or Torres Strait Islander pregnant women and mothers of children aged 0-5 years, non-Aboriginal and/or Torres Strait Islander women who are mothers of Aboriginal and/or Torres Strait Islander babies, and health professionals who predominantly care for Aboriginal and/or Torres Strait Islander mothers and babies. Participants will be recruited from multiple Aboriginal and/or Torres Strait Islander–specific health services under the local health networks around metropolitan South Australia. In this study, data collection will be carried out via culturally safe, and family-friendly yarning circles, facilitated by Aboriginal research staff to collect feedback on the existing mHealth app from approximately 20 women and 10 health professionals, with the aim to achieve data saturation. This will inform the changes required to the mHealth app. All focus groups and interviews will be audio recorded and transcribed verbatim. Data will be inductively analyzed using realist epistemology via NVivo software (Lumivero). Themes about the mHealth app's cultural acceptability, usability, and appropriateness will be used to inform the changes applied to the app.

Results: With the feedback received from participating women and health professionals, changes in the smartphone app will be made to ensure the intervention is supportive and meets the needs of Aboriginal and/or Torres Strait Islander mothers and families in South Australia. Participation of community members will promote ownership, community engagement, and implementation.

Conclusions: A co-designed, culturally sensitive, and effective digital health intervention is likely to support Indigenous mothers and their children facing health disparities due to the disruption of Indigenous culture by colaying a foundation for a potential clinical trial and wider implementation.

International Registered Report Identifier (IRRID): PRR1-10.2196/53748

(JMIR Res Protoc 2025;14:e53748) doi:10.2196/53748

KEYWORDS

Aboriginal; co-design; mHealth; maternal; child health; digital health; children; women; female; cultural adaptation; Torres Strait; research study; Indigenous; digital health intervention; diversity; South Australia; pregnant; health professional; adaption; focus group; pretesting; usability; app; health disparities; information; technology; mobile phone

Introduction

The impact of colonization on Indigenous populations' health across the globe is well recognized [1]. The ongoing disadvantages of intergenerational trauma and structural violence have resulted in disparities in health outcomes between the Australian general population and Aboriginal and/or Torres Strait Islander communities [1]. Decolonization of interventions, health care organizations, health service provision, and policies are recommended as solutions.

Mothers and babies getting optimal care and support for a good start to life is a priority of the Australian National Aboriginal and/or Torres Strait Islander Health Plan 2013-2023 [2]. However, despite policies, strategies, and funding to mitigate the disparities in pregnancy and birthing outcomes, closing the gap is yet to be achieved [3]. The importance of traditional family and kinship ties and knowledge of birthing and parenting practices remain largely unrecognized in the mainstream health services accessed by Aboriginal and/or Torres Strait Islander communities [4,5]. This contributes to poorer health outcomes experienced by Aboriginal and/or Torres Strait Islander pregnant women, babies, and young children compared with Caucasian Australians [2,4,6]. Aboriginal and/or Torres Strait Islander women of childbearing age (15 years and older) are overrepresented in behavioral risk factors impacting health outcomes. In a recent Australian National Health Survey, a large majority of First Nations women failed to meet guidelines for physical activity, and vegetable or fruit intake [7]. Furthermore, 36% reported daily tobacco smoking, and 35% reported experiencing high or very high levels of psychological distress [7]. The cumulative effects of disadvantage and poorer health outcomes of women subsequently impact infant mortality for Aboriginal and/or Torres Strait Islander babies, which is 2.1 times the rate of non-Indigenous infants [8]. This highlights the urgency of more effective, ground-up, community-led resource and service development [9].

Mobile health (mHealth) apps are being used increasingly for health promotion because of their potential for greater reach [10,11]. Despite their growing popularity, very few evidence-based mHealth interventions for Aboriginal and/or Torres Strait Islander Australians exist [12]. A recent Aboriginal and/or Torres Strait Islanders survey of 398 women aged 16-49 years found that most respondents owned a smartphone, had internet access, and used social media daily [13]. This suggests that a smartphone app may be an effective health promotion tool for Aboriginal and/or Torres Strait Islander women or carers with children.

Evidence-based literature offers many perspectives on co-design. The term "co-design" is often used in research to describe a methodology that involves stakeholders in the "design of services, strategies, environments, policies or processes that impact them" [14]. Digital health solutions designed and developed in the context of mainstream health systems predominantly neglect socioeconomic determinants that are fundamental in understanding and addressing the distinct health challenges that Indigenous communities face [15]. Such an oversight might be rectified by integrating culturally safe co-design practices during the design and development phases [15]. Consequently, this project proposes that the culturally sensitive adaptation of a co-designed mHealth intervention has the potential to significantly benefit the health of many Aboriginal and/or Torres Strait Islander families within South Australia and nationally.

The mHealth program, Jarjums, co-designed with Aboriginal and/or Torres Strait Islander people was developed in New South Wales in collaboration with Aboriginal communities and found to be highly acceptable by women and health services [12]. The co-design of the app ensured culture was weaved throughout the project and the mHealth app [12]. The purpose of this mHealth app is to provide information and health behavior change strategies in the domains identified or selected by the co-design participants. The app explores women's and babies' health and well-being topics through 6 individual modules. These include (1) smoke-free families, (2) safe drinking, (3) feeling good, (4) women's business, (5) eating, and (6) exercising. The modules exploring children's health and well-being include (1) breathing well; (2) sleeping; (3) milestones; (4) feeding and eating; (5) vaccinations and medicines; and (6) ears, eyes, and teeth. Each module includes key messages around the benefit of changing behavior related to illness progression, tips addressing barriers to behavior change, cues for action, and links to further information.

As there are over 250 language or national groups with differing laws and customs across Australia, the current project will develop an adaptation of the intervention for South Australian–based Aboriginal and/or Torres Strait Islander women. The aim of this study is to consult with health professionals, mothers, and carers to culturally adapt a mHealth program called "Growin' Up Healthy Jarjums" for use by Aboriginal and/or Torres Strait Islander mothers and carers living in South Australia. This research will directly address gaps in the health evidence base and build on existing knowledge by ensuring that programs developed and effective in 1 location, are adapted and tested before they are implemented in the intended population in another location.

Methods

Study Design

This is a multisite project and will be conducted at 3 different Aboriginal health care services.

There are 3 levels of involvement of Aboriginal and/or Torres Strait Islander people in this project. These are (1) Aboriginal and/or Torres Strait Islander chief investigators, (2) project governance by a separate Aboriginal and/or Torres Strait Islander Governance Group, and (3) Aboriginal research assistants (ARA).

The Governance Group will oversee the conduct of the project and guide the interpretation of data, dissemination, and translation of study findings. All members have extensive experience working in Aboriginal and/or Torres Strait Islander health care. Specifically, the group comprises research experts, organizational and departmental leaders from various affiliations including universities, government health strategy and research departments, local health networks, maternal and child service providers, and community representatives. The ARAs are local community members and involvement in Aboriginal health services is a crucial component of the research to build trust, safety, and engagement. The ARA involvement also supports capacity building for Aboriginal and/or Torres Strait Islander research.

The framework for the cultural adaptation process will be based on the stages of cultural adaptation stepwise model of Barrera et al [16-19]. Barerra et al [16] describe 5 stages to culturally adapt evidence-based interventions for the purposes of reducing health disparities among culturally diverse populations and include considerations for intercultural diversity. These stages of adaptation include (1) information gathering, (2) preliminary adaptation design (including modifications), (3) preliminary adaptation tests, (4) adaptation refinement, and (5) cultural adaptation trial [16].

In this qualitative study, the existing co-designed mHealth app, Growin' Up Healthy Jarjums, will be adapted by using focus groups and interviews to collect data on participants' perceptions, experiences, and ideas about the app. We will conduct sessions using traditional yarning style methodology, to ensure culturally responsive practices are respected. Yarning is an established culturally appropriate process to conduct research with Aboriginal and/or Torres Strait Islander people to both establish rapport and collect information [20]. The sessions will be predominantly conducted by ARAs.

The eligibility criteria include Aboriginal and/or Torres Strait Islander women aged 16 years and older living in South Australia, who are currently pregnant, or mothers of children aged 0 to 5 years. Non-Indigenous women, of similar age are also eligible if they are pregnant with or are mothers of Aboriginal and/or Torres Strait Islander children aged 0 to 5 years. All documents prepared to convey the study information and consent are in English. However, there is a possibility that eligible, interested women may not be able to communicate in English. Such instances will be managed on a case-by-case basis with the support of language interpreters.

Focus groups will be conducted with an estimated 4 to 6 women in each group, up to 20 women in total. It is expected that data saturation will be achieved with 2 to 3 focus groups with approximately 4 to 6 women each. The actual number may vary depending on achieving data saturation.

Recruitment of participants will involve ARAs directly approaching women in the waiting area or room of the participating sites. Information sheets, leaflets, and consent forms will be available to use for recruitment support. Eligible women may directly approach the research team after reading the study information poster at any of the participating sites or the information leaflet provided to them by clinic staff of the participating sites. Furthermore, participating clinics will have project handouts to offer to eligible women.

In addition, participants will be asked if they would like to pass the study information on to a friend or family member who can then choose to connect with the research team to obtain further information and potentially participate. Individuals will be screened for eligibility when they contact the research team by phone. Women who consent to participation will be invited to join a focus group or interview with an estimated duration of 1.5 hours. At the start of the focus group or interview, participants will be asked to complete a face-to-face survey with demographic, cultural, and socioeconomic items. The survey has been adapted from a previously piloted study and deemed to be appropriate by Aboriginal and/or Torres Strait Islander mothers [21,22]. The ARAs will also spread the information to their circle of friends or family and co-workers and recruit via word of mouth.

Health professionals who predominantly care for young Aboriginal and/or Torres Strait Islander mothers or children will also be recruited for interviews. They will be recruited to the study using a separate information sheet and consent form by either the ARAs or the non-Aboriginal and/or Torres Strait Islander Research Fellow involved in the project. This process will involve explaining the participant information sheet and consent form to the health professional. All participation is voluntary, and health professionals will be informed that their decision to participate, or not, will not impact their role or position.

The purpose of including health professionals is to ensure that the messages provided in the app are aligned with the evidence-based messages used within their practice. To garner their views on the use of the app as a tool to connect with Aboriginal and/or Torres Strait Islander families (one of the aims of the app), the appropriateness of the app will also be explored. Health professionals will be interviewed for input into the content and features of the mHealth app until data saturation is achieved.

Once the adaptation process is complete and all the suggested feasible changes are made in the app. Further work regarding the feasibility of the app will be undertaken by asking representative women or carer population to use the app for 4 weeks.

The snowball methodology is predicted to facilitate the recruitment phase of the project. Participating health service managers who agree to support the project will be sent an invitation email to circulate to their staff with the staff study information sheet.

A focus group or interview guide will be used to guide the discussion, although focus groups or interviews will be

conducted using an iterative process, with the information gathered from initial focus groups used to guide the dialogue and resources used in sequential groups. Phone interviews may be conducted with participants if this is preferred. If required, an interpreter service will be used to provide support to potential participants who require language interpretation.

The focus group or interview discussion will primarily focus on how an mHealth intervention designed for this community would differ from the "Growin' Up Health Jarjums" program. Participants will be prompted to discuss images and artwork, language, videos, content, and delivery features of the original app.

All focus groups and interviews will be audio-recorded, with participant consent, and transcribed verbatim by a professional transcription service that will sign a confidential agreement before providing their service.

Participating women and health professionals can withdraw at any time, without giving a reason, throughout the study. Consent to participate can be retracted by contacting the research team; in-person, by phone, or via email. The contact information for the study team is provided on the study information sheets.

If the participant requests a specific response to be removed from the transcriptions, then the researchers will make reasonable attempts to achieve this. However, it may not be possible to remove every detail of a participant's contributions as it can be difficult to identify individual contributions within the focus group transcriptions.

If participants become distressed during the focus group or interviews when health content for the app is discussed such as child health, smoking or alcohol, and other drugs, a study-specific distress protocol will be adhered to. All events will be recorded and follow-up will be performed.

A generalized data-driven, inductive, thematic analysis will be completed with the transcribed, deidentified data [23]. Inductive analysis is a process in which data coding is undertaken without fitting it into any preexisting coding framework. An ARA and investigator will independently code themes using NVivo software (Lumivero) and complete analysis and write-up with the project team and project Investigators. The data will be interpreted sensitively with the input of ARAs. All personal, identifiable information will remain anonymous in reporting. Deidentified data analysis will be used in manuscripts for publication in peer-reviewed journals and for poster and oral presentations at national and international conferences or symposiums.

The feedback received from women and health professionals will be used to change the app by the technical team. The edited app will be screened by women for acceptability in a follow-up study.

Ethical Considerations

This project has been granted ethical approval by the Department of Health and Wellbeing Human Research Ethics Committee (2022/HRE00262) and Aboriginal Health Research Ethics Committee (#04-22-1018). A cross-institutional approval has also been obtained from Flinders University. Participation in this study is voluntary. Potential participants will be informed, both in writing on the consent form and verbally during the consent process that they can choose to not participate. Their decision not to participate will not jeopardize their relationship with their organization, health care providers, and research team and will not affect the delivery of care to them. Data will be anonymized during the transcription process and all identifiable, personal details of participants will be removed. Participating women will be reimbursed with a Aus $50 (US $33.64) shopping voucher for their time and provided with refreshments.

Results

The short-term outcomes of this research will include the start of the development of a culturally appropriate mHealth app to support Aboriginal and/or Torres Strait Islander maternal and child health. It is anticipated that the app will be a tool for women to connect with each other, connect with health professionals, and access evidence-based, culturally responsive health information in a way that is meaningful to them. The design, content, and features of the app will be a collaboration of ideas, stories, and evidence from women, the research team, and health services. Participants will have the opportunity to suggest additional areas of health or additional modules to include in the app. Potential benefits for participating women include opportunities to learn new information, and to engage with and comment on the use of new technologies. Participation of women will also promote ownership and community engagement of the project.

The anticipated long-term outcomes of the research include the contribution of the data to the knowledge on the preferences and potential use of a mHealth app for improving health outcomes of Aboriginal and/or Torres Strait Islander women and children. The resulting data will be used to source further funding opportunities for testing the feasibility, acceptance, and effectiveness of the app in a clinical trial. Ultimately, this app aims to promote health and reduce the rates of noncommunicable and communicable diseases among Aboriginal and/or Torres Strait Islander women and children. Findings may inform local and regional policies and provide advice on how to incorporate these new technologies as part of existing programs and practices.

As of July 2024, the project is ongoing in South Australia. The first phase of data collection will finish in September 2024 and the results will be shared with stakeholders in the form of reports, peer-reviewed publications, and conference presentations.

Discussion

The data might identify additional needs by participating women and health professionals. That will determine the scope of future research and implementation of mHealth technology related to Aboriginal and/or Torres Strait Islander women and children.

We anticipate that this new digital health intervention will help to reduce health disparities among Aboriginal and/or Torres Strait Islander mothers and their children, laying a foundation for a potential clinical trial and wider implementation.

A strength of this study includes its sensitivity to culturally responsive research methodology. This is woven throughout the study design from the governance model and the inclusion of ARAs to the way in which members of the community will be recruited and the flexibility of the consultation process.

Some anticipated limitations include challenges with recruitment due to the nature of engaging with a specific cultural group. The study does rely on the shared understanding of ARAs with the community and it is anticipated this will foster the development of trusting relationships with participants and support recruitment.

Finally, while the app is currently designed for the South Australian–based Aboriginal and/or Torres Strait Islander community, there is diversity within the community and therefore, this could limit engagement. Questions about how to improve the cultural responsiveness of the app will be asked while gathering feedback.

Concurrently, a recent review on barriers and facilitators of engagement of Indigenous peoples with mHealth interventions revealed themes that echo the need for effective and timely co-design practices in this field [24]. Co-design has been identified as one of the most important factors determining the uptake of web-based therapeutic interventions for Indigenous communities or populations [25]. The review findings support the inclusion of culturally sensitive methodology as well as Indigenous governance and community consultation.

Project outcomes will be provided to organizations and participants while ensuring participants' confidentiality. Ethical reports and funding body reports will be completed and provided to the relevant figures. We anticipate that there will be numerous opportunities to share and use the data gathered from this research, including dissemination to research institutes, health organizations, and community groups.

Furthermore, this research can inform policy makers and peak organizations of the needs of mothers and families with young children.

Acknowledgments

This research was funded by The Hospital Research Foundation in 2022 (project ID: 2021/76-83100-01). We would like to acknowledge the intellectual contribution of Cassandra Brown, the Aboriginal Research Assistant, to the design of the project.

Data Availability

The data that will come out from the study will belong to the Aboriginal and/or Torres Strait Islander Community. Due to the sensitivity required in sharing and spread of that data, it will only be available upon reasonable request made to the corresponding author after approval from the project governance. The corresponding author will review any requests received with guidance from the Aboriginal and/or Torres Strait Islander Governance Group of the project.

Authors' Contributions

SI developed and designed methodology, provided resources, supervision and oversight, validation, and contributed to writing, reviewing, and editing. AD contributed to project administration and data curation. OE contributed to data curation, writing, and project administration. AB and CR contributed through review and editing. KC and KH contributed through review and editing as well as governance and design. NB contributed through review, editing, and software/application advice. CTR contributed through review, editing, and resource acquisition. SP contributed through review, editing, and study conceptualization. BB contributed through research supervision, design of methodology, resource and funding acquisition, review and editing, and conceptualization.

Conflicts of Interest

None declared.

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Abbreviations

ARA: Aboriginal research assistant
mHealth: mobile health

Edited by A Mavragani; submitted 23.10.23; peer-reviewed by TAR Sure, K Jongbloed, L Brunelli; comments to author 10.04.24; revised version received 05.08.24; accepted 16.08.24; published 10.01.25.

Please cite as:
Ishaque S, Ela O, Rissel C, Canuto K, Hall K, Bidargaddi N, Briley A, Roberts CT, Perkes SJ, Dowling A, Bonevski B
Cultural Adaptation of an Aboriginal and Torres Strait Islanders Maternal and Child mHealth Intervention: Protocol for a Co-Design and Adaptation Research Study
JMIR Res Protoc 2025;14:e53748
URL: https://www.researchprotocols.org/2025/1/e53748
doi:10.2196/53748
PMID:

Protocol

Home-Based Intervention Tool for Cardiac Telerehabilitation: Protocol for a Controlled Trial

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Abstract

Background: Among cardiovascular diseases, adult patients with congenital heart disease represent a population that has been continuously increasing, which is mainly due to improvement of the pathophysiological framing, including the development of surgical and reanimation techniques. However, approximately 20% of these patients will require surgery in adulthood and 40% of these cases will necessitate reintervention for residual defects or sequelae of childhood surgery. In this field, cardiac rehabilitation (CR) in the postsurgical phase has an important impact on the patient by improving psychophysical and clinical recovery in reducing fatigue and dyspnea to ultimately increase survival. In this context, compliance with the rehabilitation program is a key element for the therapeutic benefits of the program. The increase of mobile health care devices and software has greatly extended self-care capabilities across the spectrum of health care activities. Moreover, the possibility of telemonitoring the progress of this self-care provides elements of empowerment and awareness of one's state of health. As a branch of telehealth, CR can be optimized and facilitated using remote telemedicine devices.

Objective: The principal goal of the Innovation in Postoperative Rehabilitation Training and Monitoring (IPOTERI) study is to design, realize, and test a composite and integrated system for postsurgical rehabilitation therapies at home specialized for cardiac surgery. The secondary aims are to implement the system in a "real-life" context of postcardiac surgical rehabilitation, and to create a data set and a data collection methodology to prototype data analytics algorithms and artificial intelligence techniques for customizing the rehabilitation pathway.

Methods: The IPOTERI method consists of a telemonitoring platform that guarantees continuity of postoperative care, an intelligent home station based on an Android app for the patient with a user-friendly interface to record vital signals (electrocardiogram, blood pressure, oxygen saturation, and body weight) and access the planning of rehabilitation activities, and a decision support system that communicates with hospital medical records to transmit alerts and specific support information for the formulation and updating of the treatment and care plan.

Results: The pilot test started in June 2023 (protocol number 20406/2021) including 50 patients who will be monitored for 12-14 weeks using the developed platform, as described in the Procedures subsection of the Methods section.

Conclusions: The IPOTERI approach, based on the processing of data recorded during the monitoring of telemedicine devices used at home during the postsurgical rehabilitation of a cardiac patient, together with clinical data from the perioperative and postoperative periods could have positive effects on adherence to the rehabilitation program and clinical improvement as well as result in overall improvement of quality of life.

International Registered Report Identifier (IRRID): DERR1-10.2196/47951

(JMIR Res Protoc 2025;14:e47951) doi:10.2196/47951

KEYWORDS

cardiac rehabilitation; exercise; patient education; patient-centered approach; eHealth; artificial intelligence

Introduction

General Background

Cardiovascular diseases (CVDs) represent the leading cause of death worldwide, which are responsible for 17 million deaths annually according to the World Health Organization [1]. This figure is expected to increase, as it is estimated that 23 million people will die from CVDs worldwide in 2030, accounting for 31% of all deaths globally [2]. People with CVDs typically require steady assistance and management by both the patient and their caregivers, mainly due to comorbidity with other pathologies, including high blood pressure, diabetes, and hyperlipidemia.

Among CVDs, adult patients with congenital heart disease represent a population that has been continually increasing, mainly owing to the improvement of the pathophysiological framing, including the development of surgical and reanimation techniques that have contributed to enhanced survival of these patients into adulthood [3]. Recent studies indicate that approximately 20% of patients with congenital heart diseases will require surgery in adulthood and 40% of these cases will necessitate reintervention for residual defects or sequelae of childhood surgery [4]. In these patients, the benefits of cardiac rehabilitation (CR) techniques are particularly important and clinically impactful during the postoperative period.

Clinical Background of the CR Field

CR is an evidence-based program that is considered part of secondary prevention, which is focused on three main aspects: patient education, health behavior modification, and exercise training [5]. CR programs primarily target patients with ischemic heart disease, heart failure, or following cardiac surgery to reduce mortality and morbidity. A complete rehabilitation plan should include both a physical and psychological agenda, encompassing clinical evaluation, pharmacotherapy, psychological support, training, assessment and reduction of risk factors (both physical and psychological factors), and patient education for lifestyle modification. Thus, the gold standard of CR is an approach integrating health behaviors such as increased physical activity, improved dietary habits, and smoking cessation, along with promotion of medical adherence and psychosocial well-being strategies. There are multiple reported benefits of CR in patients following cardiac surgery. Several studies have documented that in addition to speeding up psychophysical recovery, CR improves clinical parameters, namely by reducing fatigue and dyspnea, ultimately resulting in increased survival with a drop in mortality at 10 years after surgery reaching up to 14% [6]. Interestingly, the benefit in terms of major event-free survival correlates with the number of rehabilitation training sessions to improve quality of life and reduce cardiovascular risk factors [7-9].

Although the clinical importance of CR is officially recognized, the proportion of patients admitted to a rehabilitation program remains small and there is overall low patient compliance [10]. Several factors may contribute to this low enrollment rate in CR programs, including physicians' and patients' approaches toward CR. In general, the percentage of patients who adhere to CR is variable, depending mainly on age, gender, and the presence of preexisting neurological complications [11]. Moreover, in addition to poor adherence, the capacity of services for CR in primary care is hindered due to limitations of human resources and adequate space in hospitals to support rehabilitative programs.

To overcome these problems, an alternative method to the traditional center-based CR (CBCR) model is home-based CR (HBCR), which is a new method that can be carried out in different settings, ranging from the home to a park, owing to the support of telemedicine.

Evidence from published studies comparing CBCR and HBCR has revealed that in some cases, the results are overlapping with improvements in 3- to 12-month clinical outcomes and no differences in hospitalization rates [12]. In particular, benefits have been documented regarding functional improvement, managing risk factors, and well-being perception. With respect to compliance, HBCR is associated with a lower dropout rate and higher degree of responsiveness and perseverance compared to CBCR [13]. For these reasons, an important aim will be to extend the applicability of HBCR to different patient subgroups, including older adults, women (who tend to have relatively poor compliance [14]), and high-risk patients. Based on current evidence, it is reasonable to believe that HBCR can be targeted to patients in a stable state with low to moderate risk. Furthermore, despite international guidelines recommending CR, there are no unique programs tailored according to pathology or country of origin. For example, in Italy, CR is part of the rehabilitation plan in the hospital; however, according to the Italian Survey on Cardiac Rehabilitation (ISYDE), the Italian cardiology rehabilitation network is only able to offer the intervention to approximately 60,000 patients per year against an estimated demand of more than 300,000 patients per year [15]. To reduce the imbalance between supply and demand, the ISYDE project was developed with the goal of obtaining a detailed snapshot of the number, distribution, facilities, staffing levels, organization, and program details of CR units in Italy.

Considering the increasing burden of CVD, from an economic perspective and taking into account the increasing pressures facing health systems, cost-effectiveness is an essential consideration for CR program development. Previous data on economic evaluations of HBCR have found positive effects compared to traditional care, although the heterogeneity in methodologies may limit the validity of these findings [16,17].

Mobile Health for CR

Advances in mobile networks and the proliferation of smartphones and tablet devices constitute a global service delivery platform for many industries, including health care, and could offer the potential to broadly diffuse more intensive self-monitoring, feedback, and self-management tools at reduced cost. The increase of mobile health care devices and software has greatly extended self-care capabilities across the spectrum of health care activities. Current smartphones allow users to easily access a wide range of health educational materials and services anywhere at any time. Health apps running on smartphones or other portable devices enable the remote monitoring of vital parameters to diagnose health problems, track responses to treatments of chronic illnesses, detect drifts from the control condition, and provide early warning signals of potentially dangerous changes in a patient's health status. In this context, mobile phone interventions have become increasingly popular in the global health and development sectors as a potentially inexpensive and effective way to communicate with and deliver services to people. In particular, telemedicine offers the possibility of the prolonged longitudinal monitoring of patients, which would help to highlight early and subclinical signs of diseases or complications that could manifest at a later date, and thus allow therapeutic intervention at a stage of higher reversibility. In this field, where CR is needed but insufficiently implemented, alternative rehabilitation models using new resources of communication technologies (eg, mobile- and web-based platforms, wearable sensor devices) is a new challenge to deliver supervision, education, and counseling. With these technologies, it will also be possible to consent and improve continuity of care in vulnerable populations.

HBCR, as a branch of telehealth, can be optimized and facilitated with the use of remote telemedicine devices [18]. However, some studies demonstrated that there are no substantial differences in rehabilitation programs practiced using telemedicine or according to conventional protocols in terms of functional improvement, control of risk factors, well-being, and rehospitalization and survival rates [19-21]. In contrast to CBCR, HBCR associated with telemedicine appears to be able to improve some of the shortcomings of traditional rehabilitation programs [22]. These traditional services are often associated with high costs, both to the health care system and to the patient who must make multiple trips to the rehabilitation center during the treatment process or needs to be admitted directly to intermediate care facilities dedicated to rehabilitation only.

The Box 2.0 Study Protocol is an ongoing trial with the objective of achieving the early diagnosis of complications after cardiac surgery (for atrial fibrillation, heart failure, and surgical wound infections) through the application of telemedicine and mobile devices (ie, smart technology) [23]. In particular, the Box 2.0 study is focused on the use of smartphone apps for the remote assessment of certain vital signs, including oxygen saturation, electrocardiographic tracing, arterial blood pressure, body temperature, body weight, and actigraphy. In general, the availability of remote monitoring of the patient makes it possible to customize CR programs according to the limits and functional capacity of each patient, thereby increasing adherence to the suggested rehabilitation program. In practice, telemedicine allows the realization of a patient-centered rehabilitation approach, which is an essential element of precision medicine [24]. This practice aims to encourage the independence of patients, including older adults, which would allow them to stay in their familiar environment while maintaining an acceptable quality of life.

Although HBCR based on a patient-centered perspective is capable of improving the participation rate, the effectiveness and achievement of the program depend on the patient's attitude toward technology. In recent years, technology use in health management has involved populations of all age groups; however, the age group of 65-74 years represents the principal consumers of health digital tools, with higher adoption than found among those aged 18-34 years. Specifically, in the cardiology field, cardiac telerehabilitation is a mobile health tool that uses telecommunication technologies such as smartphone apps, wearable devices, and video consultations to propose remote CR services to increase convenience for patients while reducing health care costs. In addition, HBCR may bypass several barriers at the patient level, including transport difficulties; at the health care professional level, such as low endorsement; and at the health care system level, mainly due to limited facilities available providing this method. Furthermore, administering rehabilitation pathways outside the hospital environment by using remote monitoring and communication devices with patients would enable the acquisition of data (eg, heart rate during exercise and daily physical activity) in the context of the patient's daily routine; thus, the data collected will be more realistic, enabling designing a more personalized treatment program.

Study Aim and Objectives

The Innovation in Postoperative Rehabilitation Training and Monitoring (IPOTERI) study aims to create a tailored CR intervention using a mobile platform to support treatment during the postsurgery period with the goal of achieving the improvement of clinical and functional parameters and quality of life. The overall objective of the project is the analysis, design, implementation, and testing of a composite and integrated system for postsurgical rehabilitation therapies, specializing in cardiac surgery.

The project envisages the development and industrialization of a monitoring system that applies telemedicine techniques, combines microservices with innovative devices (ie, wearable and minimally invasive devices), and enables the continuous monitoring of the patient's main vital parameters to provide real-time feedback during the execution of the rehabilitation exercises assigned to the patient in the individual phases of the rehabilitation therapy. This will be achieved through the implementation of software systems capable of not only supporting the rehabilitation pathway but also of enriching the program with innovative devices and eHealth services. This system can help to support additional and alternative pathways to traditional hospital pathways and will be further capable of integrating artificial intelligence (AI) techniques that support physicians in telemonitoring.

The hypothesis of the clinical study is that processing of data, both qualitative and quantitative, collected at home during the

postsurgery period using eHealth devices, together with clinical data related to the perioperative time window using AI algorithms will be an effective approach for personalizing and then optimizing a postsurgery CR path. We here describe the protocol for the design, realization, and clinical testing of a composite and integrated system for postsurgical rehabilitation therapies at home focused on cardiac surgery.

Methods

Ethical Considerations

The research and ethics described in this study have been reviewed and approved by the institutional review board of the Ethics Committee of the Vast Area Northwest of Tuscany for Clinical Trials (protocol 20406). All procedures performed in the pilot study will be in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. All participants will provide written informed consent after a thorough review of procedures and questions and will be informed of their opportunity to opt out of the study at any time. All study data will be deidentified. No participation fee will be given to the patients, and all patients will enroll in the study voluntarily.

Setting

The IPOTERI project is a public-private partnership comprising a multidisciplinary team, including research centers, health care facilities, technological enterprises, and cybersecurity experts.

General Aspects of the IPOTERI Rehabilitation Platform

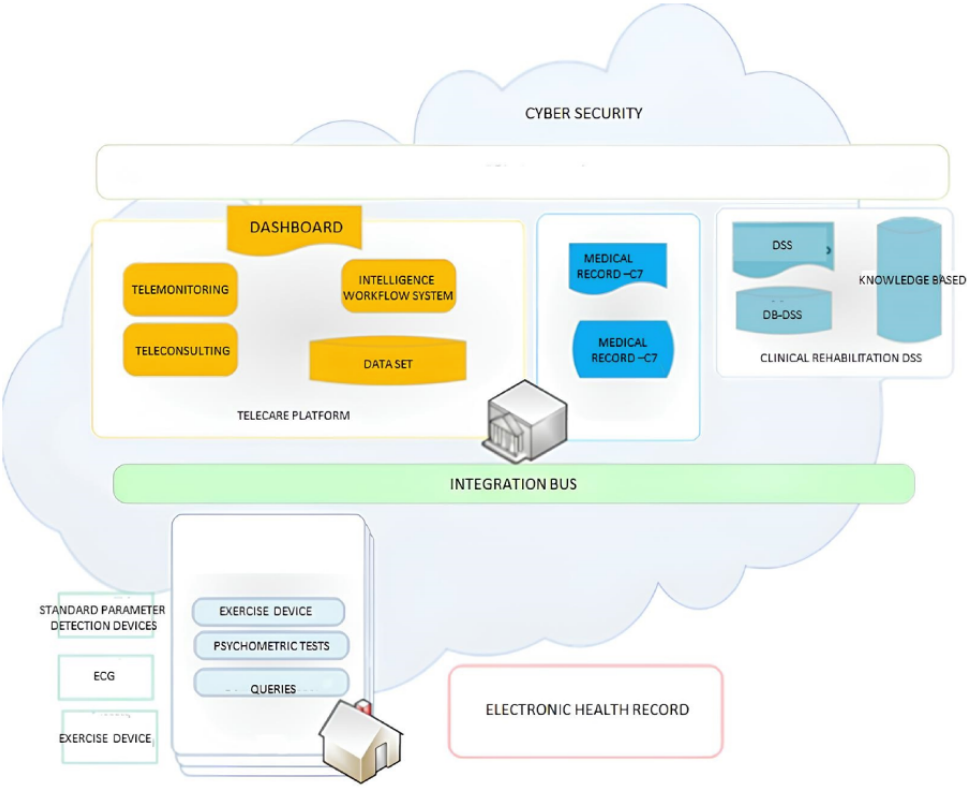
Platform Design Process and Overview

To define the best configuration of mobile support services for patients, we used the following methodology:

1. Formative research to determine the best way to implement HBCR, including a literature review, retrospective analysis of clinic data, and evaluation of eHealth devices potentially included in HBCR.
2. Development of the HBCR intervention: we implemented a software system that can support the rehabilitation pathway, but also enriched it with innovative devices and eHealth services that support the doctor in telemonitoring.
3. Pilot feasibility study: we will conduct a pilot study with patients who will receive the intervention to provide a context for testing the developed systems on a larger population sample.

The components of HBCR consist of a telemonitoring platform, an intelligent home station, and a decision support system (DSS) (Figure 1).

Figure 1. General architecture of the IPOTERI system. DSS: decision support system; C7: medical records; ECG: electrocardiogram.



Telemonitoring Platform

The IPOTERI platform guarantees continuity of postoperative care and includes the following main functions: (1) activation of the telemonitoring process with detection of vital parameters, also in continuous mode, according to a protocol set by the doctor; (2) monitoring of rehabilitation activity, with feedback on the quality of exercise; (3) management of alerts for home events; and (4) verification of the adequacy of the patient's vital

parameters and adherence to the proposed rehabilitation program through AI techniques.

The IPOTERI platform is divided into different levels: (1) the at-home level with the Intelligent Home Data Acquisition System; (2) the territorial level with the "Telecare Platform" system, a centralized system for collecting and analyzing data from patients' homes and hospital records; (3) the central level with the intelligent BUS system for connecting the components of the overall system; and (4) the hospital level with an integrated electronic medical record system that operates autonomously in the hospital and manages the clinical data of patients enrolled in the study.

Smart Home Station

The smart home station (SHS) is based on an Android app with a user-friendly interface for the self-recording of patients' vital signs. The interactive part is supported by a dashboard, as shown in Figure 2. From this dashboard, the patient can access the planning of rehabilitation activities and their illustrations by means of videos and also can request a video consultation or participate in activities planned by the doctor. The SHS is also able to integrate data and information from wearable and noninvasive devices to enable the continuous monitoring of vital parameters and support the performance of assigned physical rehabilitation activities. The devices consist of a wearable, noninvasive sensor capable of continuously recording vital parameters such as electrocardiogram (ECG), heart rate, blood pressure, and oxygen saturation, and a weight balance to detect weight variations. The SHS consists of medical devices integrated with two apps: eVoDroid that is integrated with the weight balance and Umana that is integrated with the Umana T1 sensor for ECG monitoring. The eVoDroid system is an app used to receive data via Bluetooth synchronization with integrated devices; the app detects the sensor and the acquired data are displayed in the appropriate fields. It is possible to repeat the measurement, confirm it, and cancel it. There is also a manual data screen, allowing the user to add the data directly. After specifying the type of measurement, the obtained values can be input in the editable fields provided. The Umana app allows data to be received via Bluetooth synchronization with the T1 heart monitor. Once the connection is established, continuous real-time monitoring of the ECG signal and the display of other parameters, including heart rate variability, oxygen saturation, and blood pressure, are possible. The saved data are sent to a server for further analysis of the detected signal.

At the territorial level, a dedicated "patient portal" has been defined in the Telecare Platform to carry out different activities (eg, view the agenda, carry out televisits, request a consultation) related to the rehabilitation plans along with associated video tutorials (Figure 3).

Figure 2. Smart home station. BPM: beats per minute; SpO2: peripheral capillary oxygen saturation.

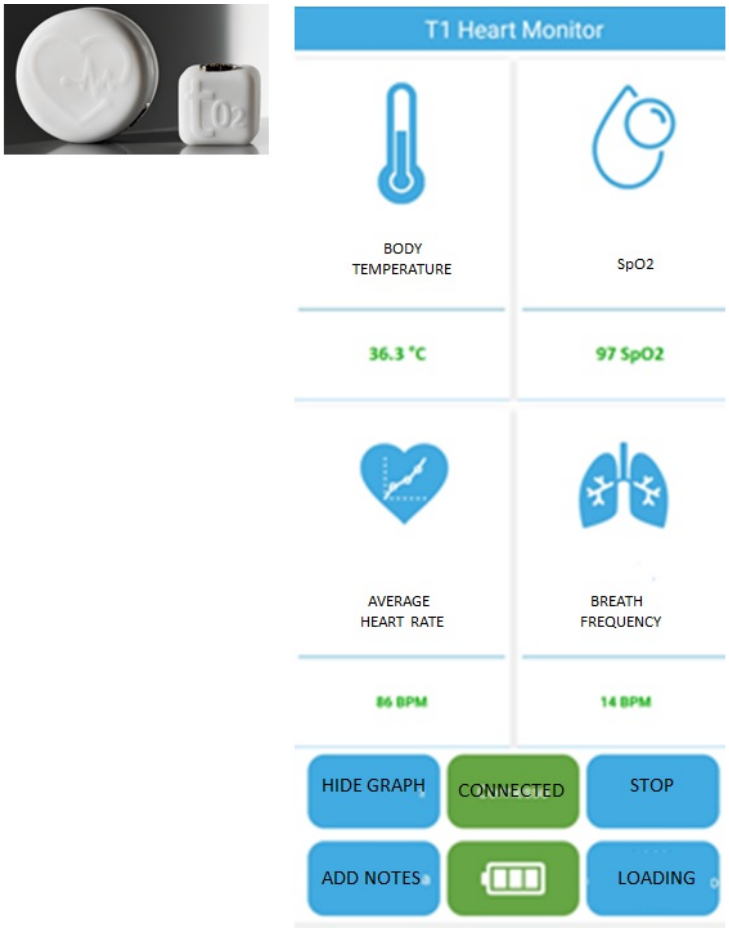
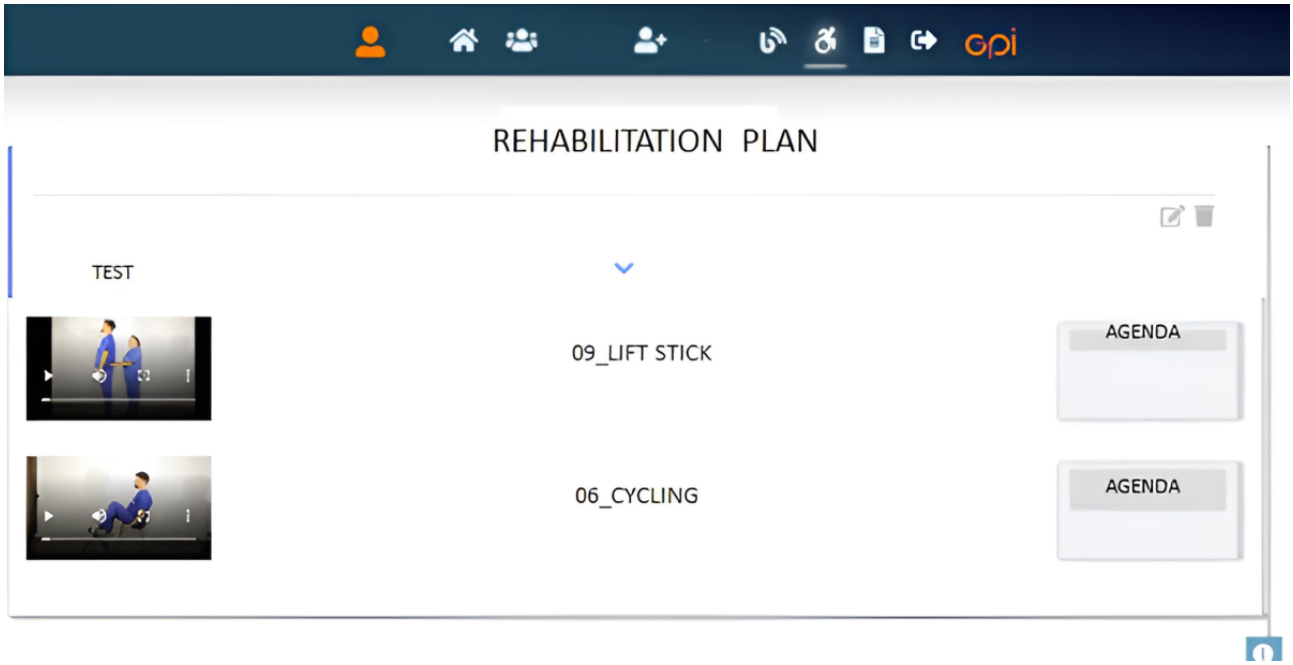


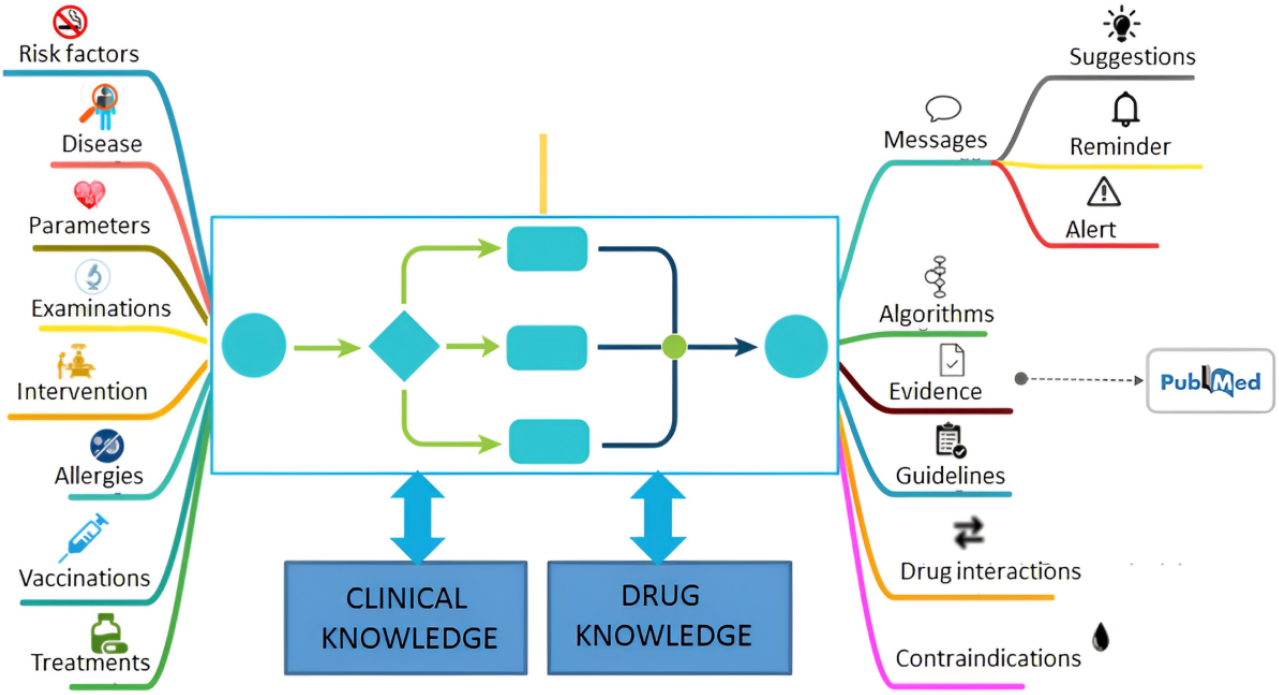
Figure 3. Telecare Platform for access to rehabilitation plans and related video tutorials.



Clinical Rehabilitation DSS

The DSS facilitates the analysis of data collected during the telemonitoring process with hospital clinical data. The DSS communicates with hospital medical records (Figure 1) to transmit alerts and specific support information for the formulation and updating of the treatment and care plan (Figure 4).

Figure 4. Clinical rehabilitation decision support system.



Pilot Test

Study Design and Aims

In the pilot test, patients will be enrolled among those receiving coronary-artery bypass grafting without complications in the postoperative period. During this pilot study, we will receive reports of several technical issues that could affect the functionality of the system. Thus, the data obtained in the pilot study will serve as a guide in the development of a telemonitoring system, including a software and hardware platform based on telemedicine monitoring microservices, to be applied within the project to a wider population.

Pilot Population to Test the IPOTERI Platform

The study participants will be divided into two groups: (1) an HBCR group and (2) a control group with the same clinical profile. The HBCR group will include all patients who will

undergo cardiac surgery procedures and will be submitted to telemonitoring. The control group will be established to have the same clinical profile as the HBCR group but without telemonitoring to serve as a comparison group. The inclusion criteria are as follows: 18 years and older, no major complications after surgery, and good internet connectivity at home. The main exclusion criteria are stage 4 renal failure or undergoing dialysis treatment, overt chronic respiratory insufficiency, previous cerebral ischemic or hemorrhagic event, and cognitive impairment. Allocation to the HBCR group will be based on the patient's preference.

Procedure

After obtaining informed consent, preintervention clinical data will be collected, including anamnestic and instrumental data as well as predischarge data (Figure 4). At 7 to 21 days after discharge, patients will return to the hospital and will be submitted to a functional assessment by performing an aerobic exercise test, the 6-minute walking test (6MWT), according to a standard protocol. The patient will walk along a flat, hard, and measured corridor, with cones marking the turning points set by a physiotherapist [25]. The heart rate, distance traveled, arterial saturation, symptoms, and blood pressure will be monitored at the beginning and end of the exercise according to the normal clinical practice of the 6MWT. The step rate, expressed as the number of steps per minute, and the total number of steps will also be recorded. Heart rate and step rate will be recorded at the onset of symptoms and in the early stages of the exercise. The pace will be measured at the onset of symptoms and in the first 3 minutes of exercise according to the exercise table prescription.

Quality of life will be assessed based on the Psychological General Well-Being Index questionnaire [26]. During the entire monitoring period (12-14 weeks), a patient, doctor, or rehabilitator will be able to activate the teleconsultation services via a home kit. At the end of the study period, patients will undergo hematochemical examinations, echocardiogram, and functional assessment with the 6MWT. Patients who will be recruited and included in the personalized rehabilitation plan will be instructed on how to perform the functional test at home, which is aimed at assessing their rehabilitation progress and to help customize the rehabilitation program. The patient will be able to choose an exercise modality involving free walking outdoors or indoors, using an exercise bike, or a walker. If the patient performs the aerobic exercise by walking, they will be required to maintain a specific cadence or heart rate throughout the exercise. The rehabilitation program will be set based on these measurements at 60% of the walking cadence or maximum frequency reached for the first week, 70% for the second week, 80% for the third week, and 90% for the fourth week. The patient should exercise for at least 20 minutes in the first week and for at least 30 minutes per day in the following weeks. If the patient has difficulty maintaining the prescribed training goals, they will have the opportunity to interact with the doctor who can either maintain the current step increase in activity or go back one step. The rehabilitation exercises will be monitored and customized during the rehabilitation pathway through feedback with the rehabilitation therapist who will have the possibility to connect with the patient and review the execution of the exercises through the devices in the kit.

During this period, vital parameters such as ECG, respiratory rate, blood pressure, body temperature, and oxygen saturation will be recorded. All data from the rehabilitation phase will be collected and stored on the information and communications technology (ICT) platform and made available to the patient via a tablet gateway connected to the data collection center. The medical and rehabilitation staff may consult the acquired data to modify the rehabilitation program based on cardiac parameters, exercise perception, and general well-being.

At the end of the rehabilitation period, patients will undergo routine hematochemical examinations, echocardiogram, and functional assessment by the 6MWT, and they will complete the quality of life questionnaires again. In the 4th week, the patient will be tested at home by performing a walk at the maximum possible speed on a flat surface, either outdoors or indoors, for 6 minutes. During this exercise, the system will measure the continuous heart rate, respiratory rate, step rate, and oxygen saturation, and the data obtained will be used by the doctor and therapist to assess any changes in the exercises compared to the baseline examination. Based on this assessment, the doctor could decide to increase the intensity of the aerobic exercise to be performed by the patient, as described above. All data from the rehabilitation phase will be collected and stored on the ICT platform and made available to the patient via a tablet gateway connected to the data collection center. These acquired data will be available for consultation by medical and rehabilitation staff to modify the physical rehabilitation program on the basis of cardiac data, perception of effort, and general well-being.

At the end of the trial, a questionnaire will be filled out to assess the ease of acquisition of the proposed system, the ease of data transmission, and the level of comfort in managing rehabilitation with the help of the devices for the monitored patients. In addition, intervention satisfaction will be assessed with the following two items: "Overall, how satisfied are you with the IPOTERI tool?" and "How satisfied are you with the possibility of jointly participating in the IPOTERI therapy?" Fatigue severity will be assessed using the Borg rating of perceived exertion scale [27]. The scale is a very simple numerical list. Participants are asked to rate their exertion on the scale during the activity, taking into consideration feelings of physical stress and fatigue, disregarding any factor such as leg pain or breathlessness but focusing on the whole feeling of exertion.

AI Tools

The application of data-driven, machine learning (ML)–powered AI tools to the data collected will help to determine patterns, assess patient stratification, or compute meaningful indices for the clinicians to interpret. In the case of an insufficient population size, data *verticality* (ie, the amount of data *per patient*), or data heterogeneity, specific ML techniques will be used to enable the subsequent definition and testing of clinically relevant tasks once the data become sufficient. More precisely, an important step will be to provide appropriate *patient embedding*, which is paramount to unlock the ability to quickly and easily define and test prediction tasks over the patient

population at a later date. *Embedding* a patient's data involves converting all of the data available for a patient into a fixed-sized vector (ideally of smaller size), which can be used to train ML models (ie, classifiers and clusters) once a sufficient number of patients are available for formal analysis.

Embedding is often performed by *encoders*, which are neural networks that are trained to perform a relatively straightforward task (eg, perform the identity function in the case of *autoencoders*), featuring an architecture with a relatively small internal layer of nodes. These nodes are therefore forced by the training process to "encode" the information presented at the input stage in a fashion that is appropriate to perform the task at hand. Encoders are used in lossy compression such as for feature extraction and several other tasks. In this study, we can use encoders to obtain a compact and actionable patient representation among all heterogeneous data types available for each patient.

Results

The pilot test started in June 2023 (protocol number 20406/2021) including 50 patients who will be monitored for 12-14 weeks using the developed platform, as described in the Procedures subsection of the Methods section.

Discussion

Projected Significance

This pilot study is designed to assess the acceptability, potential efficacy, and potential working mechanisms of the IPOTERI platform, a web-based tool for a postsurgery CR intervention.

To our knowledge, IPOTERI represents the first pilot experiment of the Italian experience of an HBCR program associated with telemedicine monitoring in a patient group who underwent cardiac surgery. The aim of the IPOTERI project is to develop a home-based patient telemonitoring system with the final goals of reducing the number of hospitalizations and outpatient visits, improving the communication between patients and hospital staff, and improving the psychological and emotional dimensions of CR. In the pilot study, we will provide a comprehensive description of the different components of the IPOTERI platform and the first release of the platform from patient enrollment to the rehabilitative program. The availability of remote patient monitoring will make it possible to customize CR programs according to the individual patient's functional limitations and capabilities. In turn, this would have the advantage of increasing adherence to rehabilitation programs.

In practice, telemedicine enables the realization of a "patient-centered rehabilitation approach," which is an essential element of precision medicine [28]. Moreover, prolonged monitoring of multiple physiological parameters of the patient can facilitate establishment of a large data bank, both in qualitative terms (number of variables) and quantitative terms with the same variable monitored over time. The accumulation of big data will necessitate the application of ML algorithms to integrate and analyze the data with a complex and dynamic approach. In this field, AI represents a potential new avenue for the integrated analysis of clinical, instrumental biohumoral data acquired longitudinally that are currently in the DSS along with data collected at single time points.

The requirement for AI in this context is becoming increasingly relevant in the age of telemedicine, which will facilitate the collection of a considerable amount of data, especially in the case of cardiovascular medicine given the complex and multifactorial physiopathological mechanisms underlying CVDs [29,30]. Scientific evidence already exists on the potential applications of AI in cardiology, using both structured and unstructured data, including data obtained from cardiac imaging methods and from eHealth devices [31-34]. For example, a recent position paper of the European Preventive Cardiology Association emphasized the usefulness of AI for the development of algorithms to improve an individual's response to exercise so as to optimize CR in the prevention and treatment of CVDs [35].

Furthermore, the introduction of AI techniques has made it possible to develop predictive variables for outcomes of interest such as adherence to a rehabilitation program and quality of life, which would otherwise likely be neglected because these have not been considered conventional clinical parameters [36].

Limitations

Although IPOTERI is a noninvasive technique offering a highly novel and potentially beneficial rehabilitation program, some patients may not be open to adopting this different approach and may prefer other traditional treatments. Moreover, although IPOTERI might improve patients' perceived well-being as the patient feels monitored, the scalability of this approach to clinical parameters is still unclear. There is a potential limitation related to the approach that could affect the adherence to the rehabilitation protocol. The results, rather than being related to methodological correctness, may be related to the usability of the different devices by the patients, who are often disinclined with technology. One way to reduce this problem will be to have the protocol managed by highly qualified operators, training patients appropriately, and enrolling them voluntarily according to a certain predisposition to using such devices.

Conclusions

The CR tool presented here could be feasible, safe, and comparable to the traditional in-hospital rehabilitation approach, indicating that rehabilitation after cardiac surgery can be carried out at home if planned with an integrated and user-friendly telemedicine service. The IPOTERI approach based on the processing of data, both qualitative and quantitative, recorded during the use of telemedicine monitoring devices at home by a patient during rehabilitation following cardiac surgery, together with clinical data referring to the perioperative and postoperative periods could have potentially positive effects on adherence to the rehabilitation program and clinical improvement, as well as in terms of quality of life. This project aims to evaluate the impact of telemedicine platforms on patients during postoperative rehabilitation. The possibility of adopting the same program in different contexts warrants future studies on a larger population to explore the actual effectiveness of telemedicine-based CR programs. The IPOTERI platform will be tested in only patients with a stable status; thus, future

developments could consider the application of this platform in the management of patients with postoperative complications. Studies are also needed to assess the possibility of adopting the same program in different clinical settings, considering the possible implementation of hybrid CR models including components of both CBCR and HBCR.

Acknowledgments

The project described in this protocol is funded by the Programma Regionale Fondo Europeo di Sviluppo Regionale Toscana 2014-2020.

Conflicts of Interest

None declared.

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Abbreviations

6MWT: 6-minute walking test
AI: artificial intelligence
CBCR: center-based cardiac rehabilitation
CR: cardiac rehabilitation
CVD: cardiovascular disease
DSS: decision support system
ECG: electrocardiogram
HBCR: home-based cardiac rehabilitation
ICT: information and communications technology
IPOTERI: Innovation in Postoperative Rehabilitation Training and Monitoring
ISYDE: Italian Survey on Cardiac Rehabilitation
ML: machine learning
SHS: smart home system

Edited by A Mavragani; submitted 06.04.23; peer-reviewed by J Claes, A Ladebue; comments to author 10.10.23; revised version received 14.11.23; accepted 13.12.23; published 22.01.25.

Please cite as:
Mastorci F, Lazzeri MFL, Ait-Ali L, Marcheschi P, Quadrelli P, Mariani M, Margaryan R, Pennè W, Savino M, Prencipe G, Sirbu A, Ferragina P, Priami C, Tommasi A, Zavattari C, Festa P, Dalmiani S, Pingitore A
Home-Based Intervention Tool for Cardiac Telerehabilitation: Protocol for a Controlled Trial
JMIR Res Protoc 2025;14:e47951
URL: https://www.researchprotocols.org/2025/1/e47951
doi:10.2196/47951
PMID:39841521

Protocol

Constructing TheKeep.Ca With Thrivers of Cancer in Manitoba, Canada, in Support of Enhancing Patient Engagement: Protocol for a Pragmatic Multimethods Study

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Abstract

Background: TheKeep.Ca was built to facilitate engagement with those experiencing cancer in Manitoba, Canada. Constructed between 2020 and 2024 with a group of patient advisors, the website includes information on engagement activities including research participation, the patient advisor role, and how those experiencing cancer can access these Manitoba activities. A link allows visitors to register to be contacted about activities that match their demographics, cancer history, and activity preferences. After TheKeep.Ca was constructed, this protocol was developed to establish TheKeep.Ca as a platform for scientific research focused on optimally engaging those experiencing cancer.

Objective: We asked the following questions: (1) What was the patient advisors' experience who participated in developing TheKeep.Ca? (2) What are the baseline characteristics of website traffic and registrants at TheKeep.Ca? (3) How does registering with TheKeep.Ca impact the cancer experience?

Methods: The planned launch date for the website and initiation of research activities is January 2025. For objective 1, the active patient advisors (N=6) participating in the website project will be invited to participate in project activities including with responses to a question prompt sheet, semistructured audio-recorded interviews, or both. Responses and interviews will be analyzed using reflexive thematic analysis to understand and inform practices for patient engagement on projects. At the website launch, TheKeep.Ca will become publicly accessible and indexable on internet search engines, but no additional promotional interventions will take place in the initial 6 months resulting in visitors primarily from web search traffic. For objective 2, Google Analytics and website registrant data collected during the first six months will be analyzed to obtain baseline characteristics of website visitors. For objective 3, an online survey will be emailed to registrants six months after the website launch characterizing their website experience, the activities they participated in, and collecting feedback on the website. For objectives 2 and 3, quantitative data will be analyzed using both descriptive and inferential statistics, and qualitative data from open-ended questions will be analyzed using thematic analysis guided by an inductive descriptive semantic approach.

Results: This study was approved by the University of Manitoba Health Research Ethics Board on December 12, 2024 (HS26614-H2024L263). Institutional approval from CancerCare Manitoba is pending as of December 23, 2024. Findings from objective 1 are expected to be finalized within the first six months after the website launch. Those from objectives 2 and 3 are expected by the 12-month mark. Reporting will include peer-reviewed journals, conferences, and a lay-language summary on TheKeep.Ca.

Conclusions: The research outlined in this protocol will facilitate understanding patient advisors' experience in developing TheKeep.Ca. It will also characterize the website' effectiveness and its impact on the cancer experience, providing a baseline and direction for future research and development.

International Registered Report Identifier (IRRID): PRR1-10.2196/63597

(JMIR Res Protoc 2025;14:e63597) doi:10.2196/63597

KEYWORDS

patient engagement; patient empowerment; translational research; patient recruitment; development and research; protocol; Manitoba; Canada; cancer; patient advisor; website; research platform; thematic analysis; semi-structured interview; online infrastructure

Introduction

Background

The experience of living with cancer is not uniform, and not limited to patients currently receiving treatment. Comprehensive definitions of survivors of cancer include not only those receiving active treatment, those diagnosed and treated in the past but also the friends and family that support them [1]. Similarly, as a leading cause of morbidity and mortality for the global community, cancer does not selectively impact a specific population defined by race, lifestyle, or geographic location.

Because cancer can, and does, impact every human community, engaging with those impacted by cancer, in a way that seeks to understand how cancer services can be improved to provide optimal biomedical care in a way that is respectful, equitable, and supportive of the diverse lifestyles and identities of those living with cancer is essential for the promotion of ethical human care. Nonclinical trial research and work designed to obtain feedback from those with lived experience (eg, such as patient advisors) on service delivery initiatives are two ways that health care professionals can learn how cancer services can be developed to support better the diverse community of those impacted by cancer. However, identifying survivors of cancer to participate in such work can be challenging.

This project started with the goal of creating a website for connecting those experiencing cancer in Manitoba, Canada, with opportunities to improve the cancer journey for others. The website would allow interested survivors of cancer (1) the opportunity to join a database that would facilitate their voluntary participation by notifying them about emerging patient engagement opportunities in Manitoba such as nonclinical trials research or to function as patient advisors. Such a website would facilitate engagement with the Manitoba population with cancer without impacting other existing programs, including clinical service delivery, in the province. The website would be a platform used to study how to better recruit individuals for cancer research; (2) and a tool for rigorously exploring how online approaches can be used to overcome challenges to achieving representative engagement with Manitoba's diverse population with cancer that includes, but are not limited to, Indigenous peoples, recent immigrants, and those living in urban, rural, and remote communities.

Understanding Barriers to Recruitment for Nonclinical Trials Research

Language barriers, lack of infrastructure, costs related to advertising and supporting accessibility, and the functional capacity of participants living with illness are just some of the barriers that can impact the recruitment of representative samples for all types of research work [2,3]. In contrast to clinical trial research, which is generally integrated into the participants' health care, conducted by well-established teams with dedicated infrastructure to support participant recruitment, and comes with the incentive of possibly receiving an experimental intervention that may be superior to the standard of care [2], nonclinical trials researchers face unique challenges. Nonclinical research, such as qualitative and quantitative survey research, as well as longitudinal observational studies, often function with less infrastructure support, clear benefit to the participant, and require commitments on behalf of the participant outside of their responsibilities as recipients of clinical care [4].

Additionally, nonclinical trial studies are often "one-offs" undertaken by trainees, such as graduate and postgraduate researchers, as part of the completion of educational programs. Those responsible for the success of such projects (ie, the trainee) may have less access to gatekept patient populations and other supportive infrastructure, such as research nurses [2]. Unfortunately, these barriers likely result in fewer high-quality research projects, ultimately involving smaller, nonrepresentative samples, and delays in project completion—negatively impacting the quality and diversity of the scientific literature, accessibility to potential participants who may find benefit in participating in such research projects, and the professional trajectory of talented researchers.

Exploring Barriers to Patient Engagement

Outside of the research recruitment setting, for health care teams, including clinicians, researchers, and administrators, being able to connect with a diverse group of individuals with lived illness experience is becoming increasingly recognized as valuable for program development and improvement [5]. Engagement with individuals functioning as patient advisors to inform project planning, research design [6,7], and infrastructure development is increasingly recognized as an essential process for evolving patient-centered care [5,8,9]. However, as an area of research, understanding how to effectively identify, recruit, and engage with individuals is still evolving [5,10,11]. For instance, it has been suggested that patient advisors may be more likely to be individuals that are passionate about engaging with the health

care system than the average patient, resulting in the population of individuals that is engaged with patient advisory work being less likely to be representative of the general patient population [8].

Important work is being carried out to explore how to create better and more meaningful patient engagement opportunities. For instance, aspects of patient engagement such as the timing of activities concerning project lifecycle [6], mitigating power imbalances [11,12], and evaluating outcomes of patient engagement [9] have an evolving body of literature in the spirit of moving from passive to authentic patient engagement [5,9,10,12]. However, questions related to recruitment for engagement appear to be less robustly addressed. A recent systematic review including 142 studies explored patient engagement as a part of research [9]. While the review did identify several different ways that participants were identified, including internet postings, paper advertisements, and invitations from clinicians, studies involving a specific analysis of the impact of different approaches on recruitment effectiveness were not found [9]. As identification of individuals for patient advisory work is often not embedded in the clinical practices of frontline care providers, it is likely that many of the same challenges to recruitment that face nonclinical trial research exist for patient engagement. Work exploring which recruitment approaches for patient engagement are most effective, and how these approaches enable engagement with different populations is important.

Using Online Infrastructure to Optimize Engagement

Using physical spaces primarily intended for clinical service delivery presents challenges for meaningfully engaging with patients and their friends and family about topics not directly related to patient care. In these clinical areas, such as in ambulatory oncology clinics, patients and their accompanying friends and family members may be already overwhelmed with information regarding their disease and its management [13]. On the other hand, online web spaces can be more easily purpose-built around the needs and interests of those experiencing specific aspects of an illness journey and can be accessed after clinical visits have concluded, during times convenient to the individual [13]. Importantly, the population with cancer is well documented to rely heavily on online information as part of the cancer journey, with some studies demonstrating daily rates of internet use related to cancer exceeding 80% [14]. If carefully developed to meet the needs of those living with cancer, online spaces may be effective at supporting engagement between those living with cancer and health care professionals working to evolve the cancer journey.

Research Objectives

This protocol outlines how a website intended to support and provide meaningful patient engagement will be studied to advance the science of effective engagement with those living with cancer. As outlined below, TheKeep.Ca website was developed through collaboration with a team of dedicated patient advisors with the aim of creating a webspace to facilitate connecting researchers and health care teams with those who have lived cancer experience as well as providing meaningful resources for those living with cancer in Manitoba and beyond. In addition to helping TheKeep.Ca evolve to better serve the needs of the cancer community in Manitoba, the outcomes from exploring the research objectives outlined in this protocol are intended to provide useful guidance for those intending to embark on pragmatic longitudinal patient engagement projects, such as the development of patient-centric websites, and contribute meaningful findings to the scientific literature regarding how to best engage, online, with those experiencing cancer.

Research Questions

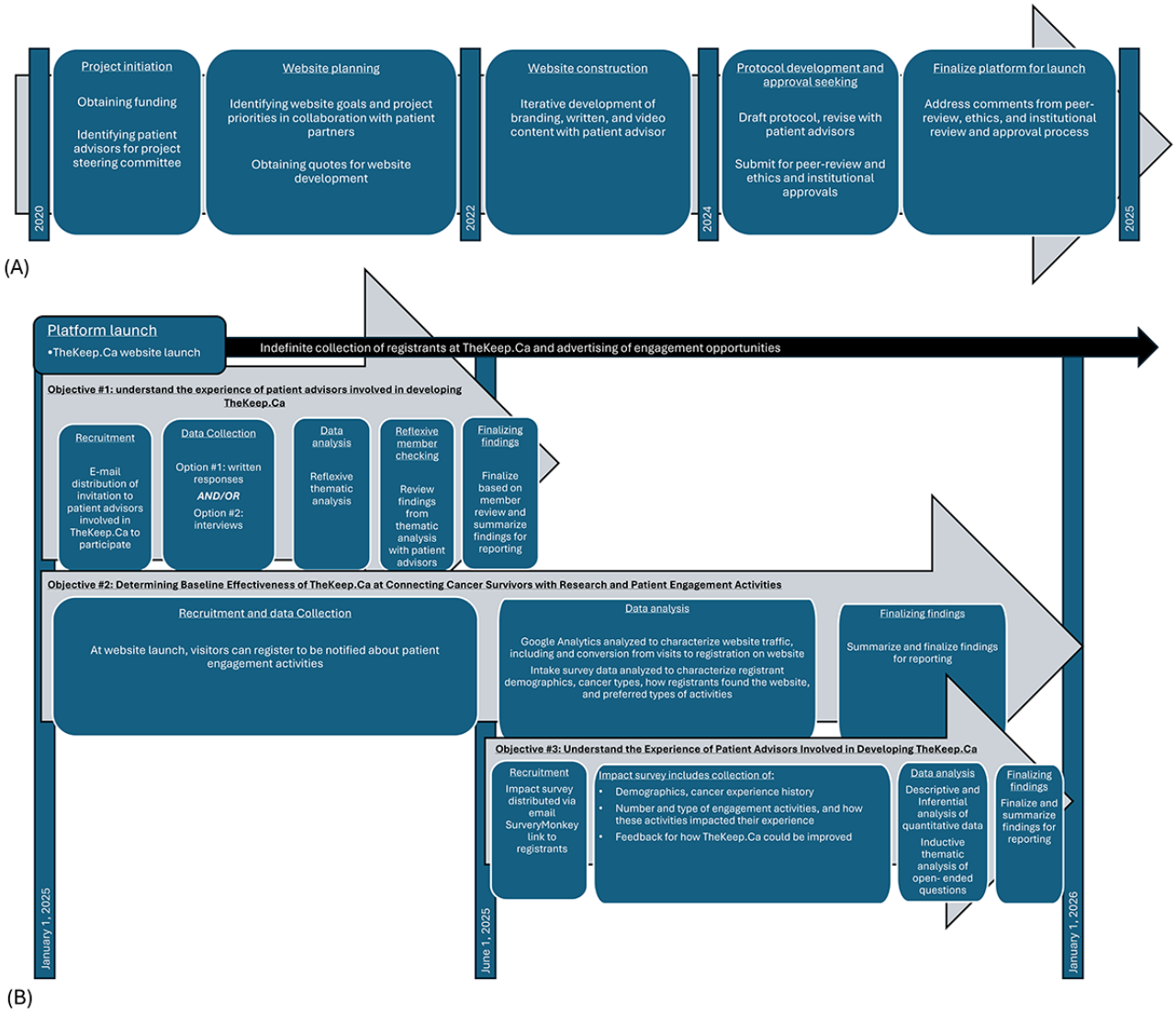
1. What was the experience of the patient advisors who participated in the development of TheKeep.Ca?
2. How effective is TheKeep.Ca at engaging with the population with cancer in Manitoba in the six months after going live?
    - What are the characteristics of website visitors?
    - What is the conversion rate from unique website visitors to website registrants?
    - What are the characteristics of registrants on the website database?
3. How do the patient engagement activities that TheKeep.Ca facilitate impact the cancer experience for website registrants?
    - How does participating in engagement activities promoted by TheKeep.Ca impact the cancer experience?

Methods

Building TheKeep.Ca

Before initiating research activities, TheKeep.Ca website was developed over 4 years through several steps (Figure 1A). After funding had been obtained for the project, patient advisors, including past and present patients with cancer at CancerCare Manitoba (CCMB), were invited to join a patient steering committee to guide the project that was facilitated by the lead author (MT). The patient advisors were recruited both through the CCMB patient advisor program and by psychosocial staff at CCMB.

Figure 1. Development of TheKeep.Ca and proposed research activities. (A) TheKeep.Ca was developed over 5 years with a group of patient partners beginning in 2020. Patient partners informed goals for the website, content development, research priorities, and methods. (B) In the six months following the website launch, the patient advisors' experience of being involved in TheKeep.Ca project will be explored using a qualitative approach. Six months following the launch, data from the registration surveys and Google Analytics will be used to characterize the website's effectiveness in engaging with the survivors of cancer population in Manitoba. A survey exploring the impact of registration on the TheKeep.Ca website will also be deployed at the 6-month mark with the results used to address the impact of the website on the cancer experience.



Through videoconferences, emails, and an online discussion board, the priorities for the website were identified by the steering committee. These included items to satisfy the requirements of the secured funding (ie, a website to inform website visitors about the role of being a patient advisor, a research participant in nonclinical trials research, and a method to populate a database of individuals interested in participating in these roles). Additionally, while the patient advisors identified several important components that could be added, developing a resource directory of supportive care for cancer resources to be hosted on the website curated by patients was selected as the initial patient advisor-championed project to be included on the website.

After the steering committee was formed and the key components were identified, the website was developed in coordination with a professional media design firm (Argyle Media Inc). Facilitated by the lead author (MT), the patient advisors on the steering committee participated in all aspects of developing the website branding, including providing both initial ideas and iterative feedback to the media firm for the logo and site design. Additionally, the patient advisors also participated in content creation for the website, including working alongside a freelance videographer and 2 science communication writers.

In total, 10 current or former patients were involved in the project, however, 4 left the project during its course for reasons including, but not limited to, competing priorities and changes in health status.

Studying TheKeep.Ca

Once the website was completed, this protocol was developed. Feedback was obtained from the patient advisor steering committee regarding what research objectives they considered important to include regarding the value of a patient engagement website. The protocol was developed by the lead author (MT) and last author (DEM), and then reviewed by the patient

advisors, with revisions to this study's tools and methods made in response to their feedback before submission for peer review.

A schematic outlining the timeline for the activities described in this protocol is presented in Figure 1, including the development of TheKeep.Ca (Figure 1A) and the research activities proposed in this protocol (Figure 1B).

Research Objective 1: What Was the Experience of Participating in Developing TheKeep.Ca?

The patient advisors who continue to participate in the development of TheKeep.ca (N=6) through membership in the patient engagement steering committee will be invited to share their experience of partnering in the development of TheKeep.Ca. This will be completed within the context of a research study as a voluntary activity. Those who are interested in participating will be invited to contact the last author (DEM) of this protocol, who will obtain informed consent (Multimedia Appendix 1 for the consent form). They will then receive a short intake questionnaire to collect demographic information and details about their cancer experience (Multimedia Appendix 2).

Those who express interest in providing a voluntary written sample following the informed consent process will be provided with a question prompt to provide open-ended written responses (Multimedia Appendix 3). For those who consent to participate in a voluntary semistructured interview, an audio-recorded semistructured interview (estimated duration 60 to 90 minutes) will be conducted following the collection of all written responses. The semistructured interviews will be guided by an interview guide (Multimedia Appendix 4). The question prompts (ie, Multimedia Appendices 1 and 2) were developed by authors MT and DEM, based on feedback MT had received from the patient advisors on the steering committee involved in the project, and reviewed and revised by the steering committee before finalizing this protocol. Transcripts of the audio recordings will be prepared using a professional transcription service (ie, Scribie), and both the written survey responses and interview transcripts will be deidentified before analysis.

Reflexive thematic analysis (RTA) [15] will be used to analyze the data collected. RTA is a nuanced iteration of the thematic analysis approach initially described by Braun and Clarke [16]. Specifically, RTA explicitly addresses several methodological questions that have been identified since the initial publication describing thematic analysis by Braun and Clarke [16]. Specifically, RTA is not considered a positivistic, descriptive, rigid methodology. Instead, it embraces constructivism, an inductive flexible approach to data analysis, consideration of latent meaning, and an emphasis on the interpretation of the data by the researcher [15,17]. Compared to other iterations of thematic analysis, RTA was chosen because the experience of the patient advisors involved in the development of TheKeep.Ca was thought to be complex, with many aspects likely to be unknown a priori to the researchers, requiring more than a descriptive summary of the data collected to provide a meaningful exploration and contribution to the literature.

The steps for data analysis will be in keeping with those described for RTA [15-17], progressing in a relatively linear manner through six phases including (1) familiarization with the data once data collection is completed, (2) generating initial codes using line by line coding, (3) generating themes, (4) reviewing potential themes, (5) defining and naming themes, and (6) producing the report. In keeping with a nonpositivistic stance, the volunteers from the steering committee will be invited to provide member reflections in a group setting as part of phase 6 once a preliminary version of the report is ready. The purpose of this activity will be to "explore gaps in understanding … and consider how to acknowledge and present these in the written report" [15], as opposed to validating findings. The final report will be revised to reflect the findings from this final group activity.

Rigor and Trustworthiness

The trustworthiness of the research findings will be facilitated by ensuring practices that enhance credibility, transferability, dependability, and confirmability [18,19]. Prolonged engagement with this study's participants and data, as well as a review of study findings with participants before finalizing study results, are techniques that will be used to address the credibility of the findings. By providing a rich description of the data, the contexts in which it was collected, and the resulting findings, as well as by considering both latent and semantic themes, the transferability of this study's findings to other contexts related to patient engagement will be supported. Dependability will be supported by recording written field notes in addition to the audio recording of semistructured interviews, the keeping of a reflexive journal to document the processes and decisions related to the generation of codes during data analysis, and the use of NVivo (Lumivero LLC, version 13, released 2020) software which provides an auditable record of the steps by which the data was coded. Conformability, or whether the research findings follow from the data collected, will be supported through the techniques described in support of credibility, transferability, and dependability [18]. Additionally, conformability will be further supported by recording additional aspects of the research process in the reflexivity journal, beyond the specific decisions and processes related to the development of the codes. For instance, it is anticipated the DEM will record information about the daily experience of completing the data collection and analysis, as well as reflections on their personal experience with the research [18,19], in support of connecting personal experience with conducting research with the data and generated findings.

Reporting of the findings will conform with COREQ (Consolidated Criteria for Reporting Qualitative Research) guidelines to facilitate rigorous reporting [20]. In keeping with this, in addition to thorough reporting of study methods and findings reflecting the checklist items, a reflexivity statement will be included in the final report which will include, but not be limited to, a characterization of DEM's professional identity, and personal biases, assumptions, and reasons and interests in the research topic.

Research Objective 2: What Is the Baseline Effectiveness of TheKeep.Ca at Connecting Survivors

of Cancer With Research and Patient Advisor Activities?

Data from website visitor metrics and registrant data collected over the first 6 months after the website goes live will be used to establish a baseline of the effectiveness of TheKeep.Ca at recruiting members of the Manitoba population with cancer for engagement activities. Google Analytics will be used to provide metrics related to user activity on the website. The methodology for using Google Analytics to understand website traffic is informed by that used by previous authors [21]. Specific metrics to be used will include, but not be limited to, total users, type of devices used, geographic locations of users, session length, websites' pages viewed, number of page views per page, bounce rate (ie, number of users leaving the site without viewing additional pages), site entrances, and page interactions.

Data from registrants on the TheKeep.Ca engagement database will be used to further characterize the effectiveness of the website, as well as the population that it effectively engages within the first six months after going live. Specifically, respondent demographics, information about their cancer experience, preferred types of activities, and how they found the website are tracked as part of the registration survey (Multimedia Appendix 5).

Data analysis will include the generation of descriptive statistics of the website metrics and registrant characteristics. Descriptive statistics will be generated from both the Google Analytics data as well as the registrant data. Inferential statistics, including chi-square and *t* test (2-tailed), will be used to describe differences in Google Analytics metrics between website visitors from Manitoba and outside of Manitoba, as well as by device. Additionally, inferential statistics will be used to describe differences in disease characteristics and engagement preferences by registrant demographics, including age, gender, and location. Open-ended question data will be summarized using a descriptive semantic inductive approach to thematic analysis [15,16], with the aim of providing a simple summary of open-ended question data.

Research Objective 3: How Does Registration on TheKeep.Ca Impact the Cancer Experience?

After the initial 6 months after TheKeep.Ca has gone live, an online SurveyMonkey survey (Multimedia Appendix 6 for the survey) will be distributed to the website registrants who consented to be contacted with a follow-up survey as part of the initial registration questionnaire. Demographic data and information about the registrant's cancer experience (ie, date of diagnosis, type of diagnosis, patient vs informal caregiver, and treatment intent) will be captured, as well as the number and type of engagement activities they have participated in that were advertised on TheKeep.Ca. Using a combination of Likert-style responses and open-ended questions the survey will evaluate the experience of being a registrant on TheKeep.Ca, the effectiveness of TheKeep.Ca in connecting individuals with engagement opportunities, the impact of engagement activities on the experience of registrants, and identify ways that TheKeep.Ca can provide a better experience to website registrants. Descriptive statistics will be generated to describe the respondent population and the overall experience of the group. Inferential statistics will be used to identify differences between populations, based on demographics and cancer experience, and the impact TheKeep.Ca had on respondents' cancer experience. Open-ended question data will be summarized using a descriptive semantic inductive approach to thematic analysis [15,16], with the aim of providing a simple summary of open-ended question data.

Development of the research protocol related to objectives 2 and 3 was informed by the CHERRIES (Checklist for Reporting Results of Internet E-Surveys) checklist to facilitate rigorous reporting [22]. For qualitative data, NVivo will be used to assist with qualitative data management and analysis. Quantitative data analysis will be conducted using SPSS (IBM Corp, version 27, released 2020).

Ethical Considerations

This study was approved by the University of Manitoba Health Research Ethics Board on December 12, 2024 (HS26614-H2024L263). Institutional approval from CCMB is pending as of December 23, 2024. Participants, including both registrants on TheKeep.Ca website as well as the patient advisors involved in the development of this project, did not receive compensation of any kind. Enrollment on TheKeep.Ca website is strictly voluntary, with informed consent being implied as part of the registration process.

All data will be deidentified before analysis. Data related to objective 1 will be linked to a master list, which will be destroyed following the completion of research activities outlined in this protocol. Data related to objective 2 (ie, registrant responses) will be deidentified before analysis for research purposes; however, names and contact information will be required to be retained on this data to facilitate screening and informing registrants of relevant patient engagement activities. However, this data will not be shared with any other party and be available only to the research team (ie, MT and DEM). Data from objective 2 is being collected in an anonymized fashion, with an absence of information that would support the identification of individuals. Notably, while the email addresses provided by registrants on the website will be used to collect data for objective 3, the responses will not be linked to the email addresses or the initial responses provided by the individuals at the time of website registration.

Patient advisor involvement, including participation on the steering committee, being listed as an author on this paper, and participation in the research activities related to objective 1, was strictly voluntary, and would not impact their ability to participate in any aspect of the activities related to this project. The patient advisors listed as authors on this protocol provided expressed written consent to be listed as such and fulfilled the criteria to be listed as authors in peer-reviewed journal publications, including active involvement in all aspects of the project and protocol development. Documentation of this consent was provided to the editor for review as part of this peer-reviewed process.

All images, names, and videos of individual thrivers of cancer presented on TheKeep.Ca website are used with expressed consent. The website does include stock images obtained from

a third party (ie, Adobe Stock Images) which are used per the images' respective licensing agreements.

Results

TheKeep.ca will go "live" after this study receives institutional approval from CCMB, becoming searchable on major search engines (eg, Google) and accessible to the public. The results related to research objective 1 are expected to be submitted for peer-reviewed publication within 6 months after the website becomes accessible to the public with results related to research objectives 2 and 3 being submitted for peer review by the 12-month mark. In addition to being presented in peer-reviewed manuscripts, the results will also be shared at national and international conferences as well as presented on TheKeep.Ca website in written and video format using layperson language.

Discussion

Principal Findings

Addressing the three research objectives outlined in the protocol is important for informing future work in several ways. Regarding research objective 1, better understanding the experience of the patient advisors who were, and continue to be, involved in TheKeep.Ca project is important for evolving how TheKeep.Ca project is conducted in the future, as well as informing how other projects where authentic longitudinal patient engagement is desired. While high-quality reviews [5,9] and frameworks to guide patient engagement activity planning exist [23], such as those available through the Patient-Centered Outcomes Research Institute [24], the findings from this work will provide real-world examples of the experiences, challenges, and lessons learned from a complex project where authentic longitudinal engagement with thrivers of cancer was foundational. Specifically, identifying what parts of this project have been frustrating, stressful, or otherwise not rewarding, for the patient advisors as well as which aspects were viewed as providing a positive and meaningful experience is expected to make a meaningful addition to the literature [10].

Regarding objectives 2 and 3, obtaining baseline data regarding how effective the website is at engaging those living with cancer both inside and outside of Manitoba, as well as the characteristics of the registrants, is important for guiding future work to better engage with the diverse population of individuals living with cancer both inside and outside of Manitoba. It is anticipated that the baseline Google Analytics data will provide meaningful insights per who engages with TheKeep.Ca website. Similarly, the initial registrant experience survey (ie, objective 3) will provide important data about how to enhance the experience of those that register on TheKeep.Ca. This data will reflect the experience of engaging with TheKeep.Ca in the absence of planned social media campaigns and advertising at the cancer center. As the website develops, and campaigns to promote the website are developed, the baseline data will provide a real-world comparison to gauge the effectiveness of promotional interventions such as social media advertising campaigns, paid Google Adwords campaigns, and posters placed in cancer care facilities, or private businesses. This data will be helpful not only for helping TheKeep.Ca evolve into a tool for engaging meaningfully with Manitoba's population with cancer but also for other groups endeavoring to engage with either specific populations or a representative sample of those impacted by cancer [8].

Limitations

This protocol has two main limitations. First, to address research objective 1, not all patient advisors who participated in the development of TheKeep.Ca will be able to be invited for interviews. At the time of protocol submission, three of the initial patient advisors involved left the project, for several reasons—not all of which were disclosed. While, from both a scientific and quality improvement perspective, it would be ideal to explore the reasons for dropping out from the project to provide a better experience for those in the future, however, out of respect for the privacy of the individuals that withdrew, this is not possible. Ideally, experience data related to participation in the project would have been captured longitudinally, throughout the project. However, the decision to establish TheKeep.Ca as a research platform was made relatively late in the project history, as such the need to formally collect rigorous experience data was not considered previously.

Second, there is a risk that initial recruitment to the TheKeep.Ca registrant database will be limited, resulting in limited data to address objectives 2 and 3. TheKeep.Ca, as a research platform, represents a novel endeavor, making predicting the initial recruitment rate and the resulting sample size for the first six-month sample size impossible. Additionally, as the goal is to obtain baseline data for traffic and engagement with the site, before additional advertising interventions as outlined above, traffic may be very low. As a result, it is recognized that the generation of meaningful inferential statistics may not be possible. Regardless, the initial data from the first six-month period will serve as an important baseline, essential for understanding the impact of future campaigns to promote the website and recruitment to the website registry.

Conclusion

The webspace that became TheKeep.Ca was initially proposed as a simple tool to connect those who have experienced cancer firsthand with opportunities to engage with researchers and other teams working to improve the cancer journey in Manitoba, Canada. However, through endeavoring to seek authentic [9] collaboration with a group of patient advisors over several years, the simple proposal evolved into something with the potential to become much more than that. In keeping with the original proposal, TheKeep.Ca is a catalyst, enhancing the capacity for connection between those willing to share their hard-won firsthand knowledge with health care professionals. However, it is also a place where patient advisors can contribute directly to improving the cancer journey, as it provides online infrastructure for patient advisor-led initiatives—such as the curated resource directory. Lastly, through a rigorous research program, beginning with the work outlined in this protocol, TheKeep.Ca project aims to achieve these goals while, at the same time, advancing what is known about patient engagement for the benefit of those living with cancer in Manitoba and beyond.

Acknowledgments

This work was supported by a grant from the CancerCare Manitoba Foundation.

Data Availability

To protect the confidentiality of the research participants, deidentified data, including qualitative data related to objective 1, and survey response data from objectives 2 and 3 will not be made publicly available. However, it may be obtained upon reasonable request to the authors, and subsequent approval of the request after review by the University of Manitoba Health Research Ethics Board.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Consent form for objective 1.
[DOCX File , 46 KB - resprot_v14i1e63597_app1.docx]

Multimedia Appendix 2
Intake questionnaire for objective 1.
[DOCX File , 28 KB - resprot_v14i1e63597_app2.docx]

Multimedia Appendix 3
Written prompt sheet for objective 1.
[DOCX File , 30 KB - resprot_v14i1e63597_app3.docx]

Multimedia Appendix 4
Semistructured interview guide for objective 1.
[DOCX File , 16 KB - resprot_v14i1e63597_app4.docx]

Multimedia Appendix 5
Registration survey for objective 2.
[PDF File (Adobe PDF File), 42 KB - resprot_v14i1e63597_app5.pdf]

Multimedia Appendix 6
Six-month follow-up survey for objective 3.
[PDF File (Adobe PDF File), 47 KB - resprot_v14i1e63597_app6.pdf]

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Abbreviations

CCMB: CancerCare Manitoba
CHERRIES: Checklist for Reporting Results of Internet E-Surveys
COREQ: Consolidated Criteria for Reporting Qualitative Research
RTA: reflexive thematic analysis

Edited by A Schwartz; submitted 28.06.24; peer-reviewed by KE Cain; comments to author 16.10.24; revised version received 08.12.24; accepted 11.12.24; published 29.01.25.

Please cite as:
Thiessen M, Jewitt K, Stromberg R, Lamontagne JM, Richardson Tanguay G, Albo A, Thurston C, McMillan DE
Constructing TheKeep.Ca With Thrivers of Cancer in Manitoba, Canada, in Support of Enhancing Patient Engagement: Protocol for a Pragmatic Multimethods Study
JMIR Res Protoc 2025;14:e63597
URL: https://www.researchprotocols.org/2025/1/e63597
doi:10.2196/63597
PMID:

Protocol

The Measurement of Vital Signs in Pediatric Patients by Lifelight Software in Comparison to the Standard of Care: Protocol for the VISION-Junior Observational Study

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Abstract

Background: Measuring vital signs (VS) is important in potentially unwell children, as a change in VS may indicate a more serious infection than is clinically apparent or herald clinical deterioration. However, currently available methods are not suitable for regular measurement of VS in the home or community setting, and adherence can be poor. The COVID-19 pandemic highlighted a need for the contactless measurement of VS by nonclinical personnel, reinforced by the growing use of telemedicine. The Lifelight app is being developed as a medical device for the contactless measurement of VS using remote photoplethysmography via the camera on smart devices. The VISION-D (Measurement of Vital Signs by Lifelight Software in Comparison to the Standard of Care—Development) and -V (Validation) studies demonstrated the accuracy of the app compared with standard of care (SOC) measurement of blood pressure, pulse rate (PR), and respiratory rate (RR) in adults, supporting certification of Lifelight as a class I Conformité Européenne medical device.

Objective: To support the development of the Lifelight app for pediatric patients, the VISION-Junior study is collecting high-quality data that will be used to develop algorithms for the measurement of VS (PR, RR, and oxygen saturation) in pediatric patients. The accuracy of the app will be assessed against SOC measurements made simultaneously with app measurements.

Methods: The study is recruiting pediatric patients (younger than 18 years of age) attending the Sunderland Royal Hospital pediatric emergency department of the South Tyneside and Sunderland National Health Service Foundation Trust. High-resolution videos of the face (and torso in children younger than 5 years of age) and audio recordings (to explore the value of crying, wheezing, coughing, and other sounds in predicting illness) are made using the Lifelight Data Collect app. VS are measured simultaneously using SOC methods (finger clip sensor for PR and oxygen saturation; manual counting of RR). Feedback from patients, parents, carers, and nurses who use Lifelight is collected via questionnaires. Anticipated recruitment is 500 participants, with subtargets for age, sex, and skin tone distribution (Fitzpatrick 6-point scale). Early data will be used to refine the algorithms. A separate dataset will be retained to test the performance of the app against predefined targets.

Results: The study started on June 12, 2023, and reached its recruitment target (n=532) in April 2024 after extending the deadline. Algorithm refinement is in progress, after which the performance of Lifelight will be compared with the SOC measurement of VS. The analyses are expected to be completed by mid-August 2024.

Conclusions: Data collected in this study will be used to develop and assess the accuracy of the app for the measurement of VS in pediatric patients of all ages.

Trial Registration: ClinicalTrials.gov NCT05850013; https://clinicaltrials.gov/study/NCT05850013

International Registered Report Identifier (IRRID): DERR1-10.2196/58334

(JMIR Res Protoc 2025;14:e58334) doi:10.2196/58334

KEYWORDS

vital signs; remote photoplethysmography; pediatric health assessment; pediatric health monitoring; pediatric; infant; infants; infancy; child; children; Lifelight; software; app; observational study; study protocol; clinical deterioration; COVID-19; SARS-CoV-2; pandemic; telemedicine; medical device; photoplethysmography; eHealth; mobile health; mHealth

Introduction

Measurement of vital signs (VS) is an essential part of clinical evaluation, providing important information about a patient's health; importantly, a change in VS may herald a deterioration in clinical condition [1] and may precede the emergence of physical symptoms during the early stages of an infection [2]. High pulse rate (PR) and respiratory rate (RR) have been shown to predict hospital admission in children [3]. Infections such as influenza, scarlet fever, and chickenpox are common causes of morbidity and mortality in immunocompromised children [4,5]. Three-quarters of children who develop severe sepsis from infection have a comorbid condition such as asthma, diabetes, cystic fibrosis, or cancer. Sepsis carries a mortality rate of almost 50% in the most vulnerable children [6]. Treatment of infection in children can be expensive, especially if intensive care is required.

Given that monitoring of VS is important in clinically vulnerable children to aid early detection of infection [7], a robust method that parents can use at home to measure VS is likely to be beneficial and would support remote initial assessment [8]. The measurement of VS is time-consuming and requires trained staff and multiple pieces of equipment, some of which need regular calibration. Accurate measurement of blood pressure (BP) using a sphygmomanometer requires the use of the correct size cuff for the patient. The physical contact of equipment can be uncomfortable and distressing for patients, particularly those with learning disabilities. Stress can affect BP, PR, and RR, such that the measurements may not accurately reflect the patient's state of health [7]. Standard of care (SOC) medical equipment is not suitable for regular measurement of VS in the home or community setting. Adherence to frequent VS monitoring using traditional technologies is low because of the inconvenience and stigmatizing nature of specialist hardware equipment (eg, thermometers, BP cuffs, and finger-clip oximeters) [7]. The COVID-19 pandemic has also highlighted the need for methods suitable for the remote or contactless measurement of VS that can be operated by people without specific medical training. The growing use of telemedicine since the pandemic also points to the need for easy but accurate measurement of VS.

Photoplethysmography (PPG) is an optical measurement technique that records changes in the light reflected from the skin surface due to volumetric changes in the facial blood vessels; small variations in perfusion provide valuable information about the cardiovascular system [9]. PPG has been used to measure PR [10,11], oxygen saturation [12], BP [13,14], and RR [10,15] and to detect atrial fibrillation [16].

Lifelight is an app being developed for the contactless measurement of VS using remote PPG via the camera on smart devices such as phones and tablets. The app captures the average color of regions of interest on the face 30 times every second for 60 seconds and sends these as red, green, and blue color values to a central server for processing, yielding VS values. The VISION-D (Measurement of Vital Signs by Lifelight Software in Comparison to the Standard of Care—Development) study in 2018-2019 measured VS in 8585 patients and healthy volunteers simultaneously using the app and SOC methods. The data were used for machine learning to develop the algorithms used to calculate VS. The subsequent VISION-V (Validation) study demonstrated the accuracy of the app compared with SOC methods for measuring PR, RR, and diastolic BP [17], providing the basis for the current Class I Conformité Européenne (CE) mark [18]. The app also received ISO 13485:2016 certification in August 2023 [19], and the accuracy of the app for measuring PR and BP against ISO standards in adults with stage 1 hypertension has recently been reported [20]. The VISION-MD (multisite development) study evaluates the app versus SOC in patients with a wide range of clinically relevant VS values, including critically ill patients, and across the full range of skin tones [21]. In VISION-MD, high-resolution full-face videos of participants' faces have been recorded, which has proved instrumental in improving the accuracy of VS measurement compared with the VISION-D and -V studies.

The VISION-Junior study explores the measurement of VS using a Lifelight app developed for pediatric patients (aged 18 years or younger) attending the pediatric emergency department. As in VISION-MD in adults, high-resolution full-face videos will be recorded. In younger children (younger than 5 years of age), the video will also include the torso to increase the surface area from which the signal is recorded, and because the torso is likely to move less than the face. Audio data will also be recorded, as crying, wheezing, coughing, and other sounds can also predict illness in children [22,23].

The aim of the VISION-Junior study is to assess whether the app can be used to accurately measure VS in pediatric patients. This protocol describes the collection of data that will initially be used to develop the algorithms for the measurement of VS in children. Later data will be used to assess the accuracy of the

app across the range of VS values encountered in children of different ages. The objectives are as follows.

The primary objective is to collect data to support the development of the app for the accurate measurement of PR, RR, and oxygen saturation in pediatric patients and to assess the accuracy of measurements against SOC methods. Secondary objectives are: (1) to assess—using the collected PPG data—whether other (direct or indirect) measurements can be made using the app, including temperature, BP, PR variability, and audio analysis; (2) to evaluate the impact of subject-specific variables on the PPG VS measurements (eg, medication, cosmetics, facial or body hair, and skin tone); (3) to obtain data to understand patient and parent or guardian or carer habits and preferences for VS measurement using questionnaires (Multimedia Appendices 1 and 2); and (4) to assess the usability of Lifelight Junior for measuring VS in pediatric patients through questionnaires completed by participating health care professionals (Multimedia Appendix 3).

Most of the data collected in the study will be used to train the app algorithms to measure VS in pediatric patients. The remaining data will be kept separate and used to assess the accuracy of the algorithms at regular intervals during the data collection period. The study delivery process will be responsive to this learning curve to increase the likelihood that the predetermined accuracy target for each VS estimation is achieved by the study end.

Methods

The design and protocol for this study have been informed by the VISION-MD study [21] and earlier VISION studies [17].

Participants and Recruitment

Approximately 500 pediatric patients are being recruited at the Sunderland Royal Hospital pediatric emergency department of the South Tyneside and Sunderland National Health Service (NHS) Foundation Trust. All pediatric patients (younger than 18 years of age) attending the pediatric emergency department are potentially eligible for the study. The exclusion criteria are critical illness (as judged by the treating physician), including unconscious patients, patients who were noncompliant in terms of excessive movement during the VS measurements, and patients whose parents, guardians, or carers do not speak English (required to give informed consent). The study aims to recruit according to age, sex, Fitzpatrick skin tone, and medical history criteria, as subsequently described.

The research nurse approaches the parents, guardians, or carers of potential participants identified by the clinical team about taking part in the study. Potential participants aged 17 or 18 years or the parents, guardians, or carers of younger children are provided with an ethics-approved information sheet explaining the study aims, what is involved, and the requirements for participation. Younger children also watch ethics-approved age-appropriate videos (for ages 5-10 and 11-16 years) explaining the study on a tablet device (Multimedia Appendices 4 and 5).

The information sheet and videos were developed in collaboration with the Young People Advisory Group North England and the South Tyneside and Sunderland NHS Foundation Trust Young Persons Group. These groups also provided feedback on the design of the study, consent/assent forms, and other study documents at 2 in-person meetings.

Study Procedures

Demographic data (age, sex, ethnicity, skin tone [Fitzpatrick 6-point scale [24] ranging from type 1 for skin that always burns to type 6 for skin that never burns]) are recorded on an electronic case report form using the Castor electronic platform. Medical history questions are limited to the presence or absence of conditions that might affect skin perfusion and pigmentation, cardiovascular processes, and any prescription medicines for these conditions.

The study staff records a set of premeasurement observations and the presence or absence of sweat on the participant's face; any facial hair on the cheeks; tattoos, jewelry, birthmarks, scars, or other features on the face; the use of foundation or concealer; and the position of the participant (seated, prone, supine or lying on one side).

Patients may also be recruited into 1 of 3 subprotocols depending on premeasurement observations (Table 1).

The study staff ensures that participants have been at rest for at least 10 minutes before VS measurement starts (which can include the period of data collection described previously).

Table 1. Subprotocols.

	Subprotocol	Description
1	Blood pressure measurement	Blood pressure will be measured at the same time as other vital signs using standard of care equipment (sphygmomanometer) in participants who are able to cooperate and stay relatively still
2	Electrocardiogram	A 3-lead electrocardiogram will be recorded to assess heart rate variability in a representative subset of participants (based on age, skin tone, and illness; see Table 3)
3	Questionnaire	Guardians, parents, or carers and children will be asked to complete a questionnaire about their preferences for Lifelight-type technologies versus standard of care methods for measuring vital signs

In each study session, VS is measured as per the subprotocol using the SOC equipment, while simultaneously capturing a video of the participant's face using the Lifelight Data Collect app running on a tablet (standard iPad). This app is a research tool that captures and uploads video data to secure cloud storage for research purposes only and is distinct from the CE-marked Lifelight medical device developed from data collected from previous studies. The Data Collect app does not display any VS estimates and is not used for clinical interpretation or analysis.

In each study session, at least 2 VS (PR, oxygen saturation, RR) and temperature are measured twice over a 60-second period using SOC equipment and methods.

A standard clinical finger clip sensor for the measurement of oxygen saturation and PR is placed on a finger. Oxygen saturation and PR are measured at 0, 30, and 60 seconds of the recording period and averaged.

RR is determined by counting chest rises throughout the 60-second period. The nurse may place their hand on the participant's chest to improve the accuracy of counting while being mindful not to obscure the camera's line of sight.

At the same time, a video of the participant's face (and torso in children younger than 5 years of age) and audio is captured for up to 3 minutes using the Data Collect app running on a tablet positioned approximately 1 meter away and angled toward the participant's face. Background luminosity is measured automatically. Recording is started and stopped by the research nurse via the iPad.

A maximum of 3 attempts at recording measurements is made. Once measurements have been completed, the study staff fill in postmeasurement questions relating to how much the participant moved, their position, whether they were wearing glasses, any hairstyle or other item (eg, face covering) that obscured any part of their face during the recording, and whether the app reported "face not found" at any point during the recording.

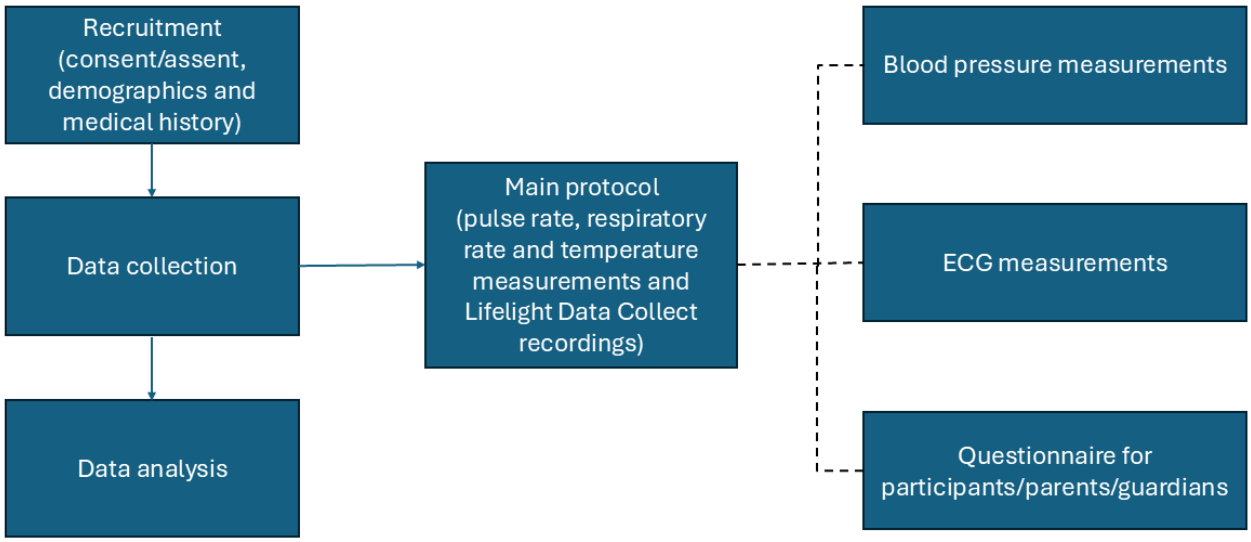
A questionnaire is also available to garner feedback on the technology from the clinical user's point of view (ie, the nurses who take the VS measurements). Questionnaire data are fully anonymized and recorded without any identifiable information.

Each study session, including approaching the participant, obtaining consent, and performing the study procedure takes about 30 minutes. Participants were not followed up after the VS measurements but continued to receive clinical care as appropriate for their condition.

Subprotocols

Participants are recruited into 3 subprotocols as appropriate (Table 1). Subprotocols 1 and 2 may be run concurrently with the main protocol if the research nurse considers it practical to also record BP and an electrocardiogram (Figure 1).

Figure 1. Study flow and data collection. BP: blood pressure; ECG: electrocardiogram.



Ethical Considerations

The study is being performed in accordance with the spirit and the letter of the Declaration of Helsinki, the Good Clinical Practice Guidelines, and the protocol and applicable local regulatory requirements and laws. The VISION-Junior protocol was approved by the Health Research Authority and Health and Care Research Wales (IRAS reference 321956) and the Newcastle North Tyneside Research Ethics Committee on March 30, 2023. Informed consent is obtained electronically using Castor eConsent, a secure NHS-compliant platform. Informed consent is provided by participants aged 16 years and older and by the parent, guardian, or carer of younger children. Children younger than 16 years of age are also given the opportunity to sign an assent form. As the study is noninterventional, participants will not receive financial compensation for participation but may be offered small incentives such as stickers or certificates. Participation in the study is entirely voluntary, and participants may withdraw from the study at any time. Specific, explicit written consent was obtained from all individuals featured in the videos provided in Multimedia appendices 4 and 5, permitting use for publication purposes.

Privacy and Data Collection

Each study participant is assigned a unique sequential patient identifier; no identifiable data are stored. All documents are stored securely and can only be accessed by study staff and authorized personnel. The code linking the patient identifier to their personal information is kept within the hospital study site and can only be accessed by the research team within that site.

For each reading, a high-quality video of the face (and torso in young children) and an audio file are saved to the internal storage of the iPad in encrypted form and transmitted directly

to the sponsor's NHS-compliant cloud server. Files were automatically deleted following upload to the server.

All data collected about participants during the study will be kept strictly confidential and handled according to the General Data Protection Regulations. Videos and audio recordings collected during the study constitute personal data as it may be possible to identify participants. Full-resolution, full-face, or torso video data are required to develop Lifelight Junior into a clinically useful device; the analysis cannot be performed using blurred videos. The data collected for research purposes only (not clinical care) are processed within the legitimate interests of Xim Ltd.

Data Handling

Analysis of the videos uses the encrypted files, which, in most cases, are processed automatically within a secure cloud infrastructure (ie, without any person viewing the videos); in rare cases, it may be necessary to analyze a video manually if the recording is not as expected. The analysis results in anonymized aggregate datasets. No decrypted files are stored at any point in the processing. The electronic case report forms are stored and managed using the Castor electronic cloud.

Performance Targets

While Lifelight is certified as a class I CE medical device [18], the performance of Lifelight Junior needs to be appropriate for routine clinical practice in pediatric patients. Table 2 lists the performance targets for Lifelight Junior for measuring VS in pediatric patients; training data collected during VISION-Junior will support progress toward these targets.

Table 2. Performance targets in VISION-Junior.

Vital sign	Performance target	Reference
Pulse rate	Root mean square error ≤5 beats per minute	[25]
Respiratory rate	Maximum error of 5 breaths per minute for 100% of measurements	Minimum standard met by all approved respiratory monitors
Oxygen saturation	Maximum error tolerance 4%	[26]

Sample Size

An estimated 500 pediatric patients (18 years old or younger) will be recruited into the study. This sample size is informed by the previous VISION-D, VISION-MD, and VISION-Acute studies [17,21]. However, the sample size cannot be formally calculated because it depends on the incremental improvement in the performance of the app achieved through machine learning using the training data generated early in the study. The split between training and testing data will be determined during the study according to the quality of the data collected. The study management team monitors the progress of data collection and accuracy and updates the study teams weekly. The study will continue until the accuracy of the app for measuring VS in pediatric patients is sufficient for various clinical use cases.

In addition, recruitment targets according to age, sex, Fitzpatrick skin tone, and medical history have been defined, as shown in Table 3, to ensure accuracy in a broad range of clinically relevant patients.

Table 3. Demographic and medical history recruitment targets.

	Targets
Age	≥12% aged 0-1, 1-2, 2-5, 5-11, 11-14, 14-18 years
Sex	≥40% male; ≥40% female
Skin tone	15% of participants will have Fitzpatrick skin tones 4, 5, or 6 (this is not a hard target as achieving this figure depends on the demographic diversity of the study region)
Medical history	≥40% in each of the following categories: • Febrile (≥38 °C) • Afebrile • Ill (as judged by the clinical staff); to ensure a spread of conditions, no more than 50% of recruited patients will have an acute respiratory illness (eg, bronchiolitis, asthma, virus-induced wheeze, pneumonia, and croup) • Well, including pediatric patients with a minor injury

Data Analysis

All statistical analyses will be performed using Python (Python Software Foundation). Training data will be used for machine learning to improve the performance of Lifelight Junior for measuring VS in pediatric patients. Appropriate machine learning models will be developed according to the data collected. This is likely to include signal processing and measurement algorithms for PR and RR, and multilayer neural network-based approaches for BP, similar to those used in the adult version of the app.

The separate set of test data will subsequently be used to determine the performance of the app for measuring VS in pediatric patients. Correspondence between VS measurements predicted by the app and the measurements taken manually using SOC methods will be compared using regression coefficients, mean error, and SD, and compared against the

performance targets set out in Table 2. An accuracy target will be considered met if the mean error and SD for the app measurements are at least equal to the target (Table 2). Heat maps or scatter plots will also be developed.

Linear regression will be used to assess the impact of skin tone on the accuracy of the app for measuring each VS, using the Fitzpatrick skin tones as the explanatory variable.

Quantitative data from the questionnaires will be summarized. Thematic analysis will be used to analyze free-text responses to identify perceptions of the app and variations in the way patients, their parents or carers, and health care professionals interact with it and any challenges they encounter.

All analyses will be completed per protocol since there is no intention to treat. There will be no imputation of missing or implausible data, and any missing, implausible, or problematic readings will be excluded from analysis.

Results

The study started on June 12, 2023, and as of December 20, 2023, had recruited 303 participants. The study was extended until the end of March 2024 to enable the target recruitment (500) to be met; 532 participants had been recruited as of April 5, 2024.

Data are currently being used for machine learning to refine the algorithms to improve clinical accuracy. We anticipate that final analyses to determine the performance of the app against the targets set out in Table 2 will be complete by mid-August 2024. The performance of the app will be determined across the range of VS values encountered in children in clinical practice by comparing the VS values recorded using PPG versus standard methods.

Discussion

Principal Findings

This paper reports the protocol for obtaining data to develop algorithms for the measurement of VS in children using the app, and to evaluate the performance of the app against SOC measurement of VS in pediatric patients of all ages.

Monitoring of VS in children is challenging because existing methods (eg, BP measurement via an arterial line or cuff; PR and RR via electrodes, adhesive pulse oximeters, and adhesive temperature probes and thermometers) are either invasive or contact-based and can cause discomfort, pain or distress, may disturb sleep, and may damage paper-thin skin, potentially increasing the risk of infection. Frequent VS measurement using different techniques is also resource-intensive. The app being developed will provide contactless noninvasive measurement of VS.

Data collected in this and other studies will be used to train algorithms to develop the app for the measurement of VS in pediatric patients. The app aims to provide a risk-measured way for nonexperts to measure VS quickly and nonintrusively, and therefore, detect any early signs of deteriorating health or infection. This will make it easier for clinically vulnerable or immunocompromised children to attend school and interact with their peer groups, meeting their mental, physical, social, and educational needs, whilst providing reassurance to parents, guardians, or carers. Early detection of infection before any significant clinical deterioration occurs means that treatment can start sooner, improving the likelihood of a full recovery [27] whilst also potentially avoiding hospital admission and intensive care, which are expensive for the child's family (lost income, expenses) and health care providers. Lifelight can also be an effective tool for at-home monitoring and triage, reducing the burden on carers, emergency services, and hospitals. It may also be useful in nonspecialist health care settings such as primary care and prehospital care where specialist pediatric equipment is not available. Several other devices for the measurement of VS are currently being developed but all require physical contact, whether through a finger, the wrist, or the chest, and only one (Biospectral) is able to measure BP.

Limitations

This research may have some limitations. BP is inherently more complex to measure than PR and RR, in terms of the data form and machine learning and because reference measurements are less accurate. As with any recording device, signal quality may be compromised if the participant moves excessively or if light levels are insufficient. However, we expect the use of high-resolution video recording to overcome such issues. In addition, measurements can be easily repeated if a recording is of poor quality.

Skin type is a potential source of error with PPG devices, as melanin absorbs green light, potentially increasing errors in measurements in dark-compared with light-skinned individuals [24]. However, we have already shown that skin type does not affect the accuracy of Lifelight [17]. Although the Fitzpatrick Skin Type Scale is the current gold standard [24], its use has been criticized because of racial bias, weak correlation with skin color, and broad within-group variations in skin tone. Spectrocolorimetry, which uses multiple variables to categorize skin tone objectively, has been proposed as an alternative [24], which may be incorporated into later studies to confirm our findings.

Conclusions

The results of this study will be disseminated via submissions to relevant journals and conferences. The study team will explore different avenues and formats for the dissemination of the study findings with the Young People Advisory Groups and other groups to ensure a wide public audience, for example, through coproduced public talks, studies in community communications, and social media.

Acknowledgments

Study activities conducted at the South Tyneside and Sunderland National Health Service Foundation Trust are funded by an Invention for Innovation (i4i) Connect award, awarded to Xim Limited by the National Institute for Health and Care Research (NIHR204468). The authors would like to thank Kirsty Parker of Xim Ltd for helping to set up the study, Prof Alison McConnell for advice on child physiology, Lieke van Putten for data analysis, and Helen Barham (The Text Doctor) for writing support (funded by Xim).

Data Availability

The datasets generated or analyzed during this study are not publicly available due to their commercially sensitive nature, as mandated by Xim Limited's grant funders and investors, but are available from the corresponding author upon reasonable request.

Authors' Contributions

The VISION-Junior protocol and patient-facing documents were developed by NM, LF, GS, MK, GM, JF, JH, and IM and informed by the Young Persons advisory group North East (YPAGne) and the South Tyneside and Sunderland National Health Service Foundation Trust Patient and Public Involvement group. Statistical methods were developed by MK.

Conflicts of Interest

MK and GM are employees of Mind over Matter Medtech, which provides contracted services to Xim Limited, including grant bid writing, clinical trial design and management, health economic analysis, and regulatory submission support. However, the company has never contributed directly to the technical design or development of Lifelight and has not received benefits from Xim Limited other than financial payment for contracted work. SW and JF are employed by Xim Limited, the manufacturer of the technology. IM and JH have received compensation from the manufacturer for advisory services and have no conflicts of interest. NM, LF, and GS were responsible for facilitating the study and have no conflicts of interest.

Multimedia Appendix 1
Questionnaire to collect data from participants in the VISION-Junior observational pediatric study in order to improve the usability of the Lifelight app.
[DOCX File , 31 KB - resprot_v14i1e58334_app1.docx]

Multimedia Appendix 2
Questionnaire to collect data from parents/guardians/carers of participants in the VISION-Junior observational pediatric study in order to improve the usability of the Lifelight app.
[DOCX File , 32 KB - resprot_v14i1e58334_app2.docx]

Multimedia Appendix 3
Questionnaire to collect data from health care practitioners conducting the VISION-Junior observational pediatric study in order to improve the usability of the Lifelight app.
[DOCX File , 20 KB - resprot_v14i1e58334_app3.docx]

Multimedia Appendix 4
Participant information video (ages 5-11) explaining the VISION-Junior observational pediatric study process to prospective participants before consent.
[MP4 File (MP4 Video), 103294 KB - resprot_v14i1e58334_app4.mp4]

Multimedia Appendix 5
Participant information video (≥11 years old) explaining the VISION-Junior observational pediatric study process to prospective participants before consent.
[MP4 File (MP4 Video), 73685 KB - resprot_v14i1e58334_app5.mp4]

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Abbreviations

BP: blood pressure
CE: Conformité Européenne
NHS: National Health Service
PPG: photoplethysmography
PR: pulse rate
RR: respiratory rate
SOC: standard of care
VISION-D: Measurement of Vital Signs by Lifelight Software in Comparison to the Standard of Care—Development
VISION-V: Measurement of Vital Signs by Lifelight Software in Comparison to the Standard of Care—Validation
VISION-MD: Measurement of Vital Signs by Lifelight Software in Comparison to the Standard of Care—multisite development
VS: vital signs

Edited by A Schwartz; submitted 19.03.24; peer-reviewed by U Sinha, R Medina-García; comments to author 29.06.24; revised version received 19.08.24; accepted 06.12.24; published 14.03.25.

Please cite as:
Misra G, Wegerif S, Fairlie L, Kapoor M, Fok J, Salt G, Halbert J, Maconochie I, Mullen N
The Measurement of Vital Signs in Pediatric Patients by Lifelight Software in Comparison to the Standard of Care: Protocol for the VISION-Junior Observational Study
JMIR Res Protoc 2025;14:e58334
URL: https://www.researchprotocols.org/2025/1/e58334
doi:10.2196/58334
PMID:

Protocol

Establishing a Digital Health Care Ecosystem in a Health Sciences University in South Africa: Protocol for a Mixed Methods Study

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Abstract

Background: Comprehensive and formalized digital health care ecosystems in health sciences tertiary education in South Africa do not currently exist, but they have the potential to influence teaching and learning, research, and community engagement.

Objective: A total of 3 key objectives underpin the study, that is, determining the health care curriculum needs and required content for the development of a formalized digital health ecosystem, determining the level of readiness of staff and students to participate in a digital health care ecosystem, and determining whether community engagement and strategic partnerships can contribute to the sustainability of a digital health care ecosystem.

Methods: A multipronged approach will be used to address the objectives, with a mixed methods design being undertaken. The qualitative phases will be phenomenological in nature, and triangulation of information along with thematic analysis will be conducted on the collected data. Quantitative data will be collected prospectively and cross-sectionally and analyzed using descriptive analysis. Sampling will include subject experts for the Delphi technique, staff and students at the University, clinical training and education partners, and community leaders. This study has received ethical approval from the Sefako Makgatho Health Sciences University Research and Ethics Committee (SMUREC/H/260/2023:PG).

Results: Data collection for the first phase will begin in January 2024 and conclude in December 2024. Phase 2 and 3 of the study will be conducted concurrently, with data collection starting in January 2025 and concluding in December 2026.

Conclusions: The establishment of a digital health care ecosystem has the potential to benefit staff, students, and communities through stakeholder collaboration, educational opportunities, research projects, and improved service delivery.

International Registered Report Identifier (IRRID): DERR1-10.2196/57821

(JMIR Res Protoc 2025;14:e57821) doi:10.2196/57821

KEYWORDS

health sciences; digital ecosystem; curriculum; community engagement; tertiary education institutions

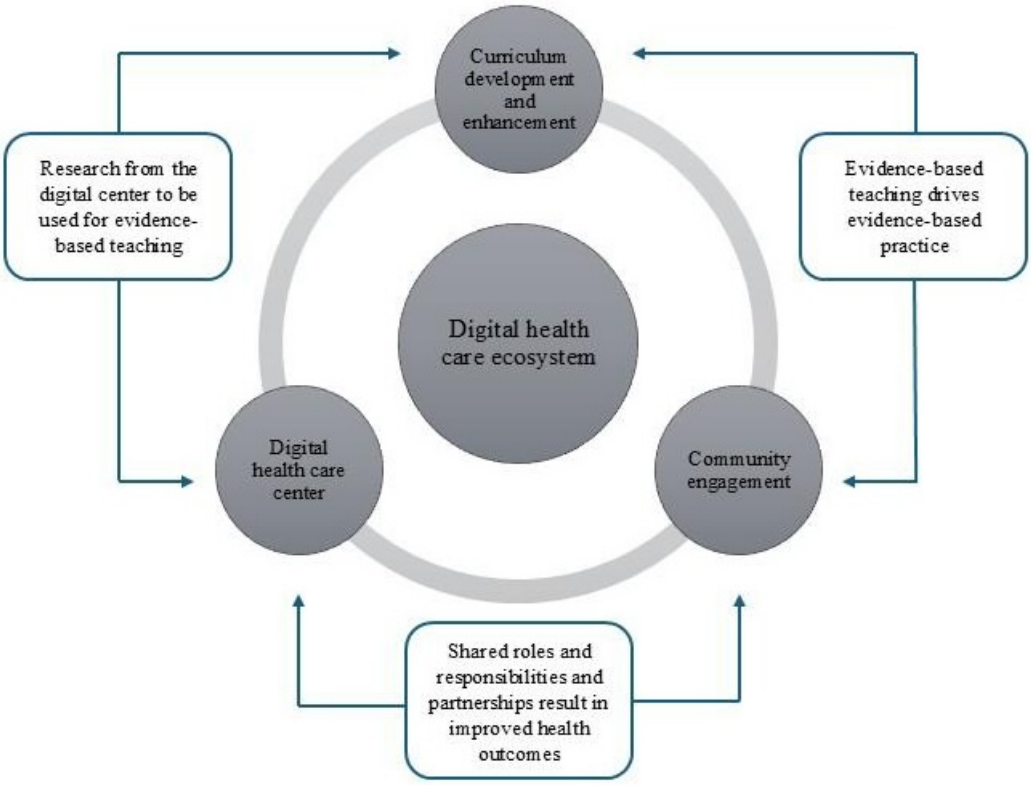
Introduction

Digital health care ecosystems are described as patient-centric models of health care delivery with the aim of encouraging collaborative, cross-organizational health care processes through technology-driven platforms [1]. The use of telecommunications and digital technologies to provide health care, monitor public health, and develop new and improved methods of delivering awareness programs is referred to as digital health care [2]. According to the World Health Organization (WHO) [2], "digital health" is a global term that encompasses concepts such as electronic health, telehealth, wearable devices, mobile health, and new developments in the field of artificial intelligence to support public health systems. The definition also includes the use of electronic patient and medical record keeping.

The benefits of digital health care are extensive, including serving populations in rural and remote areas with interventional and preventative care [3], the collation and pooling of medical data, and the organized and confidential management of patient records [2]. However, despite these benefits, there is evidence to suggest that health care professionals (HCPs) are inadequately trained to effectively use technology within the health care space [4-6]. This issue is especially true in the African context [7]. Despite Africa accounting for 23% of the global burden of disease, the continent has not optimized digital health care technologies to address challenges in health care service delivery [7]. South Africa has been passive in its efforts to ensure that HCPs are adequately trained. The COVID-19 pandemic highlighted the lack of preparedness in digital health care, which has been attributed to insufficient exposure to digital health care training during the tertiary education training of HCPs [8,9]. This is important because the lack of digital health care competencies and skills could pose significant challenges to the health care industry. Potential challenges that may arise from a lack of digital health care skills include reduced efficiency [10], ineffective use of digital health care tools [11], reduced patient satisfaction due to low HCP confidence [12], increased risk of errors [13], and lack of globally relevant skills [7].

Challenges faced by the health care system and universities during the pandemic were threefold [8,14,15]. First, staff and students were not well trained or competent in providing digital health care to patients. Second, some universities were not well invested in digital health care infrastructure. Third, the acceptance of communities to receive care via digital technologies was uncertain, considering the lack of consultation and stakeholder engagement [8,14,15]. It becomes apparent that countries, through their health care systems and tertiary training institutions, need to do the following three things: First, create, construct, and integrate curricula that align with the needs of a new era of HCPs. Second, provide the necessary infrastructure to allow student learning and clinical training opportunities within the digital health care space. Finally, to actively engage with communities to ensure their integration, involvement, and acceptance of digital health care services. The combination of these 3 elements creates what is referred to as a digital health care ecosystem [16]. Therefore, the objectives of the study were threefold: first, determining the health care curriculum needs and required content for the development of a formalized digital health ecosystem; second, determining the level of readiness of staff and students to participate in a digital health care ecosystem; and third, determining whether community engagement and strategic partnerships can contribute to the sustainability of a digital health care ecosystem. Figure 1 illustrates the envisaged digital health care ecosystem (Figure 1).

Figure 1. Digital health care ecosystem.



Methods

Study Design

A multiphase study, consisting of a mixed methods approach (ie, qualitative and quantitative designs) will be undertaken. The quantitative phases of the study will follow a prospective, cross-sectional design [17], while the qualitative phases will be phenomenological in nature, aiming to explore the experiences of participants [18]. The methodology for each of the 3 phases will be presented separately.

Phase 1: Developing and Obtaining Accreditation for a Digital Health Care Curriculum

During phase 1 of the study, the researchers aim to address 3 subobjectives to meet the main objective of this phase. The 3 subobjectives will be discussed separately, as their design and data collection procedures differ (Textbox 1).

Textbox 1. Curriculum development.

Subobjective 1

Determining digital health care content and gaps in the current curriculum using gap identification frameworks when reviewing and analyzing curricula within a Health Care Sciences School.

- **Study design:** A quantitative, retrospective document review will be undertaken.
- **Sample:** A total of 6 published curricula from the Departments of Physiotherapy, Occupational Therapy, Human Nutrition and Dietetics, Nursing Sciences, and Speech-Language Pathology and Audiology will be included for review. Curricula from other departments or those that have not been published will be excluded from the review.
- **Data collection:** Each curriculum will be reviewed by the research team using the READ approach. The competencies, skills, and attitudes questionnaire [19] will be used to capture the data. Descriptive statistics will be applied to analyze the data.

Subobjective 2

Investigating the knowledge, skills, attitudes, and graduate attributes to be included in a digital health curriculum for students in a Health Care Sciences School.

- **Study design:** A prospective Delphi technique [19] will be undertaken.
- **Sample:** Potential participants for the Delphi expert panel will be identified through author and reference lists that will be compiled from a literature review, as well as referrals from academic directors and members of the academic community. To ensure diversity and representativeness in the participant group, a purposive sampling method will be used. Expert panel members will be considered for inclusion if they have published at least 2 or more papers or book chapters on digital health care, and if they are health care professionals. Experts with competing interests (such as digital health care company owners) will be excluded from participation.
- **Data collection:** Experts in digital health care (both national and international) who meet the eligibility criteria will be invited to participate in the study. Email invitations will be sent to all identified experts to participate in the Delphi study. Once consent is obtained, the first round of the survey will be sent via a Google link. Participants will have the option to add additional topics not included in the first-round survey, which will be added in the second round. After the first round, participants will be provided with the average ratings for each topic from the previous round. The second and third rounds will involve rating, scoring, and reaching a consensus on the survey items. An 80% agreement will be considered as consensus.

Subobjective 3

Developing a digital health care curriculum for a Health Care Sciences School in terms of module outcomes, content, teaching strategies, assessment outcomes, and submitting for evaluation and accreditation.

- **Study design:** An action-based approach to curriculum development will be undertaken [20].
- **Sample:** Task-team members, consisting of the researchers participating in the study will be included.
- **Data collection:** Information collected from the document review and the Delphi technique will be combined to establish the syllabus. A curriculum matrix will be developed based on the syllabus and will be populated with learning outcomes, assessment criteria, and assessment methods. The curriculum will be developed in accordance with the guidelines of the Health Professions Council of South Africa and the Council of Higher Education (South Africa). Once the curriculum is approved, it will be implemented. After six months of implementation, it will be assessed and changes will be made as needed.

Phase 2: Developing a Teaching, Learning, Clinical, and Research Center Situated Within a Health Care Sciences School

The second phase of the study aims to address 2 subobjectives in order to achieve the main objective for the phase (Textbox 2).

Textbox 2. Establishing a digital health care center.

Subobjective 1

Conducting a readiness and needs analysis among staff and health care professionals regarding digital health care training needs.

- **Study design:** A quantitative, prospective survey design will be undertaken.
- **Sample:** All staff members associated with a Health Care Sciences School at a selected university will be included. Staff members will be selected for participation if they are part-time or full-time academic staff in the following departments: Physiotherapy, Occupational Therapy, Human Nutrition and Dietetics, Nursing Sciences, and Speech-Language Pathology and Audiology. To ensure a 50% distribution with a 5% margin of error and a 95% CI, 184 participants are required. All staff members in the School of Health Care Sciences will be targeted for inclusion to account for noncompletion of surveys and attrition during the study.
- **Data collection:** After obtaining permission from the Dean, an email with information and consent forms will be sent to all relevant staff members in the school. The questionnaire will be adapted from Bingham et al [21]. The link to the questionnaire will be emailed to all academic staff members. Once a questionnaire has been completed, access to the questionnaire will be terminated to prevent multiple submissions from the same participant. Descriptive analysis will be conducted on the collected data.

Subobjective 2

Developing a care services plan for the digital health care center and reviewing and consulting on existing technology and business plans to develop and validate the proof of concept for the establishment of a digital health care ecosystem.

- **Study design:** A qualitative explorative design will be undertaken.
- **Sample:** Snowball sampling will be conducted with at least 6 academic staff members from each department (refer to subobjective 1 for the list of departments), and data collection will cease once saturation is reached. Academic staff members with experience in clinical planning and involvement in health services programs will be included.
- **Data collection:** Staff members will be invited to participate in focus group interviews after obtaining permission from the Dean. A focus group interview schedule with open-ended questions will be used. The interviews will be voice-recorded and transcribed verbatim. Thematic analysis will be conducted using Tesch's eight-step model [22].

Phase 3: Evaluation of the Impact of Community Engagement in the Design, Establishment, Content, and Delivery of Digital Health Promotion Projects Offered Through the Digital Health Care Ecosystem

The third and final phase of the study is divided into 2 subobjectives (Textbox 3).

Textbox 3. Community engagement.

Subobjective 1

Evaluating the health needs of the local community.

- **Study design:** A cross-sectional, descriptive survey design will be undertaken.
- **Sample:** All relevant community stakeholders, including medical doctors, traditional healers, community leaders, and community health workers, will be considered for inclusion in the study. Purposive and network sampling will be used to identify as many relevant parties as possible for inclusion in the study. All community stakeholders, who have resided in the community surrounding the institution where the study will be conducted for at least 2 years, will be included. Community stakeholders with a conflict of interest (such as financial interests in the project) will be excluded from participation.
- **Data collection:** Known community stakeholders will be recruited for participation, and network sampling will be used to identify as many stakeholders as possible. Questionnaires will be circulated electronically to all participants. The questionnaires will be an adapted version of the Cooper University Health Care Health Assessment Survey [23]. Once a questionnaire is completed, access will be terminated to prevent multiple submissions. Descriptive analysis will be conducted on the collected data.

Subobjective 2

Exploring digital health care attitudes and service suggestions of shared roles and responsibilities of community members that can be implemented through digital health care in the specific community.

- **Study design:** A qualitative explorative design will be undertaken.
- **Sample:** All relevant community stakeholders (as given in subobjective 1) will be considered for participation. Purposive and network sampling will be used to identify as many relevant parties as possible for inclusion in the study. Data collection will cease once saturation is reached.
- **Data collection:** Community stakeholders will be invited to participate in focus group interviews, using a schedule with open-ended questions. The interviews will be recorded and transcribed verbatim. Thematic analysis will be conducted following Tesch's eight-step model [22].

Recruitment

The population from the institution and its surrounding areas will be recruited for the study. Staff and students from the health sciences institution will be recruited from the following departments: Departments of Physiotherapy, Occupational Therapy, Dietetics and Human Nutrition, Public Health, Nursing Sciences, and Speech and Language Pathology and Audiology. The student population will consist of undergraduate students who are enrolled at the Health Sciences institution. All part-time and full-time staff members employed at the institution, who do not have a financial interest in participating, will be included in the study. Community stakeholders recruited for the study will be restricted to a 30-kilometer radius from the institution. Recruitment will be conducted through email communication, flyer distribution within the institution and surrounding community, and word of mouth.

Statistical Analysis

Due to the vast nature of the study, statistical analysis will vary for each subobjective. Quantitative data will be analyzed using SPSS (version 27; IBM Corp) software, while qualitative data will be analyzed using NVivo (Lumivero). To ensure optimal analysis of the qualitative data, Tesch's eight-step method of data analysis will be conducted before uploading the data into NVivo. Data will be prepared by transcribing all interviews verbatim. Coding will be conducted on data segments that share similar themes. Thereafter, categories and coding schemes will be developed based on the identified themes from a sample of the text. The coding scheme will first be tested on a relatively small sample to ensure that the scheme is applicable before being applied to the entire dataset. A researcher, who will not be involved in the initial development of the coding scheme, will assess coding consistency, after which conclusions will be drawn from the coded data [22].

Data Exclusion

For all quantitative phases of the study, data will be excluded from analysis if the dataset is incomplete (ie, if questionnaires are not fully completed). Data from all phases of the study will also be excluded if participants withdraw voluntary informed consent.

Validity and Reliability

The questionnaires that will be used in this study are adapted from previously developed and tested questionnaires, with additional questions drawn from the literature [19,21,23]. The content validity of the questionnaires will be conducted to ensure that the questionnaires have a fair representation of the constructs to be measured. Construct validity will be ensured by providing evidence that the theoretical structure of the questionnaire is relevant. Face validity will ensure that the questionnaire is transparent and relevant, as it appears to elicit information from the participants. A pilot study will be conducted with the aim of ensuring that the data collection tools are reliable. Construct and face validity will be determined by asking 10 health care professionals from different institutions across the country to provide feedback to the researchers. Health care professionals will be identified through purposive sampling to ensure that they have the necessary expertise regarding digital health care. Reliability will be determined by assessing whether the questionnaires answer the stated research questions, whether the questions are clear and unambiguous, and whether the language and terminology used are easy to understand. Following the pilot study, the questionnaires will be revised if needed.

Trustworthiness

Credibility will be ensured by building rapport and trust with the participants. The participants will be engaged in interviews to gain insights and understand their views. The researchers will ensure that honesty is maintained by giving information regarding the study to the participants. Dependability will be ensured by making the voice recorder and transcripts available to an external auditor for verification. Conformability and credibility will be ensured by conducting interviews until saturation is reached. Transferability is the ability to transfer research findings from one context to another [24]. The researchers will provide a thorough description of the research methods and setting in the research publications or any form of dissemination so that the applicability of the data to another context can be evaluated.

Ethical Considerations

As human participants will be used during the course of the study, ethical approval for the conduction of the study was obtained from the Sefako Makgatho Health Sciences University Research and Ethics Committee (SMUREC/H/260/2023:PG). Participants in all phases of the study will be provided with information pertaining to the phase that they are participating in, before being asked to sign a voluntary informed consent. Participants hold the right to withdraw from the study without providing reasons, and without prejudice. All data collected will be anonymized to ensure participants' privacy, and data will be stored in an encrypted electronic folder accessible only to the researchers. During the dissemination of results, the researchers will ensure that no identifying information is published. Participants in the study, regardless of the phase, will not receive remuneration for their participation. The research will be conducted in line with the regulations set forth by the Declaration of Helsinki.

Results

Phase 1 of the study will be conducted from January to December 2024. The second and third phases will be conducted concurrently, from January 2025 to December 2026. A detailed schedule of the study is provided in Table 1 below.

Table 1. Projected time frames of the study.

Phase	Subobjective	Timeline
1	To determine digital health care content and gaps in the current curriculum by applying the gap identification framework when reviewing and analyzing curricula within a Health Care Sciences School.	January-June 2024 (completed)
1	To investigate which knowledge, skills, attitudes, and graduate attributes should be included in a digital health curriculum for students in a Health Care Sciences School.	April-October 2024 (completed)
1	To develop a digital health care curriculum for a Health Care Sciences School, in terms of module outcomes, content, teaching strategies and assessment outcomes, and submit it for evaluation and accreditation.	October-December 2024 (completed
2	To conduct a readiness and needs analysis among staff and health care professionals regarding digital health care training needs.	January-April 2025
2	To develop a care services plan for the digital health care center and to review and consult on existing technology and business plans to develop and validate proof of concept for the establishment of a digital health care center within a Health Sciences School.	May-December 2025
3	To evaluate the health needs of the local community.	January-June 2025
3	To explore digital health care attitudes and service suggestions, as well as shared roles and responsibilities of community members that can be implemented through digital health care in the specific community.	July-October 2026
4	Final write-up of all information collected in the study	October-December 2026

Discussion

Principal Findings

The establishment of digital health care ecosystems in tertiary institutions has the potential to have a significant positive influence on health care delivery in a country [2-6]. To successfully establish a digital health care ecosystem, it is essential to develop relevant curricula. Curricula represent an institution's vision and mission and are expected to be contextually relevant and globally responsive to the diverse needs of communities [25]. A digital health care curriculum will ensure the long-term viability of such ecosystems, and studies have shown that both academics and students agree that the integration of digital health ecosystems is long overdue [26,27]. The proposed changes to the curricula will inevitably alter clinical training opportunities for students to ensure the development of digital health care competence.

The introduction of clinical digital health care training into formal education allows students to participate in areas such as interprofessional education, offering care to rural and remote areas (including exposure to international contexts), as well as improving their digital literacy and awareness of trends within the Fourth Industrial Revolution [8,28,29]. Literature indicates that the theoretical and practical components are connected and their combination ensures that students acquire not only the knowledge but also the clinical skills, competencies, attitudes, and important graduate attributes to provide excellent patient care [30,31].

In the development of digital health care curricula and clinical training, partnerships with community stakeholders are important to ensure that the integration of technology will empower community members [32]. Communities must be involved in the conceptualization, technology innovation, development, implementation, and monitoring of the health care system to ensure health care democracy and sustainability [32,33]. Well-structured community engagement has the potential to minimize the gap between research and policy by ensuring support from key stakeholders [34]. In addition, community involvement is an essential aspect of good health governance [35].

Due to the geographical limitations of the study (ie, recruitment of participants from a 30 km radius of the institution where the study will be conducted), the results that are obtained from the study may not translate to other health care institutions. However, the principles followed in the design and establishment of the digital health care ecosystem may be universally applicable.

Conclusions

The establishment of a comprehensive digital health care ecosystem will be used for providing digital health care knowledge, conducting clinical training with students using a variety of digital health care approaches and technology, and conducting research into digital health care. The center aims to encourage stakeholder collaboration, provide educational opportunities, stimulate research, and provide service delivery using digital health care services. Important activities, such as interprofessional collaboration and community engagement, will be facilitated through the establishment of a digital health care ecosystem. The center would offer multidisciplinary and transdisciplinary health care services to multiple rural and remote contexts, including schools, old age homes, hospitals, and homes.

Data Availability

Datasets generated or analyzed during the study are available from the corresponding author on reasonable request.

Authors' Contributions

SG contributed to conceptualization, funding acquisition, methodology, writing—original draft. MEC handled conceptualization, methodology, writing—original draft. MM assisted with formal analysis, methodology, visualization, writing—review and editing. RG contributed to investigation, methodology, writing—review and editing. TT handled project administration, visualization, writing—review and editing.

Conflicts of Interest

None declared.

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Abbreviations

HCP: health care professional
WHO: World Health Organization

Edited by A Schwartz; submitted 27.02.24; peer-reviewed by C Janse van Vuuren, H Alshawaf, K Slater; comments to author 09.08.24; revised version received 19.08.24; accepted 21.11.24; published 25.03.25.

Please cite as:
Govender S, Cochrane ME, Mogale M, Gordon R, Tshephe T
Establishing a Digital Health Care Ecosystem in a Health Sciences University in South Africa: Protocol for a Mixed Methods Study
JMIR Res Protoc 2025;14:e57821
URL: https://www.researchprotocols.org/2025/1/e57821
doi:10.2196/57821
PMID:

Protocol

The Utility of a Smartphone-Based Retinal Imaging Device as a Screening Tool in an Outpatient Clinic Setting: Protocol for an Observational Study

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Abstract

Background: Glaucoma, a disease leading to the degeneration of retinal ganglion cells, results in changes to the optic nerve head that are often diagnosed late when visual problems arise. With the prevalence of glaucoma surpassing 76 million adults worldwide and with glaucoma being the leading cause of irreversible blindness in the world, the early detection and management of glaucoma is imperative. Digital ophthalmoscopes, such as the D-EYE (D-EYE, Srl), have emerged as a technology that uses smartphone cameras with an attachment on the lens to visualize the retina and optic nerve head without the need for dilation. The purpose of this pilot study is to examine the acceptability and feasibility of a D-EYE digital ophthalmoscope to screen for ocular pathology involving the optic nerve, particularly glaucoma.

Objective: This study aimed to demonstrate the effect of a smartphone-based ophthalmoscope as a potential vision screening tool for optic nerve head pathology in participants enrolled in this study. The first specific aim was to determine the ability of the D-EYE smartphone ophthalmoscope to gather high-quality imaging to be used for grading the fundus into low- and high-risk categories for eye pathology. The second specific aim was to determine the difference in the quality of data capture between still retinal images and 30-second retinal video recordings produced by D-EYE smartphone ophthalmoscopes.

Methods: This observational pilot study enrolled 110 patients receiving routine eye care at the University of Florida Health from February 2019 to February 2022 to assess the use of the D-EYE device in capturing still images and 30-second videos of the bilateral retina and optic nerves of each participant. Study participants completed a survey to gather demographics and past medical history data with a particular focus on previous eye health history. Images were reviewed by 5 ophthalmology residents with interrater reliability analysis performed to assess findings.

Results: Ophthalmology resident review indicated greater visualizability and clarity of the bilateral retina and optic nerves with 30-second videos of retinal imaging compared with still-image ophthalmic capture. Furthermore, an increase in visualizability and clarity allowed for a more accurate measurement of the cup-to-disc ratio, a diagnostic marker for glaucoma. In addition, the likelihood of referral of the glaucomatous and healthy sample groups to ophthalmologists indicated a greater sensitivity of digital ophthalmoscopes in being able to detect retinal abnormalities requiring early intervention and management, supporting the technology's use as a screening tool.

Conclusions: This investigation suggests that the use of smartphone-based digital ophthalmoscopes can be more effectively applied as a screening tool by capturing 30-second videos compared with still images alone. This novel assessment of an emerging technology in the field of ophthalmology may better equip further research as smartphone camera technology advances.

International Registered Report Identifier (IRRID): DERR1-10.2196/52650

(JMIR Res Protoc 2025;14:e52650) doi:10.2196/52650

KEYWORDS

digital health; digital ophthalmoscope; ophthalmology; smartphone-based; mobile health; applications; screening tool; retinal imaging device; glaucoma; eye disease; visual problems; ophthalmoscope; ocular disease; cost-effective; mobile phone

Introduction

Vision Screening and Digital Ophthalmoscopes

Vision screening is a valuable component of health maintenance as loss of vision may lead to severe impairment in everyday tasks, such as driving, ambulating, reading, and social participation [1,2]. Glaucoma, the second leading cause of permanent blindness in the United States, is the acquired loss of retinal ganglion cells within the optic nerve, resulting in the progressive loss of peripheral vision [3,4]. The 2 most common types of glaucoma in the United States are primary open-angle glaucoma and primary angle-closure glaucoma, with most patients presenting asymptomatically until the optic nerve damage is severe enough [5]. It was estimated that by the year 2020, over 3 million adults would have glaucoma in the United States with nearly half not knowing that they have the disease [6].

Existing methods of screening for glaucoma involve comprehensive eye examinations performed by ophthalmologists. Often, patients who are at a higher risk for eye pathologies, such as glaucoma, do not participate in such screening efforts, and even when diagnosed, do not attend follow-up visits for complete eye examinations to monitor the progression of the disease. This is especially true for patients in low-income socioeconomic demographics. A study examining poor longitudinal glaucoma follow-up in India found that, adjusting for age and sex, independent predictors of poor follow-up included lack of formal education, lack of escort, and belief that follow-up is less important if one has no noticeable visual changes [7]. In addition, studies at a tertiary hospital eye department found various social and demographic factors contributing to poor adherence to follow-up, as patients who are African American or Latino, or who live far from their eye care provider are at a greater risk of nonadherence to follow-up appointments [8]. Studies performed in 3 major hospital departments found that patients presenting with advanced glaucoma are more likely to come from an underprivileged area and be of lower occupational class, to have no access to transportation, and to have a lower education level [9]. Factors such as income, education, ethnicity, and lack of transportation suggest an association between low socioeconomic status and prevalence of eye disease as well as lack of follow-up for eye health appointments.

With vision loss from glaucoma being irreversible and there existing a multitude of barriers to follow-up, early detection and management of the disease is imperative and solidifies a need for easily accessible, highly sensitive diagnostic technology. In a study assessing the comparison of smartphone ophthalmoscopy with slit-lamp biomicroscopy for grading vertical cup-to-disc (CtD) ratio (VCDR) on 110 patients, smartphone ophthalmoscopy showed substantial agreement with slit-lamp examination for the estimation of the VCDR [10]. This success in the estimation of VCDR can be used for glaucoma screening in low-resource environments. When compared with the use of a traditional direct ophthalmoscope, a 2018 Nature publication found that smartphone ophthalmoscopy produced more accurate clinical descriptions of findings in a fundal examination than direct ophthalmoscopy [11]. In addition, the study suggested that the use of a smartphone-based alternative to the direct ophthalmoscope may improve the accuracy and quality of fundal examinations by nonophthalmologists [11]. Implementation of smartphone ophthalmoscope technology may potentially be an effective way to screen patients for diseases of the eye within primary care clinics. Such an intervention would address the loss of follow-up to specialty ophthalmology clinics for complete ophthalmologic examinations in low socioeconomic status patients with eye disease. Early intervention may allow for the timely, evidence-based management of eye disease and prevent late-stage morbidities such as progressive loss of vision and permanent blindness.

Specific Aims

This study aimed to demonstrate the effect of a smartphone-based ophthalmoscope as a potential vision screening tool for optic nerve head pathology, particularly glaucoma, in participants enrolled in this study.

- Specific aim 1: to determine the ability of the D-EYE (D-EYE, Srl) smartphone ophthalmoscope to gather high-quality imaging to be used for grading the fundus into low- and high-risk categories for eye pathology
- Specific aim 2: to determine the difference in quality of data capture between still retinal images and 30-second retinal video recordings produced by D-EYE smartphone ophthalmoscopes.

Methods

Participants

This pilot study will use an observational research design to assess the ability of the D-EYE to capture high-quality imaging that can be interpreted by ophthalmologists. Furthermore, the study will investigate the difference in quality of imaging between still images and 30-second videos of the retina for clinical use based on ophthalmology resident feedback. Trained research assistants who are familiar with the protocol for recruitment and eligibility to participate in this study will recruit patients in coordination with medical staff at their respective clinical sites.

The sample population will consist of 110 adults between the ages of 18 and 99 years (N=110). University of Florida (UF) Health Eye Center is the designated site where this study will be conducted.

Criteria to participate in this study include being a patient currently seen at the UF Health Eye Clinic and being between the ages of 18 and 99 years. The study will exclude patients matching the criteria such as loss of vision, blind patients, patients who require urgent procedures or are otherwise deemed unstable by medical staff, and patients with photosensitivity that prevents prolonged exposure to bright lights.

Participant data will be blinded from resident graders for review, and their existing medical records will provide a reference to determine the accuracy of interpretation from the ophthalmologist's review and offer insight as to the quality of imaging and preferred modality based on the reported interpretability and accuracy of the 5 resident reviewers.

Recruitment

Participants will be recruited in the study under the title, "The Utility of a Smartphone-Based Retinal Imaging Device as a Screening Tool in an Outpatient Clinic Settings." After identifying eligible participants for this study, trained research assistants will approach and recruit them. If these eligible participants are interested, a trained study member will review and obtain consent directly from the participant. A standardized informed consent script will be adhered to ensure consistency in the consenting process. Participants will receive a copy of the informed consent document.

Procedure

Research assistants, working in coordination with medical staff, will identify and determine the eligibility of patients entering the UF Health Eye Center for medical care. Consent will be obtained directly from the participants.

Before collecting the retinal imaging data, participants will complete a survey that provides pertinent demographic data, past medical history, and ophthalmology-specific questions regarding whether or not they have a diagnosed eye condition. After completion by the study participants, the paper files will be stored in a secured holding unit in accordance with the UF Institutional Review Board's guidelines.

Next, participants will have their retinal imaging collected by trained research assistants using the D-EYE. The D-EYE is a US Food and Drug Administration (FDA)–approved smartphone ophthalmoscope that was used over the course of this study. It is capable of gathering high-quality images and videos of the retina. The eye exam will occur in a low-lit room. Bilateral eyes will be examined by the D-EYE for 25-35 seconds. This footage will then be temporarily stored in the D-EYE encrypted app, along with the patient's medical record number and the patient's known eye pathologies (if any). The smartphone camera attachment is compatible with the D-EYE app, a Health Insurance Portability and Accountability Act (HIPAA)–compliant smartphone app. From the D-EYE app, the images collected (both still images and 30-second videos) can be uploaded to a UF-affiliated, secured Dropbox (Dropbox Inc.) that has been approved for data storage. The D-EYE smartphone app requires either a 4-digit password login, fingerprint scan, or face ID to access. Video and image recordings will not be stored on the device capturing the images but will be housed on the HIPAA-compliant UF Dropbox account.

The UF Dropbox cloud-hosting service will only be accessible to study personnel and resident ophthalmologists who are required to view the retinal imaging. Access to the UF Dropbox requires logging into the UF Health VPN and accessing the site through a password combination containing uppercase letters, lowercase letters, numbers, and punctuation marks.

The footage taken by the D-EYE will be reported to UF Ophthalmology residents through Dropbox. Five residents will then grade each fundus image based on (1) the clarity of the footage on a scale of 1-10 (still image vs 30-second videos), (2) whether the residents would refer the participant to an ophthalmologist for eye care, (3) whether to categorize the sample into the "healthy" or "unhealthy or needs care" category, and (4) if there are any optic neuropathies (glaucoma) present, stratifying the findings as either low, moderate, or high risk. Their responses will be cross-referenced with the patient's known eye history and the responses will be categorized as either hits, type I misses (resident lists as unhealthy but history suggests the eye is healthy), or type II misses (resident lists healthy but history suggests the eye is unhealthy).

Outcomes Measures

Certain listed measures will be collected for all participants. All data will be stored through a secured, university-affiliated Dropbox account approved by the Institutional Review Board, a HIPAA-compliant and university-supported app used for data capture and storage.

Primary Outcomes

Image Quality

The clarity of both the still images and 30-second videos will be rated on a scale of 1-10. Accuracy in determining CtD measurement will be assessed between the still imaging and 30-second videos with a determination of any differences in quality and measurements of data between the still images and 30-second videos.

Categorization

Based on the imaging results, the ability of residents to categorize participants' retinal imaging into either broad "healthy" or "unhealthy or needs care" groups.

Likelihood for Referral

Based on the imaging results, the residents will assess whether or not they would refer participants to an ophthalmologist for further specialized eye care.

Stratification

If there are any detectable optic neuropathies present, they will be stratified into either low-, moderate-, or high-risk groups based on the extent of the disease.

Secondary Outcomes

Interpretability

Assessment of eye health will be grouped into either hits, type I misses (resident lists findings as unhealthy but history suggests the eye is healthy), or type II misses (resident lists findings as healthy but history suggests the eye is unhealthy).

Interrater Agreeability

Assessment of the level of agreement between independent resident ophthalmology graders regarding the image quality, categorization, likelihood for referral, and stratification of retinal images (still images and 30-second videos) captured from the D-EYE camera attachment.

Statistical Analysis

The information collected from the study consists of categorical data, distinguishing between accuracy and inaccuracy. The authors will be performing an interrater reliability test using the Cohen coefficient for each of the ophthalmology residents making a diagnosis. This will provide the authors with a level of agreement. All tests will be 2-sided and *P* values <.05 will be considered statistically significant.

To test the first aim, the authors will have 5 ophthalmology residents grade D-EYE images on a scale of 1-10 for clarity for the use of low-risk and high-risk stratification. Low-risk and high-risk stratification will be judged based on the likelihood that the resident will refer the patient to a specialist. Their grades will then be averaged, the SD will be calculated, and interrater reliability will be determined. Furthermore, the authors will test the extent to which clarity can be used for making a diagnosis. They will ask the residents to make a diagnosis and compare their judgments to existing patient history. These results will be stratified into hits, type 1, or type 2 misses. These will be used to calculate proportional variability (PV; PV+ and PV) values. Interrater reliability will also be calculated.

Ethical Considerations

This study, which includes human participant research, was approved by the Institutional Review Board of the Florida Department of Health (UFIRB201801242). The informed consent forms used in this study provide participants with a description of the study, its qualitative and quantitative measures, potential risks and discomforts, and explicitly ask the participants for a voluntary agreement to participate and allow their data to be collected. To maintain privacy and confidentiality protection, study data are de-identified as all participants are assigned a numerical code. This code follows the format of OC001. Anonymity of all study participants is ensured. No compensation of any sort is offered to the human participants. This is stated in the informed consent form. No identification of individual participants is present in any images of this paper or any supplemental material.

Results

A total of 110 participants underwent retinal screening assessments using the D-EYE attachment to iPhone 7 (Apple Inc). Both still images and 30-second videos of the participants' bilateral fundi were captured and were then compared in order to assess the clarity and quality of the imaging.

The D-EYE video footage showed the ability to achieve optic nerve head visualization with an overall proportion of 0.827 being visualized by graders. This was a notable improvement compared with still images, where graders were only able to visualize the optic nerve head with an overall proportion of 0.752. As such, video footage captured by the D-EYE suggests efficacy compared with previously established tools, and when combined with portability and cost, it may prove to be a useful clinical tool for physicians who want to assess optic nerve head health. One previous study that assessed the D-EYE showed that still imaging was possible in 74% of undilated cases [11]. This research corroborates this finding and also suggests that more consistent and better visualization could be achieved through the use of video rather than still imaging.

The intraclass correlation coefficient found when comparing grader CtD assessments was 0.576, thus suggesting statistically significant consistency in analysis across graders. Literature on interobserver agreement of VCDR has found moderate agreement between 6 glaucoma experts (median weighted of 0.67) while using stereoscopic conditions [11]. Compared with standard-of-care technology, D-EYE video footage suggests comparable efficacy in making CtD measurements.

Discussion

Based on the review of 110 participants' fundal imaging by ophthalmology residents, the pilot study indicated greater visualizability and clarity of 30-second videos of retinal imaging through the D-EYE as compared with still-image ophthalmic capture. Furthermore, the CtD measurement was more reliably measured in the 30-second video group. In addition, the likelihood of referral between the glaucomatous and healthy sample groups indicated a greater sensitivity of digital ophthalmoscopes in being able to detect retinal abnormalities, supporting the technology's use as a screening tool. Participants noticed no change in compliance or pain associated with either of the methods used in the study.

By comparing grader assessments of the overall health of the eye (measured as a likelihood of referral) with self-reported glaucoma status by participants, the authors aimed to ascertain whether D-EYE video footage could be used to provide valuable judgments on the need for additional ophthalmic care. The use of this technology, based on the results, shows that this tool has similar value as specialized ophthalmology examinations in assessment for glaucoma. With vision loss from glaucoma being irreversible and the prevalence of glaucoma rising worldwide, implementation of this easily accessible, highly sensitive diagnostic technology could provide a multitude of health benefits while addressing any barriers to health care.

One primary limitation in the study design is the subjectivity that is associated with grading fundus images by ophthalmologists. This study attempts to limit that by operating with the input of 5 ophthalmologists grading each image acquired in an effort to reach a fair conclusion for each fundus image.

Integration of D-EYE technology into clinical settings confers advantages such as portability and steadily decreasing costs. This study has found that still images taken by the D-EYE are not yet clear enough to provide consistent optic nerve head visibility. Video footage, however, shows not only the ability to provide optic nerve head visualization, but also to assess important health metrics that can be useful both within ophthalmology clinics and in primary care settings. Future research should be aimed at assessing D-EYE efficacy in a larger population.

Acknowledgments

Thanks to the work of Dr Siva Iyer, MS, and Dr Sonal Tuli, Equal Access Research's research assistants, and the UF Health System that this study was made possible. Generative artificial intelligence was not used in any portion of the paper writing.

Data Availability

The data sets generated during and/or analyzed during this study are available from the corresponding author on reasonable request.

Conflicts of Interest

None declared.

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Abbreviations

CtD: cup-to-disc
FDA: US Food and Drug Administration
HIPAA: Health Insurance Portability and Accountability Act
PV: proportional variability
UF: University of Florida
VCDR: vertical cup-to-disc ratio

Edited by A Mavragani; submitted 11.09.23; peer-reviewed by C Baxter, Y Wang; comments to author 02.01.24; revised version received 25.03.24; accepted 02.04.24; published 25.03.25.

Please cite as:
Mittal A, Sanchez V, Azad NS, Zuyev Y, Robles R, Sherwood M
The Utility of a Smartphone-Based Retinal Imaging Device as a Screening Tool in an Outpatient Clinic Setting: Protocol for an Observational Study
JMIR Res Protoc 2025;14:e52650
URL: https://www.researchprotocols.org/2025/1/e52650
doi:10.2196/52650
PMID:

Protocol

Conversion of Sensitive Data to the Observational Medical Outcomes Partnership Common Data Model: Protocol for the Development and Use of Carrot

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Abstract

Background: The use of data standards is low across the health care system, and converting data to a common data model (CDM) is usually required to undertake international research. One such model is the Observational Medical Outcomes Partnership (OMOP) CDM. It has gained substantial traction across researchers and those who have developed data platforms. The Observational Health Care Data Sciences and Informatics (OHDSI) partnership manages OMOP and provides many open-source tools to assist in converting data to the OMOP CDM. The challenge, however, is in the skills, knowledge, know-how, and capacity within teams to convert their data to OMOP. The European Health Care Data Evidence Network provided funds to allow data owners to bring in external resources to do the required conversions. The Carrot software (University of Nottingham) is a new set of open-source tools designed to help address these challenges while not requiring data access by external resources.

Objective: The use of data protection rules is increasing, and privacy by design is a core principle under the European and UK legislations related to data protection. Our aims for the Carrot software were to have a standardized mechanism for managing the data curation process, capturing the rules used to convert the data, and creating a platform that can reuse rules across projects to drive standardization of process and improve the speed without compromising on quality. Most importantly, we aimed to deliver this design-by-privacy approach without requiring data access to those creating the rules.

Methods: The software was developed using Agile approaches by both software engineers and data engineers, who would ultimately use the system. Experts in OMOP were used to ensure the approaches were correct. An incremental release program was initiated to ensure we delivered continuous progress.

Results: Carrot has been delivered and used on a project called COVID-Curated and Open Analysis and Research Platform (CO-CONNECT) to assist in the process of allowing datasets to be discovered via a federated platform. It has been used to create over 45,000 rules, and over 5 million patient records have been converted. This has been achieved while maintaining our principle of not allowing access to the underlying data by the team creating the rules. It has also facilitated the reuse of existing rules, with most rules being reused rather than manually curated.

Conclusions: Carrot has demonstrated how it can be used alongside existing OHDSI tools with a focus on the mapping stage. The COVID-Curated and Open Analysis and Research Platform project successfully managed to reuse rules across datasets. The approach is valid and brings the benefits expected, with future work continuing to optimize the generation of rules.

International Registered Report Identifier (IRRID): RR1-10.2196/60917

(JMIR Res Protoc 2025;14:e60917) doi:10.2196/60917

KEYWORDS

data standardization; OMOP; Observational Medical Outcomes Partnership; ETL; extract, transform, and load; data discovery; transparency; Carrot tool; common data model; data standard; health care; data model; data protection; data privacy; open-source

Introduction

In health research, there are dozens of standards that can be used to represent data, and a recurring challenge surrounding the adoption of existing standards versus the creation of yet more. The retrospective adoption of standards is conceptually simple but is much harder to implement in datasets that are still actively collecting new data. Clearly, if everyone adopted a single standard from the start of all data capture, then such a problem would not exist; the reality of course is very different and data handling practices still vary considerably between research projects and health care organizations. The Observational Medical Outcomes Partnership (OMOP) Common Data Model (CDM) [1,2] is an international open community standard to standardize the schema and contents of the data by using a standardized vocabulary and medical terminology into clinical domains of OMOP CDM. As a concept, the ability to map between a research ontology, such as the International Classification of Disease (ICD) and Systematized Nomenclature of Medicine Clinical Terms (SNOMED-CT), with a single representation within the vocabulary is of immense value [3]. For an organization with data that are not in OMOP, there will always be an effect required to convert the data from the source standard to the OMOP CDM.

The Observational Health Care Data Sciences and Informatics (OHDSI) [4] program collates a suite of open-source tools [5,6] that can assist in the process of the extract, transform, and load (ETL) stages to convert data from the original format to OMOP. There are also tools that can assist in finding the most appropriate concept to use from the vocabulary using a similarity search [7]. Therefore, tools and options do exist that can assist in the conversion of data to the OMOP common standard. However, if the organization either does not have the knowledge or the capacity to undertake the conversion, the “final mile challenge” can be significant. White Rabbit [6] can profile the data and produce a metadata extract. Rabbit-in-a-Hat [5] can allow a data engineer to capture the required transformations in note form. What is missing, though, is an end-to-end process and the conversion of the outputs into actionable code. At present, an individual would most likely generate an SQL command or software script to convert the data based on the interpretations of the Rabbit-in-a-Hat output. This would require local expertise to create. Organizations may have a desire to adopt or curate data to a single standard, but the local capabilities do not always exist.

The European Health Care Data and Evidence Network (EHDEN) [8] is a Horizon IMI program established to help with this gap that funds approved organizations to work with data owners to convert their datasets to OMOP. This is a competitive process that will support datasets that can bring the most value to the wider OHDSI [4] consortium for data sharing. Not all datasets will qualify for support from EHDEN given its finite resources (it clearly cannot support every project seeking to transform to OMOP), and as so, it has eligibility criteria on the periodic calls it makes for support [9].

Most ETL processes work based on having access to the data at the time of designing the conversion, and indeed, the OHDSI tools run on the source data; allow notes to be curated for how data should be converted; and typically require manual development of scripts to convert data from source to OMOP. This approach relies on a team having access to the data, which may not for privacy reasons be desirable in relation to health care and sensitive research datasets. Some organizations may be cautious in allowing external organizations with OMOP knowledge access to core systems and data to undertake the ETL process. In many cases, this will involve setting up legal agreements such as data sharing or confidentiality agreements or generating pseudonymized versions of the data, which are often lengthy and complex tasks.

While, OMOP offers significant power and opportunity as a unifying standard, allowing differences in terminology to be mapped to a single standard, it does suffer from the challenge that curating data to OMOP can still be quite an art form with different curators taking different approaches. The vocabulary used within the OMOP CDM can be downloaded from the website Athena [10]. There is not a single vocabulary set to use, and therefore, the curators may have preferred vocabularies to represent the data. The vocabulary is also periodically updated resulting in a concept changing domains between releases, such as from being in the Observation domain to the Clinical Occurrence domain. The consequence is that someone curating the data today may make a different decision in the future because the vocabulary has changed. The vocabularies in Athena are in English, and therefore, a base assumption of Carrot is that English is the language in use.

The FAIR (Findable, Accessible, Interoperable, and Reusable) principles [11] are a globally accepted set of standards to promote best practices in datasets. CDMs can aid datasets to become interoperable, as they standardize all data to a single model. However, in the quest for interoperability, it is important that the provenance of the data is not lost when it is converted, as there is a risk of an illusion being created because data from multiple organizations are the same. Therefore, while converting

data to OMOP can assist in making data FAIR, as it simplifies many of those challenges, it cannot be at the expense of understanding how data have been converted to OMOP.

There are many existing mechanisms to map and covert data [12-14] to the OMOP CDM, and those processes are well established. This paper does not seek to suggest the work presented here is better than any existing processes and protocols. The processes described here were in response to a specific set of constraints, such as limited availability of technical staff members, a desire to create a FAIR resource as a consequence, and most importantly that access to data was not available in most circumstances.

In this paper, we introduce Carrot, a software tool that aims to address these difficulties—namely the governance requirements around bringing OMOP expertise to the datasets, variations between individual curators within the OMOP framework, and the gap between current OHDSI tooling—while also automating as much of the process as possible. Carrot enables curators to map data to OMOP without needing access to the underlying data. This allows a central team of OMOP experts to undertake data curation of many datasets to enhance quality control and standardization while fulfilling a desire to ensure this central team never has access to data that would be in the scope of General Data Protection Regulation (GDPR). Separating the specialized OMOP knowledge from the application of the ETL process allows reduced and shortened governance work, saving data owners time and money in converting their datasets.

Similarly, Carrot provides tooling to guide curators toward standardization of their used OMOP terms wherever possible and automates much of the ETL process. In solving these challenges, Carrot brings reproducibility and transparency to the OMOP data curation process to assist datasets in meeting the increasing FAIR requirements.

Methods

Development Principles

The Carrot tools were developed using the Scrum Agile methodology [15] to deliver minimum viable products of each component followed by iterative development to expand the functionality over time. The team consisted of data engineers, OMOP experts, research software engineers, clinical academics, and patient and public representatives. All tools were made available via an MIT license [16] and hosted in GitHub repositories [17,18].

Privacy-by-Design Principles

The data held by an organization, referred to as a data partner, are identifiable personal data and within the scope of the Data Protection Act 2018 [19]. As such, we wanted to ensure the team undertaking the data mapping never had access to the underlying data and only operated on metadata that were outside of the scope of data governance regulations. Throughout the process, the only people to have access to or process personal data were the data partners. Such an approach was low risk and ensured privacy-by-design and data minimization principles were strictly followed.

Two software packages were created to separate the data conversion from the creation of transformation rules. The first software package was to handle the creation of mapping rules based solely on the metadata. This tool is called Carrot-Mapper [17,20]. The second software package was designed to reside within the data partner's network and use the rules to convert the data. This tool was called Carrot-CDM [18]. This approach defines two separate processes: one process to create the rules for mapping and a separate process that takes those rules and applies them to the data.

Reuse and Reproducibility

FAIR principles seek to ensure the required metadata are captured across the 4 categories of FAIR. Our desire is to embed these same principles into the design of Carrot such that the mappings generated were also FAIR. A key requirement of the software is that mappings from one dataset can assist in the mapping of another, reducing wasted effort. For example, significant work was undertaken in the United Kingdom to standardize questionnaires in response to COVID-19 that were used across many national cohorts [21], that way many different research cohorts agreed to use the same questionnaire rather than each creating their own to gather data from their participants related to COVID-19. Therefore, we wanted to ensure that once the questionnaire had been mapped for one data partner, it can be instantly applied to other datasets. Over time the efficiency can be increased as the mapping rules from previous work can be used in new work.

Data curation to a new standard could be considered an art form, as each individual undertaking such an activity may do so in a different way. As an artist may have a signature brush stroke, it is also true that data engineers will have their preference for how to convert data to OMOP. Therefore, to promote reproducibility our key principle was to minimize individual decision-making and the development of a standardized pipeline that produces the same results after each execution. That process was supported by features designed to provide feedback to the user regarding any curation issues compared with previously mapped datasets (see Mapping Standardization Tools section below).

Process Architecture

Overview

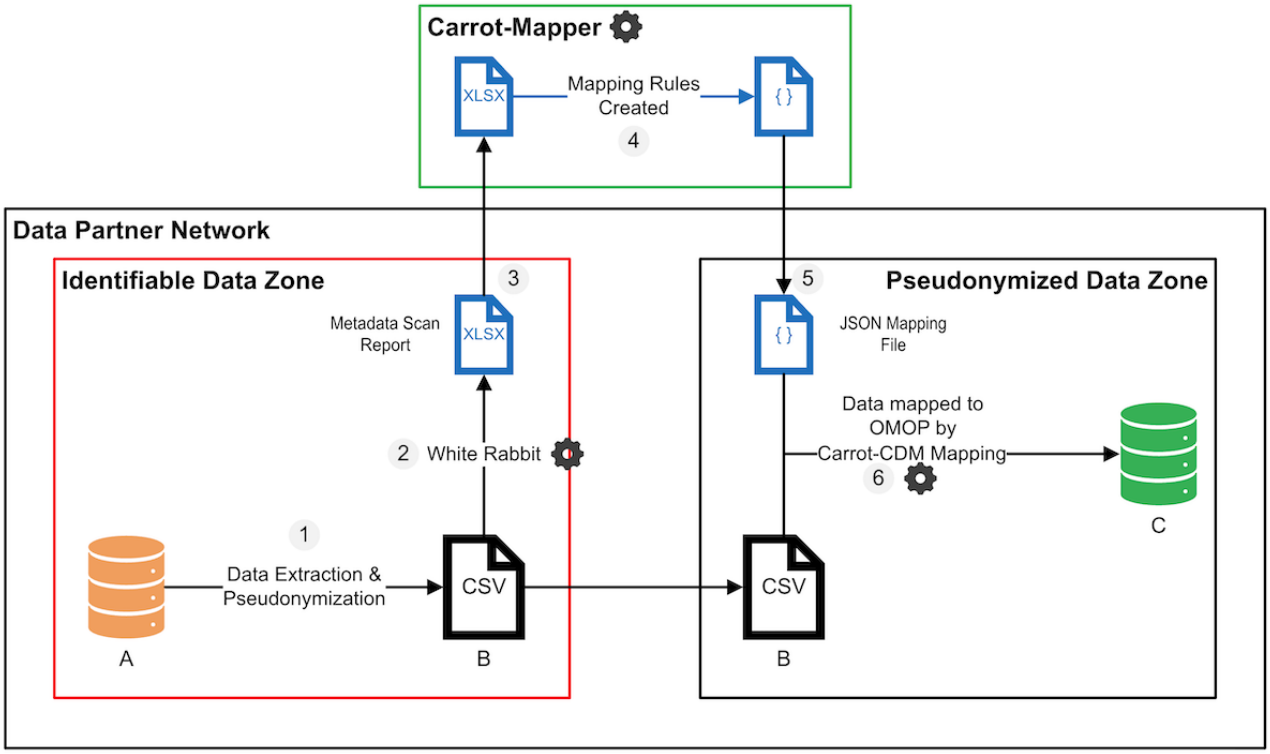
The mapping rule generation web application Carrot-Mapper is built using the Django Python web framework (Django Software Foundation), with the React JavaScript library for user interfaces, and PostgreSQL database. These are supported by serverless Azure Functions written in Python for asynchronous processing of the large amounts of data ingested with each new file upload. The Carrot-Mapper web application automatically deploys via GitHub Actions to Microsoft Azure infrastructure with each new release.

The minimal Carrot pipeline consists of 6 steps that are illustrated in Figure 1: (1) preprocess data to remove identifiable data and apply the standards in [22], (2) generate metadata report via White Rabbit [6], (3) transfer metadata file to Carrot infrastructure, (4) generate rules using Carrot-Mapper, (5) transfer rules to system housing data, and (6) use Carrot-CDM

to apply generated rules to transform pseudonymized data to OMOP standard.

Note that Carrot-Mapper and Carrot-CDM handle steps 4 and 6, respectively, of the above pipeline. The formats of the metadata report and mapping rules file are open, ensuring that data partners have the option to implement their own drop-in solutions instead of one or the other software tools to fit their own infrastructure if desired. The Carrot team runs a central deployment of Carrot-Mapper, which can be used by multiple projects. A private instance of Carrot-Mapper can also be run within the data partner's infrastructure, although this reduces the utility of the system as it cannot draw on existing mapping rules generated for previous datasets and nullifies some of the benefits of reduced governance requirements. We ask all data partners to check the metadata and the contents of the scan reports to validate that no identifiable or personal data leaves the data partner's network at any time.

Figure 1. Carrot pipeline overview. (A) The raw, identifiable dataset. (B) Deidentified data. (C) The OMOP standardized deidentified dataset. OMOP: Observational Medical Outcomes Partnership.



Minimizing Input From Data Partners (Step 1)

Each data partner remains responsible for the management of their data, including generating a pseudonymized and deidentified extract. There are some preprocessing steps that they must perform to use the tool, but we have minimized the workload on each data partner. In order to simplify the later steps of conversion to OMOP, we also ask the data partner to follow the steps at [22] under "Data Preparation," namely, presenting the data in a series of CSV files, with one CSV containing demographic data, all measurements in the metric system, dates and date times in the ISO-8601 format, digit grouping symbols removed, decimal numbers rounded to a maximum of 2 decimal places, CSV files encoded with UTF-8 and Unix and Linux line endings; and CSV file names limited to 30 characters.

The data partners do have a vital role in ensuring their data is represented correctly and all local insight is maintained during the process. What we have sought to minimize at this stage is the involvement of technical teams and to remove that burden.

Generating Metadata (Step 2)

The pseudonymized dataset held within the data partner's infrastructure (as generated by step 1 of the above 6-step process) is profiled by the open-source White Rabbit [6] data profiling tool, resulting in a metadata file known as a scan report. Alternatively, the scan report can be generated by hand or by other tools, so long as the resulting scan report file (an Excel file containing multiple sheets) has the correct structure.

The scan report details the tables and fields of the dataset, along with values present in each field. The Carrot data standards [22] instruct the data partner in the correct setup of the White Rabbit tool to ensure identifying data is not inadvertently present in the scan report. This includes setting the "Minimum Cell Count" to at least 5 to reduce the probability of possibly reidentifying conditions being included. The scan report should then be checked to remove any remaining data values that could be deemed confidential or sensitive.

A data dictionary may be optionally supplied. This can provide (1) vocabularies associated with certain fields and (2) descriptions of values when the field names and values are not self-explanatory. As an example, it would be possible to specify that a column contains SNOMED values. As the system is using

the contents of the Athena system for OMOP, 18 existing vocabularies (eg, SNOMED-CT [23], ICD v9 [24], and Healthcare Common Procedure Coding System [25]; Multimedia Appendix 1) can be specified. The structure of the data dictionary is defined on the Carrot standards page [22].

Importantly these scan reports can also be used by the data partner to register the datasets within publicly available metadata repositories, such as the Health Data Research Gateway [26]. In doing so, we continue our theme of reducing the burden and ensuring one process can result in many benefits.

Uploading Scan Report and Data Dictionary Files (Step 3)

Both the scan report and optional data dictionary files are then transferred to the OMOP experts. The OMOP experts upload the scan report file and optional data dictionary file to Carrot-Mapper via a web form. This creates a new scan report instance within the system, with the user able to specify accompanying settings such as the project and dataset to which the scan report belongs, and the visibility and access to the scan report for other users. See the Users and Projects section below.

Upon upload of the scan report file (which can take a few minutes to process large and complex datasets), the Carrot-Mapper tool records all tables, fields, and values within the scan report file. This enables users to visually navigate the structure of the dataset within the mapping tool for the purposes of manual mapping (below) via the browser.

Each scan report has a status field that can be used to track the progress of the scan report upload and the manual mapping process, using the statuses “Upload in Progress,” “Upload Complete,” “Upload Failed,” “Mapping 0%,” “Mapping 25%,” “Mapping 75%,” “Mapping Complete,” and “Blocked.” This status field is automatically updated and can also be set manually from the main scan reports list page, for example, to progress through the stages from “Mapping 0%” to “Mapping Complete.”

The centralized system allows previous mapping rules to be reused. For example, assume a field “Sex” is provided with the value “M,” and this has previously been manually mapped to the OMOP concept 8507 “Male” in one scan R=report. In the case where a later scan report is uploaded with another field “Gender” and the value “M,” the system automatically applies the previous mapping rule to this value in this field in the new scan report. In this way, the utility of the system increases over time, as mapping rules are saved, and the manual effort required to generate mapping rules is reduced. This is particularly the case where a new scan report is supplied that describes a dataset that has been previously partially mapped, or where multiple datasets adhere to a shared standard. Only mappings from scan reports marked with the status “Mapping Complete” are eligible to be considered for reuse. This mechanism allows trusted and verified rules to be replicated, while works in progress are not mined for rules to apply to new scan reports. This mapping reuse algorithm runs at the time when a scan report file is first uploaded. The limitation is that it can only reuse rules when the column name is an exact match and the value is also an exact match. It has no intelligent processes to either translate from languages (such as Spanish to English) or to auto-correct for potential spelling mistakes (“Gendar” to “Gender”).

Additionally during this initial upload process, there is the automated mapping from recognized vocabularies. In the case where an entry in the data dictionary indicates that a field is encoded in a recognized vocabulary, the system will automatically create mappings to the (possibly multiple) standard and valid OMOP concept codes associated with each source code. Some scan reports can contain thousands of unique values in such fields, and as such, this feature can save days of repetitive and error-prone work for OMOP experts.

Throughout this stage, it is always clear how a rule was generated, whether it was manual, a reuse of an existing rule, or using the OMOP in-built relationships (such as mapping ICD to SNOMED). The interfaces of Carrot indicate this as M for manual, R for reuse, and V for vocabulary-based rule generation.

Generating Rules (Step 4)

Carrot-Mapper has been created as a web-based tool to assist in the generation of rules. A core reason for establishing a central tool for creating rules is that they can then be reused across projects and datasets. However, the requirement that Carrot-Mapper support rule reuse, and thus mappings related to multiple datasets be stored in a single location, also necessitates user authentication and granular permissions to control access to uploaded data (see Users and Projects section below for more details).

Once a scan report file has been uploaded and processed, manual mapping can proceed. The OMOP expert can navigate the contents of the scan report, organized in a hierarchical manner. The system allows the user to select a field or value and mark it with the desired target OMOP concept codes, as well as remove any incorrect codes (including reviewing those generated through vocabulary lookup or mapping rule reuse in step 3 above). At any stage in the mapping process, the user can see a summary view of the mapping rules currently extant and review, discuss, and remove any mapping rules. Once a user is satisfied that they have mapped all of the required fields and values, they can set the scan report status as “Mapping Complete,” which also makes the mapping rules defined in that scan report available for reuse by other scan reports. Mapping rules can be exported in CSV format (for human readability and review) or in JSON format for ingestion into the Carrot-CDM ETL tool at the next stage of the pipeline.

Mapping Rule Generation

Rules are generated using internal logic to minimize the work required from a user who wishes to add a new rule. Each table must have one field identified by the user as a “Person ID” field and one field as “Date Event,” which can be defined via the web application. For every field and value, the user can input the target OMOP concept ID. The web application handles this by looking up the OMOP ID in the OMOP database to access the OMOP term. This term is then mapped to a valid term and the related domain. These data points (valid term, domain, person ID, and date event) are sufficient to define a mapping rule. This feature removes some of the technicalities of OMOP

from view, allowing the user to focus purely on the most accurate OMOP representation of the data.

Transfer Mapping Rules to Data Partner Network (Step 5)

The mapping rules JSON file, as exported in the previous step, is transferred into the data partner's network. These are the only data that enter the data partner's network.

Data Transformation (Step 6)

Within the data partner's infrastructure, the data partner sets up a machine with the Carrot-CDM tool installed. The Carrot-CDM package is an ETL tool to convert a dataset to OMOP using supplied rules. Built with Python, the package can be readily installed in the environment hosting the dataset. The task of Carrot-CDM is to convert the CSV files containing the dataset into an OMOP dataset, based upon the mapping rules generated by Carrot-Mapper.

Carrot-CDM operates by constructing a CDM object, containing a number of tables representing the tables or domains used in the OMOP schema. At present, these tables are a subset of all of those defined by OMOP, due to the priorities of the datasets and pipelines that have used Carrot until now. Once the CDM has been appropriately constructed, then conversion of the contents of the dataset can proceed. The OMOP mapping experts send the mapping rules in JSON format to the data partner, and the data partner loads the mapping rules file into the machine. The data partner also copies their pseudonymized dataset into the machine. Carrot-CDM is used to transform the dataset to the OMOP standard using the mapping rules provided. Carrot-CDM is platform independent and can be used via either command-line interface or graphical interface, depending on the user's preference.

Carrot-CDM handles both one-time data transformation and incremental transformation of an expanding dataset as new data is made available, using the same mapping rules as in the one-time case. Carrot-CDM can either monitor for the addition of new data and perform the transformation immediately or run on a schedule to run a transformation of new data added in each period, such as via a server-based scheduler. This means that longitudinal datasets, or those otherwise growing over time, can be efficiently mapped to OMOP. Carrot-CDM supports streaming, enabling essentially infinite datasets to be processed, as working memory is not a limiting factor.

Data Partner Validation

The data partners clearly hold the vital contextual information to provide assurance that the data mapping is appropriate and correct. Therefore, through steps 1, 2, and 6 (Figure 1) of the process, the data partner is consulted and many questions and clarifications are sought between both parties. The metadata extraction and initial upload can often highlight some discrepancies in data format and can highlight where the data dictionary does not exactly match all of the data picked up in the scan report. Therefore, the recommended process is for a highly collaborative and iterative process whereby the Carrot team has the insight in the process of curating data to OMOP, while the data partner has the insight and understanding of their data.

Users and Projects

Carrot-Mapper assigns user accounts to individuals and has an internal data model to organize dataset mappings and administrate access to them. These structures are projects, datasets, and scan reports. The basic unit is the scan report, formed from a single uploaded scan report file generated by the White Rabbit tool. Each scan report is a member of a single dataset. Multiple scan reports can be organized into a single dataset to represent successive iterations of a single dataset, such as with the addition of new tables, fields, or values. The usage pattern of datasets and scan reports is left to the user's choice.

At the highest level, projects represent the abstract notion of a view of a collection of datasets that are of interest to a particular group of users. A user must be a member of a project to access the datasets associated with that project. A many-to-many relationship means that datasets can be present in multiple projects, and it is sufficient that a user is a member of any related project to access a given dataset.

Assuming that a user has access to a given project, user access can then be further controlled on the level of datasets and individual scan reports. Permission to view datasets and scan reports is controlled first by setting their visibility as either "Public" or "Restricted," and then more granular viewing, editing, and administration operations can be controlled at the per-user level.

Mapping Standardization Tools

An additional internal tool within Carrot-Mapper highlights related OMOP concepts that are the target of mappings in the dataset corpus. This is provided as feedback to the mapping team to highlight misaligned target concepts (ie, those which are descendants or ancestors of other target concepts in the hierarchical OMOP structure) and encourage iterative convergence on a standardized OMOP vocabulary. Users are free to ignore this guidance if they choose, but the presentation of the potential inconsistencies places this information in the user's hands without extra effort.

Management

Carrot-Mapper presents users with a dashboard to show relevant statistics such as the total number of scan reports processed and mapping rules generated, grouped by data partner, and to track the progress of scan reports from the upload stage through to the completion of the mapping process.

User access to datasets and scan reports is configurable via dedicated administration pages for each, placing the user control into the hands of the dataset administrators to reduce reliance on the central Carrot-Mapper team.

Ethical Considerations

Research ethics approval was not required for this project as each data partner maintains their own governance and ethics for the original research studies. Anyone requiring access to the platform to perform research needs to apply for their own ethics

approval. The data partners who use the Carrot system and methods in this paper will need to have the required ethics in place for the collection, storage, and use of data in place.

Results

As of July 2024, the installation of Carrot-Mapper has been used to generate mappings for 39 scan reports to the OMOP standard. There are 129 dataset objects across 13 projects. A total of 60,269 mappings have been generated, through manual means (n=6159), automatic (n=45,316), and reuse between scan reports (n=8794). These numbers are only for those scan reports marked as "Mapping Complete," indicating that they have been accepted as correct by the users, and their associated mappings are now available for reuse by new datasets. More (n=92,071) mappings are currently in progress without having been marked as archived or as completed.

This use of Carrot tools has been adopted by a number of projects, including COVID-Curated and Open Analysis and Research Platform (CO-CONNECT; see below), Alleviate [27], Defining Mechanisms Shared Across Multi-organ Fibrotic Disease to Prevent the Development of Long Term Multimorbidity (DEMISTIFI),

Mother and Infant Research Electronic Data Analysis (MIREDA), the National Institute for Health and Care Research Nottingham Biomedical Research Center, and most recently the East Midlands Secure Data Environment. Carrot is therefore an integral part of ongoing efforts by several organizations to standardize health data to the OMOP standard. Since Carrot-Mapper can be deployed by any user, with a separate database, it is not possible for the authors to accurately gauge the use of Carrot-Mapper beyond the centrally installed system deployed by the Carrot team.

Most mappings (over 75%) were automatically generated from vocabularies, indicating the importance and time-saving nature of the automated mappings feature. Existing mappings that have been verified are automatically reused on newly uploaded scan reports where they match, reducing wasteful replicated effort. While the proportion of mapping that is from reuse is currently low (less than 15%), we anticipate (and have seen even thus far) that as the number of mapped values increases, and iterations of the same dataset are progressively remapped over time, the number of reused mappings will rise compared with the number of manually added mappings. Even at this early stage, nearly 60% of the mappings that are not automatically generated from known vocabularies are from reuse.

Discussion

Principal Findings

Accessing and combining multiple datasets can be handled in a variety of ways. Principally, the choice of whether to standardize vocabularies then drives the choices available in further steps in any processing pipeline. Leaving datasets in their original formats requires later processing steps to understand and handle the heterogeneity in the underlying data sources. While this can be handled on a case-by-case basis for small numbers of datasets, at scale, this requires the creation and maintenance of a large number of connectors and middleware given the plethora of possible data sources. This is the approach taken by systems with a limited number of data sources such as OpenSAFELY [28] but is not an approach that is sustainable for many smaller datasets and data partners.

Converting datasets to a standardized vocabulary reduces the heterogeneity of the datasets at an earlier step in the pipeline, simplifying later processing steps and reducing the dataset-specific knowledge required by users of the data. However, it places the onus on formulating a consistent and correct mapping to the standard vocabulary. It is also not possible to cover every use case with a single standardized vocabulary, so some pipelines may be best served by using the raw data, while other use cases may lend themselves to a specific standardized vocabulary that is inappropriate for other uses.

In choosing a common standard vocabulary, a number of competing factors must be considered, including the suitability of the vocabulary to represent the original datasets, ease of conversion, availability of required expertise and tooling, and adoption by others. A wealth of standard vocabulary candidates exist, including OpenEHR, OMOP, and PCORnet [29].

Converting a dataset to a common standard can sometimes be partially automated—in the case of OMOP, many research ontologies such as SNOMED can be mapped directly—but in almost all cases this conversion requires a human element to decide the most appropriate mapping. This brings with it privacy and data protection implications if the process of manual mapping relies upon providing access to the dataset. The EHDEN program funds the conversion of datasets to the OMOP standard by using approved organizations to perform the conversion. This relies on governance assurances to ensure that only trusted and approved individuals are granted access to the dataset under conversion. This can be a relatively quick method for converting high-priority datasets to the OMOP standard but will not enable the conversion of lower-priority datasets given the competitive nature of the process.

The Carrot tools take a different approach, by only extracting to a central system the metadata required from the dataset to formulate a mapping. In this way, experts in OMOP conversion with access to the central Carrot system can create a mapping from the original dataset to the OMOP standard without ever having access to either identifiable or pseudonymized and anonymized data. This removes some of the governance requirements. In addition, it allows the creation of a corpus of mapping rules that can be shared and reused between datasets, and compared and aligned over time. Finally, Carrot can automate much of the mappings required from recognized standard vocabularies, reducing costs and opportunities for error.

The generation of rules by automated processes does have the ability to create more harm than good, as a human has to check and correct any potential errors. The use of automation in Carrot is limited to two scenarios. The first is where a concept has already been formally mapped by the OHDSI vocabulary from a nonstandard to standard concept. The second is where a previously human-approved mapping can be reused because the column and values exactly match. The user is presented

with these and can see which rules were mapped from the vocabulary (marked with a V) and from reusing existing rules (marked with an R). We are currently gathering more evidence on the utility of these automated approaches and whether other automation is useful, such as the adoption of large language models.

The novel nature of the metadata access required by Carrot tools has created some additional governance issues, since many organizations did not have existing data access processes that were used to process lower risk metadata. In the use-case of CO-CONNECT, this required an extensive collaborative effort between our team and data partner organizations to satisfy them with the nature of the requests and to create new processes to enable them. This delayed some of the mapping work but is also an important output from the wider CO-CONNECT project.

Phenotype Generation

Bringing together the metadata from multiple datasets and their mappings to the OMOP standard enables leveraging the combined data to build phenotypes. For example, all fields and values across all datasets that are mapped to the OMOP concept code 317009 for asthma can be queried. In future work, we plan to provide a publicly available tool to present this information, allowing interested parties to interrogate the source values that map to a given OMOP concept code. This is valuable for understanding the varying ways in which this data is captured across datasets and allows external validation of the mappings generated by the central team.

Pipeline Integration

The Carrot tools have been built in such a way to be integrated into wider pipelines, as demonstrated in the CO-CONNECT project. The separation of the tasks into separate tools based on their requirements for human intervention provides a natural fit for integration into semiautomated pipelines. Work in this area continues, such as future extensions to support the postprocessing of OMOP data to encode relationships, work to further develop the JSON mapping rules file specification to fit common standards, and support of data-profiling tools in addition to White Rabbit.

Limitations

The Carrot tools remain under active development to extend and improve their functionality. In particular, work remains to monitor and handle the continual changes made to the OMOP vocabulary to provide reproducibility and transparency to the processes. The priorities of the initial use cases shaped the development process, in particular regarding support for OMOP tables. Further work is ongoing to widen the target OMOP tables the Carrot tools can support. The work presented has not run different methods in parallel; therefore, we make no claim over whether this approach is better, faster, or more efficient or uses less computing resources than others. Where data governance and protocols would allow such a comparison could be useful to evidence the benefits of the system. What we have sought to lay out is a protocol, supported by software, that was driven by the underlying constraints and challenges experienced.

The matching algorithm for reusing mappings across datasets is relatively simple, and ripe for further refinement as well as further user customizability. That is because even a small spelling mistake would prevent a match from being found. Additionally, Carrot cannot undertake any natural language processing, nor can it translate between languages.

Finally, further development remains to provide greater user ease, particularly around the self-administration of user accounts and streamlining the user journey to eliminate known areas that could be further automated.

While reducing some aspects of technical knowledge that are required by users (eg, removing the need for SQL knowledge typically required in most other workflows and automating the details of which OMOP concept codes relate to which target OMOP table), Carrot does still rely on an expert understanding of OMOP to be used to greatest effect. In this regard, it is to enhance rather than replace the capabilities of human curators and makes no claim to be able to process full datasets from end to end without human oversight and intervention. There is still a need for clinical specialties (eg, chronic pain) to agree on correct and consistent usage of terms to improve the interoperability of disparate datasets.

Conclusions

We have presented the Carrot tools, namely the Carrot-Mapper and Carrot-CDM software tools. These enable expert or novice curators to transform health datasets to the OMOP standard with access only to metadata, rather than the potentially sensitive data. This has the potential to radically reduce the governance work and cost required to perform this transformation, without sacrificing the expertise that can be brought by external curators.

Carrot-Mapper contains functionality to specifically reduce the repeated work required to map multiple datasets by reusing mappings between datasets. It further contains tools that can guide curators toward standardized mappings over time, reducing the dependence upon individual curators' different approaches to the preferred terminologies to represent data. All of this is achieved without ever exposing the sensitive data to the external team with OMOP knowledge.

Carrot-CDM is a robust and scalable ETL tool that can run within the data partner's infrastructure, completing the journey to an OMOP dataset without data movement beyond the data partner's boundaries, nor requiring external users to be granted access. In combination, the Carrot tools provide a means for OMOP experts to convert health care datasets to OMOP in a standardized manner, with reduced governance requirements compared with the existing tools available.

Acknowledgments

This work uses data provided by patients and collected by the National Health Service as part of their care and support. We acknowledge the support from COVID-Curated and Open Analysis and Research Platform (CO-CONNECT) funded by United

Kingdom Research and Innovation (Medical Research Council) and the Department of Health and Social Care (National Institute of Health and Care Research) (MR/V03488X/1) and supported by a consortium of 22 partner organizations whose infrastructure made this research possible.

The work builds on early pilot work supported by the University of Nottingham Impact Acceleration Account (EP/R511730/1) from the Engineering and Physical Sciences Research Council.

Subsequent work on Carrot was supported by Alleviate Hub (MR/W014335/1), the Advanced Pain Discovery Platform Data Hub, funded by the Medical Research Council, Eli Lilly, and Versus Arthritis, with support from Health Data Research UK.

It was also supported by the European project, Beyond COVID (BY-COVID).

Data Availability

There is no data to make available, but all the Carrot software is available on an open-source license.

Conflicts of Interest

AS, PRQ, and EJ were a part of the CO-CONNECT project. CC is director of the Alleviate pain data hub.

Multimedia Appendix 1
Details of the vocabularies that are used in Carrot-Mapper as default.
[DOCX File , 15 KB - resprot_v14i1e60917_app1.docx]

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Abbreviations

CDM: common data model
CO-CONNECT: COVID-Curated and Open Analysis and Research Platform
DEMISTIFI: Defining Mechanisms Shared Across Multi-Organ Fibrotic Disease to Prevent the Development of Long Term Multimorbidity
EHDEN: European Health Care Data and Evidence Network
ETL: extract, transform, and load
FAIR: Findable, Accessible, Interoperable, and Reusable
GDPR: General Data Protection Regulation
ICD: International Classification of Diseases
OHDSI: Observational Health Data Sciences and Informatics
OMOP: Observational Medical Outcomes Partnership
SNOMED: Systematized Nomenclature of Medicine
SNOMED-CT: Systematized Nomenclature of Medicine Clinical Terms

Edited by A Mavragani; submitted 28.06.24; peer-reviewed by T Karen, M Pajusalu, C Gao; comments to author 27.08.24; revised version received 12.09.24; accepted 19.12.24; published 02.04.25.

Please cite as:
Cox S, Masood E, Panagi V, Macdonald C, Milligan G, Horban S, Santos R, Hall C, Lea D, Tarr S, Mumtaz S, Akashili E, Rae A, Urwin E, Cole C, Sheikh A, Jefferson E, Quinlan PR
Conversion of Sensitive Data to the Observational Medical Outcomes Partnership Common Data Model: Protocol for the Development and Use of Carrot
JMIR Res Protoc 2025;14:e60917
URL: https://www.researchprotocols.org/2025/1/e60917
doi:10.2196/60917
PMID:

Protocol

Evaluation of a Global Initiative for Asthma Education and Implementation Program to Improve Asthma Care Quality (CARE4ALL): Protocol for a Multicenter, Single-Arm Study

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Abstract

Background: Poor symptom control and exacerbations of asthma diminish quality of life and pose a significant burden to patients and society. Implementing evidence-based management as recommended by the Global Initiative for Asthma (GINA), especially introducing inhaled corticosteroid–containing treatments, has the potential to vastly reduce exacerbations and the high burden of asthma in China. However, domestic implementation of the GINA recommendations has been unsatisfactory, especially in lower-level hospitals; thus, an enhancement to the awareness of and adherence to the GINA recommendations among Chinese physicians is needed to improve patient outcomes.

Objective: This study aims to bridge the gap between the GINA recommendations and the current clinical practice in China by demonstrating the benefits of an asthma quality improvement program (QIP).

Methods: A single-arm study will be conducted at around 30 hospitals across China to assess the impact of a specially designed asthma QIP. Approximately 1500 patients with asthma aged ≥14 years will be enrolled in participating hospitals and followed up for 48 weeks. The QIP—targeted at all pulmonologists and specialist nurses—will include an initial comprehensive training (including a pretraining questionnaire and posttraining quizzes) provided by a dedicated, qualified training team based on the GINA 2021 recommendations, followed by regular reinforcement learnings (integrated into the regular department lectures delivered by department directors), with multiple offline and online approaches (eg, an online patient management platform) provided as supportive tools. During this study, GINA implementation performance will be continuously monitored to inform necessary adjustments at the hospital level. The primary end point is change from baseline in the proportion of participants with an inhaled corticosteroid–based maintenance or reliever treatment at week 48. Secondary end points and exploratory end points include changes in clinical practice and patient outcomes such as treatment patterns, asthma control, and hospitalization rates due to exacerbations.

Results: This study has been completed, with 1500 patients enrolled and 1271 patients completing the study. The last visit of the last patient was on September 3, 2024, and the database lock was on September 28, 2024. Final analysis of data has started in October 2024.

Conclusions: The Change Asthma Clinical Practice through GINA Education and Implementation for All Patients With Asthma (CARE4ALL) study will hopefully help improve asthma management and patient outcomes in China by bridging the gap between evidence-based GINA recommendations and the current clinical practice.

Trial Registration: ClinicalTrials.gov NCT05440097; https://clinicaltrials.gov/study/NCT05440097

International Registered Report Identifier (IRRID): DERR1-10.2196/65197

(JMIR Res Protoc 2025;14:e65197) doi:10.2196/65197

KEYWORDS

asthma; management; quality improvement program; Global Initiative for Asthma; GINA; guidelines; implementation; health care; delivery

Introduction

Asthma is a chronic inflammatory disease, characterized by repeated episodes of breathlessness, wheezing, chest tightness, and coughing, which affects more than 330 million people worldwide [1]. Within China, as reported by the China Pulmonary Health study, the prevalence of asthma is 4.2% among adults aged at least 20 years, representing 45.7 million patients, and it is anticipated to increase further due to changes in environment and lifestyle [2]. However, the current status of asthma management in China is far from satisfactory.

Asthma control is defined as the level to which the various manifestations of asthma have been reduced or eliminated by treatment [3]. As it is closely linked to patients' health status, the achievement of good asthma control has been set as the key element that drives patient management [3-6]. The rate of well-controlled asthma, as defined by the Global Initiative for Asthma (GINA), is only 28.5% in China's urban areas [7] and is expected to be even lower in remote areas [8]. Moreover, poor asthma control is associated with a much higher risk of exacerbations, which is a major cause of disease morbidity and medical resource use [9]. According to a multinational, cross-sectional survey, 17.8% of patients with asthma in China experienced at least one exacerbation within the past 12 months [10], much higher than 8.4% in the United Kingdom and 12.5% in the United States [11]. Previous studies revealed that the suboptimal asthma control and the high exacerbation burden in China might be largely attributed to underdiagnosis and undertreatment in asthma management [2,10,12]. Though the underlying reasons may be complicated, low awareness of and adherence to guideline recommendations among physicians, insufficient disease awareness, and poor treatment adherence (including incorrect technique of inhalers) among patients might all play a part [12,13].

The GINA strategy report (also known as GINA) has been updated annually since 2002 to provide physicians with up-to-date, evidence-based recommendations for asthma prevention and management [6]. Commencing asthma treatment with short-acting β_2-agonists (SABAs) alone has been a long-standing approach in the field [14], but concerns were raised as overuse of SABAs was shown to be associated with an increased risk of asthma-related death [15]. As more relevant evidence emerged, in 2019, GINA concluded that adults and adolescents with asthma should not be treated with SABAs alone for consideration of safety, regardless of asthma severity [14]. Since then, inhaled corticosteroid (ICS)–containing therapies have been recommended for all patients with asthma by both international and Chinese guidelines [6,8,14]. However, ICS-containing therapies are largely underused in China. For example, in a multinational cross-sectional survey conducted in 2020 on physicians (including general practitioners, family medicine physicians, or internal medicine physicians), the results from China showed that 31.9% of the respondents regarded inhaled SABAs only as the typical treatment of mild asthma, suggesting the suboptimal awareness of guideline recommendations among Chinese physicians [16]. Considering the critical role that physicians play in the delivery of asthma care, limited understanding and implementation of guideline recommendations would inevitably translate to compromised patient outcomes.

The unsatisfactory quality of medical care and the high disease burden call for national actions to increase physicians' awareness of and adherence to management recommendations to improve patient outcomes [17]. Studies from China have shown that interventions targeted by health care professionals at the hospital level can increase physicians' adherence to guideline recommendations and, in turn, improve patient asthma outcomes [18,19]. However, the existing studies either only conducted a short-term, one-off intervention program [18] or were limited to a single study center [19]. Such interventions can be better delivered in the form of a quality improvement program (QIP), which is a set of systematic and continuous activities designed to monitor, analyze, and improve the quality of health care processes [20]. QIPs for asthma care have been demonstrated to effectively change physician practices and improve clinical outcomes in other countries [21]. For example, the Enhancing Care for Patients With Asthma study, developed to augment the implementation of the Expert Panel Report 3 Guidelines in four American states [22], successfully improved the consistency of practices with the Expert Panel Report 3 Guidelines and subsequently decreased asthma-related emergency department visits and hospitalizations by 37.7% and 47.1%, respectively, based on a retrospective analysis [23]. QIPs have also been successfully conducted in China for other

diseases [24,25], but the feasibility and benefits of such QIPs for asthma care have not been assessed in China.

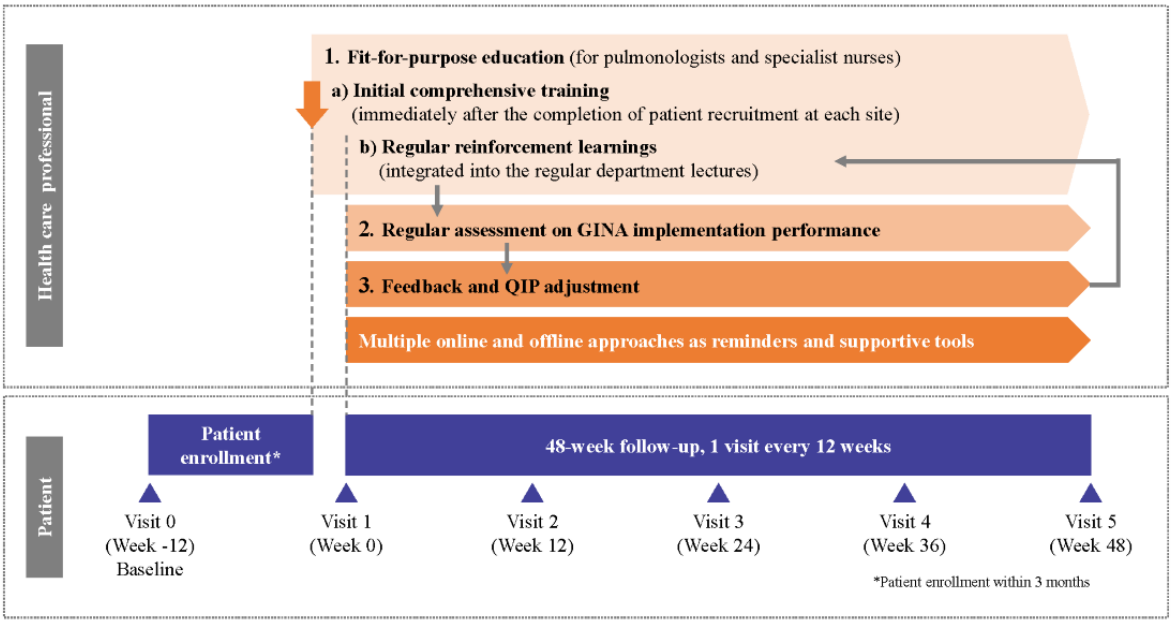
The Change Asthma Clinical Practice through GINA Education and Implementation for All Patients With Asthma (CARE4ALL) study will conduct the first-ever multifaceted QIP for China asthma care, targeting physicians with a specialization in pulmonary or respiratory care. The QIP aims to bridge the gap between the recommendations from the GINA 2021 (the latest update at the time of study design) and the clinical practice among participating health care professionals, and to improve patient outcomes through enhanced quality of care. By evaluating the clinical impact of such a QIP in a nationwide cohort, the ultimate objective of the CARE4ALL study is to pilot and establish a widely applicable QIP model for improving domestic asthma management in China.

Methods

Study Design

This is a multicenter, single-arm study (NCT05440097) with primary data collection to assess the impact of an asthma QIP in improving the adherence of health care professionals specializing in pulmonary or respiratory care to recommendations from the GINA 2021 and quality of care. This study's methodology and procedures are shown in Figure 1.

Figure 1. Study design. GINA: Global Initiative for Asthma; QIP: quality improvement program.



Study Sites and Participants

Site Selection

This study selected a total of around 30 tertiary and secondary hospitals that met all the following criteria: (1) classified as public general hospitals (excluding traditional Chinese medicine hospitals), (2) having an emergency unit and a respiratory department with wards and fundamental equipment (eg, spirometry), (3) having access to GINA-recommended treatment regimens, (4) visited by ≥500 patients with asthma in the past one year, and (5) willing to provide all pulmonologists with regular GINA education and comply with GINA 2021 recommendations. To represent the real-world asthma care situation in mainland China, hospitals were selected across as many provinces or municipalities as possible located below an altitude of 1500 meters, with a balance of hospital levels (preferably around 20 at the tertiary level and around 10 at the secondary level).

Patients

Outpatients with physician-confirmed asthma will be consecutively recruited at participating hospitals. Patients will be eligible for enrollment if they are ≥14 years old and provide written informed consent. Exclusion criteria include previous diagnosis of clinically relevant chronic respiratory disease other than asthma (eg, chronic obstructive pulmonary disease); any significant medical conditions that may put the patient at risk, influence this study's results, or hinder the participants from fully complying with this study's procedure; any medical conditions other than asthma that requires treatment with systemic or oral steroids; and participation in another clinical study with an investigational product administered in the last three months before visit 1 (Figure 1).

Study End Points

As the QIP aims to align physicians' clinical practice with GINA recommendations, study end points measured to what extent the physicians' practice complied with GINA-recommended best practice, which could be reflected in various aspects. First, patient medication patterns directly reflected whether physicians had prescribed asthma medications as recommended by GINA. Thus, the primary end point measured the change from baseline at week 48 in the proportion of patients receiving ICS-based maintenance or reliever medications (as the mainstay of the GINA-recommended asthma medication scheme), while several secondary end points were designed to characterize more fully the patients' asthma medication patterns (Textbox 1). Second, the physician's knowledge, skill, and action together reflected

their understanding of and ability to implement GINA strategies. Thus, the exploratory end points included measurements on the proportions of patients whose pulmonologists develop or review an asthma action plan (a GINA-recommended management tool) for them and check to ascertain their inhaler technique, as well as scores measuring the physicians' own asthma knowledge and inhaler technique (Textbox 1). Moreover, the physicians' patient management skills and the quality of their communication and education for the patients were expected to improve through the QIP, which in turn would positively influence the patients' disease knowledge levels and self-management behavior. As such, the exploratory end points included assessments of the patients' asthma knowledge, inhaler skills, and compliance, to serve as indirect indicators of the physicians' patient management proficiency (Textbox 1).

By aligning current clinical practice with GINA recommendations, the ultimate goal of the QIP is to enhance patient outcomes, as improved quality of care is expected to bring about better asthma management results. Therefore, several key secondary end points sought to evaluate changes from baseline in patients' asthma control (assessed by the five-item Asthma Control Questionnaire), and patients' health-related quality of life and incidence of severe asthma exacerbation were also evaluated as exploratory end points (Textbox 1). Together, these end points on patient outcomes will help demonstrate the clinical benefits that can be actualized through the QIP.

Textbox 1. Study end points and outcome measures. Asthma treatment at each study visit refers to the treatment received within the prior 12 weeks according to medical records. For instance, in the primary end point, "a participant with an ICS-based maintenance or reliever therapy at week 48" is defined as a participant who has used inhaled corticosteroid (ICS)–based maintenance or reliever therapy between week 36 and week 48 based on medical records and in-hospital or out-of-hospital prescriptions.

Primary

- Change from baseline in the proportion of participants with an ICS-based maintenance or reliever therapy at week 48.

Secondary

- Change from baseline in the proportion of participants with well-controlled asthma (five-item Asthma Control Questionnaire [ACQ-5] ≤0.75) at week 48.
- Distribution of ACQ-5 scores [proportion of participants with well-controlled (ACQ-5 ≤0.75), partially controlled (0.75<ACQ-5≤1.5), and not well-controlled (ACQ-5 >1.5) asthma] at weeks 12, 24, 36, and 48.
- Change from baseline in the proportion of participants on the treatment of ICS-formoterol as a reliever at weeks 12, 24, 36, and 48.
- Change from baseline in mean ACQ-5 scores at weeks 12, 24, 36, and 48.
- Change from baseline in the proportion of participants achieving an improvement in ACQ-5 of ≥0.5 units at weeks 12, 24, 36, and 48.
- Change from baseline in the proportion of participants with an ICS-based maintenance or reliever treatment at weeks 12, 24, and 36.
- Distribution of asthma treatment (eg, ICS-containing medications, ICS-long-acting β_2-agonist, ICS-formoterol, oral corticosteroids, leukotriene receptor antagonists, theophylline, and traditional Chinese medicine) at baseline and weeks 12, 24, 36, and 48.

Exploratory

- The proportion of participants whose pulmonologists developed or reviewed the written asthma action plan at weeks 0, 12, 24, 36, and 48.
- The proportion of participants whose pulmonologists watched the patient using their inhaler to check their technique at weeks 0, 12, 24, 36, and 48.
- Annual hospitalization rate due to asthma exacerbations per patient.
- Number of severe asthma exacerbations at baseline, weeks 12, 24, 36, and 48.
- Change from baseline in health-related quality of life evaluated by mean Standardized Asthma Quality of Life Questionnaire for 12 years and older scores at weeks 0, 12, 24, 36, and 48.
- Change from baseline in the proportion of participants with an ICS-based maintenance or reliever actual treatment at week 48.
- Change from baseline in mean Medication Adherence Report Scale for Asthma scores at weeks 12, 24, and 48.
- Change from baseline in the inhaler skill scores of pulmonologists at weeks 12, 24, and 48.
- Change from baseline in the inhaler skill score of patients at weeks 12, 24, and 48.
- Change from baseline in the scores of the asthma knowledge questionnaire for patients at weeks 12, 24, and 48.
- Change from baseline in the scores of the patient expectation of asthma treatment questionnaire at weeks 12, 24, and 48.
- Change from baseline in the scores of the asthma knowledge questionnaire for pulmonologists at weeks 12, 24, and 48.
- Level of asthma control at baseline by self-assessment and by the Global Initiative for Asthma assessment.
- Level of asthma control at baseline, weeks 0, 12, 24, 36, and 48.
- Patient characteristics and related symptoms after COVID-19 infection.

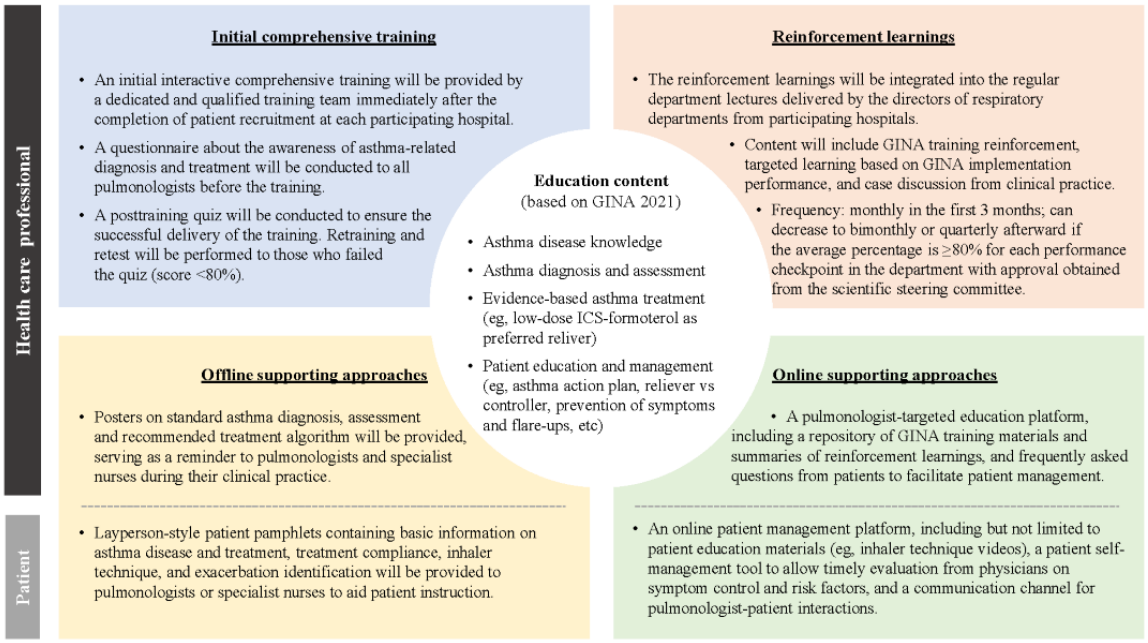
Interventions

The QIP delivered at the hospital level targeted all pulmonologists and specialist nurses at each participating hospital with the goal of encouraging asthma management per the GINA 2021 recommendations in their routine clinical practice. The program included initial comprehensive training, which was delivered by a dedicated qualified team (including asthma experts in the same province or region as the participating hospital) immediately after the completion of patient recruitment at each site. This timing of training commencement was designed to avoid biasing the baseline data of clinical characteristics by training-induced behavior changes. The education content was based on recommendations from the GINA 2021, including, but not limited to, asthma diagnosis and assessment, evidence-based asthma treatment and the scientific rationale, and patient education and management (eg, asthma action plan, the rationale for medication adherence, etc). A posttraining quiz was conducted to ensure the successful delivery of the training. Thereafter, pulmonologists and specialist nurses were required to attend regular reinforcement learnings to enhance their understanding of GINA-recommended asthma management and address practice gaps identified from the GINA implementation performance assessment. During this study's period, multiple online and offline approaches served as supportive tools to increase adherence to the GINA recommendations (Figure 2). In addition to pulmonologists- or nurses-targeted efforts, layperson-style patient pamphlets and an online patient management platform were developed to help enhance patients' adherence to asthma treatment (Figure 2). The platform housed patient education materials, incorporated a patient self-management tool, and provided a communication channel to facilitate physician-patient interactions.

A scientific steering committee consisting of external asthma experts, most of whom are committee members of the Asthma Group of the Chinese Thoracic Society, was established to control the overall quality of the QIP. The committee reviewed and approved the overall design of this study and ensured that the education plan and related materials were scientifically and clinically appropriate. The committee was also involved in the review and interpretation of this study's results.

Monthly assessments of GINA implementation performance were conducted to guide QIP adjustments (eg, targeted reinforcement learnings) at the hospital level. GINA implementation performance was assessed against 6 predefined key performance indicators (Textbox 2) for each participant's visit. The proportion of participants achieving each checkpoint was calculated at the hospital level, which can help identify gaps in GINA implementation and determine future targeted training needs. Assessment feedback was provided to the scientific steering committee and the directors of participating departments. If the GINA implementation performance was unsatisfactory at a participating department (defined as the average percentage at the department level lower than 80% for at least one performance checkpoint), the scientific steering committee discussed the root cause with the department director and provided instructions for an improved plan.

Figure 2. Multifaceted approaches designed to facilitate GINA implementation in the QIP. GINA: Global Initiative for Asthma; ICS: inhaled corticosteroid; QIP: quality improvement program.



Textbox 2. Key performance indicators for Global Initiative for Asthma implementation performance and data source.

Questionnaires collected from participating patients after each visit

- Whether or not the pulmonologist or the specialist nurse assessed the patient's symptom control over the past four weeks?
- Whether or not the pulmonologist or the specialist nurse watched the patient using their inhaler?
- Whether or not the pulmonologist discussed treatment adherence?
- Whether or not the pulmonologist developed or reviewed the written asthma action plan?
- Whether or not the pulmonologist reduced the dosage of asthma treatment? If yes, whether the patient had a pulmonary function test before dosage reduction?

Medical records

- Whether or not the pulmonologist has provided ICS-containing medication for maintenance or as a reliever?

Assessment and Data Collection

The electronic data capture system was used for data collection and query handling, and all data was recorded in the electronic case report form per prespecified instructions. All data were obtained from medical records generated during routine clinical practice except for the questionnaires to be completed by patients. During this study, usual care activities were performed as needed and no additional examinations were required.

At each study visit (including baseline and follow-up visits, Figure 1), medical records on asthma-related assessment and treatment during the past 12 weeks were collected, and two patient-reported outcome questionnaires—a five-item Asthma Control Questionnaire and Standardized Asthma Quality of Life Questionnaire—for patients aged 12 years and older was administered. The Medication Adherence Report Scale for Asthma, the asthma knowledge questionnaire for patients (study-defined, designed based on The Validity and Reliability of an Asthma Knowledge Questionnaire Used in the Evaluation of a Group Asthma Education Self-Management Program for Adults With Asthma), the patient inhaler skill assessment and the patient expectation of asthma treatment questionnaire (study-defined) will also be administered at baseline or follow-up visits (Multimedia Appendix 1). Additionally, patients' demographics, clinical characteristics within three months, and historical data (eg, asthma history, comorbidities, and comedication history) were collected at baseline, and hospitalization and outpatient visit records related to asthma were collected at follow-up visits (Multimedia Appendix 1). To better reflect real-world conditions, no free medications were provided in this study, and information on the sources from which patients purchase their medications was collected at baseline. Participants were encouraged to return to this study's hospital if they had asthma-related conditions or worsening symptoms. In case of emergency, they could choose to visit a hospital other than this study's hospital but were required to report it to study pulmonologists or study staff with supporting documents (eg, medical record of hospitalization summary). Data generated from other hospitals were collected as per protocol. A patient might withdraw from this study at any time at their own request; at the time of withdrawal from this study, an early study discontinuation visit was conducted for any data that needed to be collected.

Data Analysis

Sample Size Estimation

With a 30% dropout rate and a within-participants correlation of 0.25, approximately 1500 patients are required to provide an 80% power at a significant level of .05 to detect an increase from baseline of 5% at week 48 in the proportion of patients with an ICS-based maintenance or reliever therapy, which is assumed to be 40% at baseline [26].

Statistical Plans

The main analyses that assess the impact of QIP were performed using the full analysis set (FAS), which consisted of all enrolled participants with at least one nonmissing postintervention GINA treatment assessment. Baseline demographics and characteristics will be presented for all enrolled participants and FAS. Continuous variables will be summarized descriptively as appropriate. Categorical variables will be presented as frequency counts and percentages. When applicable, 95% CIs will be presented with estimates of proportions.

Analysis of the primary end point were conducted in the FAS with a mixed effect logistic regression model, considering the measurement time point (baseline or post baseline) as the fixed effect and hospital, pulmonologist, and patient as the random effects. In case of lack of convergency, the hospital and pulmonologist were removed from the model. A sensitivity analysis was conducted with a generalized estimating equations model including the same covariates as in the primary analysis. Secondary and exploratory end points were presented primarily with summary statistics. For the analysis of end points, by-visit end points were analyzed using observed data, and missing data were not imputed.

Subgroup analyses were performed as appropriate according to age (<18, 18–65, or >65 years), age of asthma onset (<20, <40, or ≥40 years), phenotype of asthma (allergic or nonallergic), hospital level (tertiary or secondary), occupation (asthma-related or not), baseline characteristic, questionnaire response status (with or without response), adherence, patient expectation of asthma treatment, asthma history, asthma severity class, type of the participating hospital department (pulmonary and critical care medicine or nonpulmonary and critical care medicine), geographic region (North or South), change from baseline in ICS-containing treatment (with-to-with, with-to-without,

without-to-with, or without-to-without ICS-containing treatment), and change from baseline in ICS-formoterol as reliever (with-to-with, with-to-without, without-to-with, or without-to-without ICS-formoterol as reliever). Any participants with a missing value for a predefined subgroup were excluded from the analysis of that subgroup.

Ethical Considerations

This study's protocol had been approved by the Ethics Committee of Beijing Chao-Yang Hospital, Capital Medical University (2022-KE-22).

Informed consent was obtained from a participant or their legally authorized representative before conducting any procedure specifically for this study on the participant.

Participants were assigned a unique identifier by the sponsor. Any participant records or datasets that were transferred to the sponsor contained the identifier only; participant names or any information that would make the participant identifiable were not transferred.

Participant payment outlines were discussed in the informed consent process. Participants were paid a CN ¥ 200 (approximately US $27.50 as of December 12, 2024) transportation fee per on-site visit for reasonable expenses incurred due to their participation in this study.

Results

This study has been completed, with 1500 patients enrolled and 1271 patients completing the study. The last visit of the last patient was on September 3, 2024, and the database lock was on September 28, 2024. Final analysis of data has started in October 2024.

Discussion

Rationale and Study Design

Poor symptom control and exacerbations of asthma impair work and activities, diminish quality of life, and pose a significant burden to patients and society [9,27]. Implementing evidence-based management as recommended by GINA has the potential to improve the quality of domestic asthma care and vastly reduce the disease burden of asthma in China [17]. In line with GINA recommendations, the latest versions of the Chinese guidelines and an expert consensus for asthma management also advocate for ICS-based maintenance and relieving treatment [8,28]. Meanwhile, ICS-containing medications such as budesonide and budesonide-formoterol have been included in China's National Essential Drug List and National Reimbursement Drug List, ensuring patients' access to these asthma medications (including those with special needs such as school-aged patients who may require more than one canister with a single prescription to maintain medication availability both at school and at home). However, at present, domestic asthma control is still unsatisfactory with patients' treatment patterns deviating from the GINA recommendations, suggesting that Chinese physicians' suboptimal awareness of and adherence to the recommendations [2,12,16] may be an important underlying factor that warrants further improvement. Experience from other countries has demonstrated that clinical benefits can be achieved through QIPs for asthma care [21-23]. As such, the CARE4ALL study will conduct China's first-ever nationwide multifaceted QIP targeting physicians with a specialization in pulmonary or respiratory care, which aims to transform the suboptimal asthma control status in China by bridging the gap between GINA recommendations and current clinical practice among Chinese physicians.

Expected Results

We expect that the physicians' awareness of and adherence to the GINA recommendations will be enhanced through the QIP, which would be manifested as more widespread clinical practices that are per evidence-based asthma management, including the implementation of standard, GINA-recommended treatment. We further anticipate that the improved quality of care provided by the physicians would translate to better asthma control and health-related quality of life among the patients. If this study demonstrates these benefits of the QIP in standardizing asthma management in China, this QIP could be considered as a standard model that the whole country can apply to reduce the burden of asthma in China.

Strengths

As the first nationwide QIP for asthma care with a prospective evaluation of clinical impacts in China, the CARE4ALL study has several strengths in its design which differentiate it from previous simple, small-scale educational interventions. First, multifaceted intervention will be provided for physicians to aid understanding and encourage close adherence to the GINA recommendations. The initial comprehensive training intends to familiarize physicians with GINA, which will be reinforced by regular learning sessions typically unseen in routine educational events. Additionally, both online and offline supporting materials are readily available to physicians for easy reference and patient education. Second, different from routine physician-oriented educational events and toolbox, this QIP will also provide physicians with support to facilitate patient management in clinical practice. As effective asthma care requires patients to be actively engaged in multiple self-management behaviors, improving patients' adherence with GINA-recommended practices (eg, ICS-containing medications, appropriate device technique, use of an asthma action plan, etc) is of great importance to the ultimate success of the GINA implementation. Notably, apart from layperson-style patient education materials aiming to raise patients' awareness of disease management and treatment strategies, an online patient management platform will be developed to facilitate timely evaluations of symptoms and effective physician-patient communications. These interventions are expected to improve patients' treatment adherence and consequently asthma control as demonstrated by previous studies [29,30].

Third, the GINA implementation at the hospital level will be monitored based on the 6 performance indicators and dynamically improved based on feedback from the scientific steering committee, which consists of national asthma experts. Therefore, all the participating hospitals can benefit from constructive instructions from the committee. Finally, while primary health care facilities in remote rural areas will be

excluded due to their inadequate administrative and data management capacity, this study will encompass both tertiary and secondary hospitals from as many provinces or municipalities as possible, aiming to provide unprecedented coverage to better represent the real-world situations in China [18,19]. In China's current medical system, most asthma patients are diagnosed and treated under specialist care rather than by general practitioners, thus this study, by specifically targeting pulmonologists, will exert a direct and substantial effect on shaping the clinical practice of asthma care in China's medical system. As such, experiences and lessons from the program will hopefully inform a valuable model for asthma care improvement in the whole of China as well as for similar programs for other chronic diseases.

This QIP is expected to exert a sustained impact on asthma care practices. First, unlike brief educational events [18], the intervention for our study will last for one year, providing a sustained framework for cultivating evidence-based clinical practice behaviors in physicians. Second, both online and offline supporting materials used during the QIP will continue to be accessible to physicians after the program finishes; coupled with continuous assessments of GINA implementation performance, these resources will aid in maintaining physicians' awareness and adherence to GINA-recommended asthma management. Lastly, by not providing free medications, this study will closely mirror any potential influence that medication accessibility or affordability may have on patients in real-world conditions, thereby enhancing the generalizability of the findings.

Limitations

This study has two key limitations. First, it lacks a concurrent control arm. Instead, it follows the before-and-after design and compares variables measured before and after the QIP, which is an approach often adopted in QIP-evaluating studies for the purposes of better reflecting real-world settings and maintaining simplicity. The effectiveness of this before-and-after design in reflecting the effects of QIP interventions has been widely demonstrated [23,31,32]. Second, multiple sources will be used for data collection, likely leading to missing and inconsistent data. Given that patients may be admitted to other hospitals due to exacerbations, data collection from multiple sources will be inevitable. Past and new hospitalizations out of the study hospital due to exacerbations will be recorded based on medical records rather than patients' personal accounts to reduce missing data and minimize recall bias.

Conclusions

In summary, the CARE4ALL study should help improve asthma management and patient outcomes in China by bridging the gap between evidence-based GINA recommendations and the current clinical practice. This multifaceted QIP is expected to provide valuable insights for further quality improvement in asthma care at the national level.

Acknowledgments

The authors would like to thank Mu-Lu Wu, PhD, from Costello Medical for medical writing support and editorial assistance, which complied with international guidelines for Good Publication Practice (GPP3). This study was funded by AstraZeneca. Medical writing support and editorial assistance by Costello Medical were funded by AstraZeneca.

Data Availability

The datasets generated or analyzed during this study will be available from the corresponding author upon reasonable request.

Authors' Contributions

All authors handled the conceptualization of this study. KH wrote the original draft. WW, YW, YL, XF, HS, and CW reviewed and edited the writing. All authors (except HS, who died on April 16, 2024) read and approved the final version of this paper. HS had read and approved a previous version.

Conflicts of Interest

AstraZeneca is involved in this study design, data collection, data analysis, and preparation of this paper. The authors declare no other conflicts of interest.

Multimedia Appendix 1
Protocol schedule of activities.
[DOCX File , 22 KB - resprot_v14i1e65197_app1.docx]

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Abbreviations

CARE4ALL: Change Asthma Clinical Practice through Global Initiative for Asthma Education and Implementation for All Patients With Asthma
FAS: full analysis set
GINA: Global Initiative for Asthma
ICS: inhaled corticosteroid
QIP: quality improvement program
SABA: short-acting β2-agonist

Edited by A Schwartz; submitted 12.08.24; peer-reviewed by A Yorgancioglu, B Ariue; comments to author 16.10.24; revised version received 14.11.24; accepted 25.11.24; published 08.01.25.

Please cite as:
Huang K, Wang W, Wang Y, Li Y, Feng X, Shen H, Wang C
Evaluation of a Global Initiative for Asthma Education and Implementation Program to Improve Asthma Care Quality (CARE4ALL): Protocol for a Multicenter, Single-Arm Study
JMIR Res Protoc 2025;14:e65197
URL: https://www.researchprotocols.org/2025/1/e65197
doi:10.2196/65197
PMID:

Protocol

Standardized Outcomes for Randomized Controlled Trials Targeting Early Interventions in Patients With Moderate-to-Severe Traumatic Brain Injury: Protocol for the Development of a Core Outcome Set

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Abstract

Background: *:* With more than 60 million new cases around the world each year, traumatic brain injury (TBI) causes substantial mortality and morbidity. Managing TBI is a major human, social, and economic concern. In the last 20 years, there has been an increase in clinical trials in neurocritical care, leading mostly to negative results. The evaluation of neurological outcomes, predominantly as primary outcomes, using clinical scales (Glasgow Outcome Scale) has limitations that could explain these results. Moreover, patient-centered outcomes are seldom reported despite their recognized clinical relevance.

Objective: *:* The aim of this project is to establish a core outcome set (COS) for patients with moderate-to-severe TBI in randomized control trials in neurocritical care research.

Methods: This study will follow five distinct steps: (1) systematic review to identify outcomes that have been reported in trials; (2) semistructured interviews with patients and their families to identify their priorities after TBI and explore potential patient-centered outcomes; (3) health care stakeholder focus groups with clinicians, researchers, and policy makers to describe potential outcomes; (4) an eDelphi survey with stakeholder groups to make a list of previously identified core outcomes; and (5) a consensus workshop to establish a COS for moderate-to-severe TBI clinical trials.

Results: : The systematic review was published in August 2024. Regarding Step 2, 30 semistructured interviews of patients and relatives were performed from July 2021 to December 2023, and analyses were completed in October 2024. Step 3 is currently under development, and Step 4 is planned for the end of 2025. Step 5 is expected to occur during fall/winter 2026. **Conclusions**: Establishing a COS, to be consistently measured and reported in TBI trials in neurocritical care will ensure rigorous reporting, avoid bias, and improve the integrity, transparency, and usability of clinical research. The French context of the study is the main limitation, but we are seeking international collaboration on the project. The results of each step of the project will be disseminated through abstracts, publications, and patient associations.

Conclusions: Establishing a COS, to be consistently measured and reported in TBI trials in neurocritical care will ensure rigorous reporting, avoid bias, and improve the integrity, transparency, and usability of clinical research. The French context of the study is the main limitation, but we are seeking international collaboration on the project. The results of each step of the project will be disseminated through abstracts, publications, and patient associations.

International Registered Report Identifier (IRRID): DERR1-10.2196/54525

(JMIR Res Protoc 2025;14:e54525) doi:10.2196/54525

KEYWORDS

core outcome set; outcomes research; patient-centered outcomes; traumatic brain injury; patient outcome; head trauma; patient-centered

Introduction

Despite advances in critical care medicine in the last decades, mortality in patients with traumatic brain injury (TBI) remains high at approximately 15% after trauma [1]. Survivors of TBI experience major consequences: mood disturbances [2], memory loss, neuropsychological impairment [3,4]. Caregivers also experience major burdens with strain, isolation, and disappointment [5,6].

Many work groups recommend that various outcome domains or outcome measurements [7,8] be collected to assess neurological recovery after TBI, mainly in the continuum of rehabilitation. Most often, this involves a combination of multiple measurement scales that collectively capture all dimensions affected by a TBI [9,10].

Nevertheless, in neurocritical care, the primary outcome in most randomized controlled trials (RCTs) is the Glasgow Outcome Scale [1,11]. Indeed, given the broad spectrum of sequelae after acute brain injury, Jennett and Bond [12] proposed the use of the Glasgow Outcome Scale in 1975 to assess neurological recovery after TBI. Since then, this 5-grade scale (death, vegetative state, severe recovery, moderate recovery, and good recovery) has been extensively reported in the neurocritical care literature to compare the efficacy of various treatments after trauma [13-15]. The Glasgow Outcome Scale was considered too simplistic, leading to the creation of an 8-grade extended version in 1981 [16]. The Extended Glasgow Outcome Scale is used extensively in neurocritical care literature to evaluate neurological recovery, often as a primary outcome in clinical trials [17].

Recently, major concerns have been raised regarding the relevance of these scales and their methodological limitations in neurocritical care clinical research. The Glasgow Outcome Scale has substantial interobserver variability, albeit possibly decreasing over time [18]. Nevertheless, this puts score reliability and accurate patient classification into question [19,20], which could lead to erroneous results despite rigorous analysis. Moreover, analysis of data from this scale is often inappropriate, since these data are generally considered continuous when they are ordinal [21]. In addition, assessment conditions can vary and affect patient evaluation. Evaluation can be performed via telephone [22] or face-to-face interviews, for only brain injury or all injuries (brain and peripheral body parts), or by trained or untrained assessors. These variables are frequently not described in other studies [3,11,18]. However, it is recommended that such assessments should be performed by a certified expert in the presence of the patient and caregiver [23]. Certain authors have recently questioned the consistency between these scales and patient quality of life [24,25]. This raises the question of a patient's understanding of their situation and handicap, which is never evaluated in randomized controlled trials, despite being recognized as an important factor [26]. The aforementioned methodological issues and limitations associated with these scales could explain the litany of negative results in neurocritical care research over the past 30 years [1,15,17,27,28].

Core outcome sets (COSs) can minimize reporting bias, promote consistency in clinical trials, enable direct comparisons of the effect of different interventions, and ensure that outcomes are relevant and important to patients, health care professionals, and caregivers [29]. Hence, the use of COSs for patients with TBI in neurocritical care could reduce the considerable inefficiencies in biomedical research. With more than 60 million new cases of TBI diagnosed globally each year [30,31], there is an urgent need to develop COSs in this area. Accordingly, this project aims to establish a COS for trials in patients with moderate-to-severe TBI included in interventional trials performed during the early phase of the pathology and other types of research including observational studies (eg, registries and other quality indicators for clinical care). This core outcomes set will improve the quality of trials, respond to patient needs, and help rectify decades of negative results.

Methods

Overview

The project will be developed in 5 steps according to the methodology of the Core Outcome Measures in Effectiveness Trials (COMET) initiative. The aim of the COMET initiative is to create a COS built by stakeholders, including patients [32,33]. First, we will perform a systematic review of the outcomes in TBI clinical research at the acute phase. Second, we will organize semistructured interviews with patients who survived moderate-to-severe acute TBI and their family caregivers. Third, we will organize semistructured interviews and focus groups of stakeholders involved in the health care pathway of patients with TBI. Fourth, we will perform an eDelphi survey. Finally, a consensus workshop will finalize the process.

Step 1: Systematic Review

Step 1 was completed in August 2024, and the original article was published [34]. We identified 29 domains related to the 557 different outcomes that will be used for interviews with health care professionals (Step 3) and the eDelphi survey (Step 4).

Step 2: Semistructured Interviews With Patients and Their Families

Explanation and Overview

We will organize semistructured interviews with patients in the late phase of TBI and their family caregivers. To the best of our knowledge, semistructured interviews involving both patients with TBI and their families have been poorly explored. Throughout the qualitative research, we will follow the Interpretative Phenomenological Analysis (IPA), a methodology described by Smith et al [35].

Participants and Recruitment

Patients with TBI aged 18 years and older and a family caregiver (the patient's choice) will be eligible to participate. A purposive sampling strategy will be used to organize a minimum of 15 semistructured interviews with the dyad (patient and their family caregiver). The aim is to perform individual semistructured interviews with patients alone and then perform another individual dedicated interview with relatives alone to avoid cross-contamination of interview responses between the 2 parties. However, given the potential challenges for patients (mood disorders, speech disorders, and difficulties in concentration), relatives may attend the patient's semistructured interview to assist them. The final interviews will depend on when data saturation is reached. We will define saturation as the point when new themes or variations of a given theme cannot be identified. Participants will be recruited from participating centers across France (Bordeaux, Nantes, Rennes, and Saint-Etienne, along with any other contacted centers). The patients and their caregivers will be asked by physical and rehabilitation specialists to participate in the study. Patients in the late phase of TBI will be recruited—defined as the moment when a patient has been discharged at least partially, meaning they no longer require full-time care in a health care facility. The consequences of TBI on their social and personal environments will be assessed.

The steering committee will carry out a sampling strategy to achieve maximum variation in demographics (age, sex, and socioeconomic status) and clinical characteristics (patients with good or poor recovery). We will follow the Consolidated Criteria for Reporting Qualitative Health Research (COREQ) guidelines [36].

Data Collection

Each semistructured interview, performed with an IPA approach according to participants' life experiences, will last a maximum of 90 minutes and take place remotely via videoconference. This is due to the uncertainties in the aftermath of the COVID-19 pandemic. In any case, these interviews will take place outside the hospital to encourage open discussion and limit the stories due to the feeling of disempowerment that could occur in a clinical setting. Each interview, performed by a nurse researcher (senior in qualitative research) and a PhD student, will cover the following for both patients and families: (1) an introduction (5 minutes), where the facilitator will explain the aims of the study and ask the participants to introduce themselves; and (2) the interview (60 minutes), where the participants and families will be asked to discuss their experiences of living with the consequences of TBI, including perceived benefits, harms, and complications related to the pathology and its treatments. The topic guide was tested with 3 dyads and adjusted accordingly (Multimedia Appendices 1-2).

Data Analysis

The interview transcripts will be imported into NVivo 12 software (v.1.8; QSR International) [37] to facilitate qualitative data analysis. We will follow the 7 IPA steps described by Smith et al [35]: (1) reading and rereading, (2) exploratory noting, (3) constructing experiential statements, (4) searching for connections in experiential statements, (5) naming the personal experiential themes and consolidating and organizing them, (6) moving to the next case, and (7) working with personal experiential themes to develop group experiential themes across cases. The IPA method reflects the experience, beliefs, values, attitudes, and reasons underlining participant choices, along with those of their relatives. The preliminary themes will be discussed with other investigators to ensure that the full range and depth of data are captured (investigator triangulation) and with patient associations for the full themes.

Step 3: Stakeholder Interviews

Explanation and Overview

Field investigations, in-depth and semistructured interviews, and focus groups will be performed to capture the expectations and practices regarding the management of TBI patients and to detail the range and depth of individual values, beliefs, and attitudes toward outcomes. These interviews or focus groups will not quantify the frequency of opinion. Reporting will adhere to the COREQ guidelines.

Participants and Recruitment

Interviews and focus group discussions will be conducted with the following stakeholder groups: (1) health care providers

(anesthesiologists, intensivists, neurosurgeons, rehabilitation specialists, nurses, and psychologists); (2) representatives from research, funding, policy, and other stakeholder organizations; and (3) patients and their relatives. A minimum of 60 stakeholders is expected at this point and will be identified from the investigator networks and by snowball effect. At this stage, the steering committee will reach out to stakeholders in other countries to participate in specifically dedicated interviews. Participants will be identified to obtain a maximum variation of representation in professional experience and responsibilities (health care providers and representatives from stakeholder organizations). Recruitment will continue until saturation has been achieved. Informed consent will be obtained from all participants and specific institution review board (IRB) approval will be sought.

Data Collection

From a grounded theory perspective [38], field investigations will be conducted in intensive care and rehabilitation units. Interviews and focus groups will incorporate the results from the systematic review and semistructured interviews with patients and their families, allowing other stakeholders to discuss these elements as well. Stakeholders will be asked to reflect and talk about (1) caring for patients with TBI, (2) the benefits and harms of TBI-related outcomes, (3) outcomes believed to be relevant and important to include in future clinical research, and (4) the results obtained from the semistructured interviews with the patients and their families. Face-to-face interviews will be conducted; however, if this is not feasible, web or telephone conferences will be arranged. Each interview will last between 60 and 120 minutes. The interviews will be recorded and transcribed verbatim.

A field researcher has been hired for a 24-month postdoctoral position to complete Step 3. She is a former intensive care nurse with a PhD in sociology from the University of Nantes and has extensive experience in field investigations and conducting interviews. She has no conflicts of interest related to the topic.

Data Analysis

Data analysis is expected to begin in 2025. Verbatim transcripts from interviews and focus groups will be transcribed word for word and anonymized. Following the grounded theory methodology [38], each transcript will undergo a constant comparison across individuals and stakeholder groups. Analytical themes will be developed inductively to identify the concepts relevant to the participants, from which a list of outcomes will emerge.

Step 4: Delphi Consensus Survey

Explanation and Overview

At this stage, international contacts will be established to conduct an international eDelphi survey [29,39,40]. This survey will gather opinions and organize the outcomes into a prioritized list. The Delphi method is an iterative consensus technique involving sequential surveys completed anonymously by a panel of participants with relevant knowledge and expertise, ensuring equal influence among all participants [41]. We will aim to retain a minimum response rate of 70% for all rounds.

Participants and Recruitment

There is no standard sample size required for Delphi processes. At this point of the protocol, there is no goal regarding the minimum number of stakeholders that will be involved in the Delphi process (ie, patients, family caregivers, nurses, allied health professionals, policy makers, and clinicians in critical care, rehabilitation, and neurosurgery). To ensure maximum variation in sampling, participants will be recruited by using a similar strategy, and approximately one-third of each stakeholder group will be recruited from the participating regions. The participants will be recruited through participating hospitals or institutions and patient organizations. Informed consent will be obtained from all participants.

Data Collection

Overview

The list of outcomes will be obtained from Steps 1, 2, and 3. The outcomes will be listed individually and grouped under each relevant domain according to the COMET initiative definitions [32,42]. The survey will be reviewed by the steering committee. The surveys will be completed over the internet by using a unique identifier, which will enable us to identify participants completing all 3 rounds of the eDelphi survey. At least 3 reminders will be sent to participants during the Delphi rounds.

Round 1

Participants will be asked to rate each outcome using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) process [43]. The process recommends a 9-point Likert scale to rank importance. Rankings between 7 and 9 indicate outcomes of critical importance, those between 4 and 6 indicate outcomes that are important but not critical, and those between 1 and 3 indicate outcomes of limited importance. An option “unable to score” will also be available. All outcome domains will be randomized to minimize ordering bias. Participants can suggest additional outcomes and provide reasons for their rankings. The additional outcomes will be recorded (if not duplicated with a previous outcome), grouped in the relevant outcome domain by 2 members, and reviewed by the steering committee. We will review the distribution of scores for all outcomes for each stakeholder group (ie, patients/caregivers, clinicians, health professionals, etc). Any outcomes with a median or mean over 7 will be retained for round 2, along with additional outcomes retained by the steering committee.

Round 2

Participants will review the group scores and their own scores for each outcome. They will rerank the outcomes (including additional outcomes identified in round 1) using the 9-point scale and explain the reasons for any changes in their scoring. An outcome with a median or mean over 7, and with 70% or more participants in both stakeholder groups (ie, patient/family member and health professionals) rating the outcome to be of critical importance (7-9), will be included in round 3.

Round 3

Participants will be shown their own scores, along with the distribution of scores for each outcome across all stakeholder groups and within individual stakeholder groups. A summary of the results from Steps 2 and 3 will be provided. Participants will be asked to rerank all outcomes and indicate whether they should be included in the COS. To assess the relative importance of the outcomes, they will choose the most important and least important in each outcome domain.

At this point, the recruitment of stakeholders for Step 4 and the Delphi process will not be undertaken for at least 2 years. Data analysis of Step 4 (Delphi process) will be further elaborated and will not be more detailed at this stage.

Step 5: Consensus Workshop

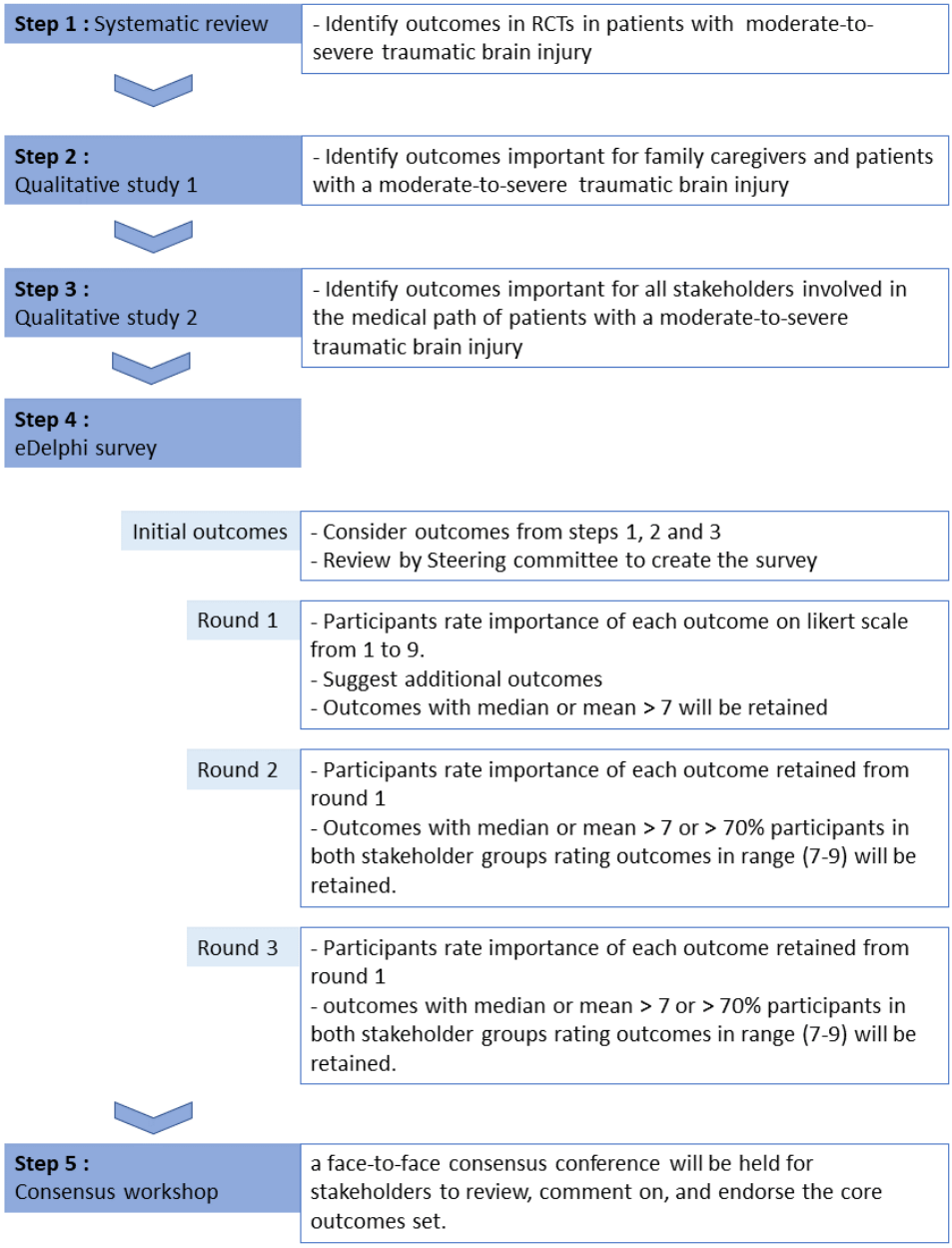
A face-to-face consensus conference will be held for stakeholders to review, comment on, and endorse the COS. This conference will be chaired by members of the steering committee. As of yet, the number and origins of participants at the workshop have not been established. This sample size is based on the Outcome Measures in Rheumatology (OMERACT) consensus workshop. Purposive sampling will be carried out to ensure maximum variation of demographic and clinical characteristics. Informed consent will be obtained from all participants. All discussions will be recorded and transcribed. The overall conference program is outlined in Textbox 1.

Given the timeline of the project, Step 5 will not be undertaken for another 3 years (around mid-2026). The articulation, organization of the workshop, and data analysis will be further elaborated but not detailed here. Figure 1 articulates the differences between the 5 steps.

Textbox 1. Conference program details.

1. Presentation of results: Detailed results from Steps 2, 3, and 4 will be distributed to the participants. The results will be presented during a plenary session of the consensus workshop, and the outcomes will also be shown according to the consensus classification.
2. Breakout group discussion: Participants will be divided into several groups. A trained facilitator will moderate a group discussion on the results from Steps 3 and 4, consensus classification of outcomes, similarities and differences in stakeholder groups, and the resolution of any disagreement, uncertainties, or issues identified.
3. Plenary discussion: Each breakout group will present a summary of their discussion. The conference chair will moderate the discussion.
4. Endorsement of core outcome set (COS): Participants will be asked to formally endorse the core outcomes set which will include the outcome classified as consensus.

Figure 1. Summary of the project regarding the development of a core outcome set in neurocritical care for patients with traumatic brain injury (TBI). RCT: randomized controlled trial.



Ethical Considerations

All steps will be performed according to the appropriate guidelines and regulatory processes.

Step 1

Ethical approval is not required for this step.

Step 2

Patients and relatives provided informed consent to participate in the semistructured interviews (CERAR IRB 00010254 - 2022–093). The analysis of the interview transcripts will be anonymized to respect privacy and anonymity. Finally, patients and relatives will receive €50 (US $52.12) each for compensation for their time to perform these interviews.

For the elaboration and recruitment of patients for Step 2 (semistructured interviews), the group is currently working with the association of patients and families (“Union Nationale des Associations des Familles de Traumatisés Crâniens”).

Step 3

Interviews and focus groups with health stakeholders will also comply with rules and regulations. Although no IRB is necessary in France regarding surveys [44], oral consent will be collected from participants. Verbatim analyses and data will be anonymized and deidentified.

Step 4

No health data are collected in Step 4. Moreover, IRB approval is not mandatory in France for this type of research. However, we will comply with all national authorities’ guidelines in case

of international collaboration. We will also comply with laws and regulations for the publication process.

Step 5

No health data are collected in Step 5. Moreover, IRB approval is not mandatory in France for this type of research, but we will comply with all national authorities' guidelines in case of international collaboration. We will also comply with laws and regulations for the publication process.

Results

Step 1 was completed, and the paper was published in August 2024 [34]. This systematic review was performed from January 2021 to October 2023.

Regarding Step 2, 30 semistructured interviews were carried out (15 patients and 15 caregivers) throughout France. The interviews were performed between July 2021 and December 2023. The results of the verbatim analysis (ie, group experiential themes through cases) were finalized in September 2024, and we expect to begin the publication process by the end of 2024. We aimed to understand the quality of life of both patients and family caregivers, focusing on what matters most to them in their daily lives. The elaboration of Step 3 began in May 2024. The aim of this part of the project is to understand different stakeholder points of view regarding the choice of end points in clinical research.

Although Steps 2 and 3 have not yet been achieved, we have already begun engaging with the scientific community, clinicians, health professionals, other health care stakeholders, and patient associations for the upcoming Delphi process, which is scheduled for the beginning of 2026. This proactive approach ensures that we will have the most comprehensive group of participants for the Delphi process. Step 5 will mark the finalization and dissemination of the COS. This step is preplanned to start in fall/winter 2026.

Discussion

Principal Findings

This project introduces a novel clinical research methodology for TBI through the development of a COS. This COS includes a rigorous multidimensional evaluation of the outcome of patients and encourages the integration of Patient-Reported Outcome Measures (PROMs) in this context. We believe this initiative will address decades of negative findings on this topic, emphasizing the urgent need to improve patient outcomes amid strained resources. The project involves various stakeholders, especially patients and family caregivers, in a rigorous methodological approach that has been successfully tested in other medical disciplines [32,45].

Many work groups have published common data elements [46,47] recommended for RCTs. However, these common data elements are unsuitable for RCTs targeting early interventions in neurocritical care. Notably, our systematic review [34] highlighted the low use of patient-reported outcomes in RCTs, despite increasing advocacy for their use by researchers [26,45].

The study's French context is its main limitation, but we are pursuing international collaboration to ensure its global relevance. Furthermore, given that health systems in high-income countries are often comparable, the findings should be globally applicable.

The results of each step will undergo scientific validation and publication. The dissemination plan includes communications in both national and international congresses involving key stakeholders in TBI research, such as anesthesiologists, intensivists, neurosurgeons, trauma leaders, neuropsychologists, and nurses. Targeted congresses include the French Society of Anesthesia and Intensive Care, European Society of Intensive Care Medicine, the European Society of Anesthesia and Intensive Care, and the International Brain Injury Association—among others. Publications will be submitted to peer-reviewed journals. Where resources allow, we intend to publish our findings in open access whenever possible. Finally, the final COS will be published in a major journal (eg, British Medical Journal, Lancet Neurology), given the initiative's importance and its potential to improve research quality.

We also intend to share our findings with patient associations and through social media. We will disseminate our findings through public engagement activities, based on existing initiatives in their respective countries/institutions, such as European Researchers' Night, alongside collaborations with private insurance companies (ie, AXA and MMA).

The COS will emerge from a consensus process designed to improve the quality and relevance of research evidence in neurocritical care RCTs involving patients with TBI. We expect that the COS will be used only in the RCTs but may also be valuable in other types of research, such as observational studies (eg, registries) and as quality indicators for clinical care.

Conclusion

This project aims to improve the integrity, transparency, usability, and impact of research related to patients with moderate-to-severe TBI. It will ensure that outcomes relevant to all stakeholders are consistently reported in trials, thereby minimizing outcome reporting bias. Ultimately, this will protect patients from potential harm, enable patients and clinicians to make informed treatment decisions, and allow researchers and policy makers to maximize the public value of research.

Acknowledgments

For this project, RC received grants of €345,000 (US $359,655) from Agence Nationale Pour la Recherche, the Région Pays de Loire "Programmes Investissements Avenir" (grant RC22_0349_1), Les Gueules Cassées, and the French Society of Anaesthesia and Critical Care (Société Française d'Anesthésie-Réanimation).

Data Availability

Publications will be made accessible as much as possible (eg, the Step 1 systematic review), depending on available funding. Full data may be available provided upon adequate request to the corresponding author.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Topic guide for patients with traumatic brain injury (TBI) used in Step 2 of developing a core outcome set (COS) in neurocritical care.
[DOCX File , 17 KB - resprot_v14i1e54525_app1.docx]

Multimedia Appendix 2
Caregivers' topic guide used for Step 2 of developing a core outcome set (COS) in neurocritical care for patient with traumatic brain injury (TBI).
[DOCX File , 18 KB - resprot_v14i1e54525_app2.docx]

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Abbreviations

COMET: Core Outcome Measures in Effectiveness Trials
COREQ: Consolidated Criteria for Reporting Qualitative Health Research
COS: core outcome set
GRADE: Grading of Recommendations, Assessment, Development, and Evaluation
IPA: Interpretative Phenomenological Analysis
IRB: institutional review board
OMERACT: Outcome Measures in Rheumatology
PROM: Patient- Reported Outcome Measure
RCT: randomized controlled trial
TBI: traumatic brain injury

Edited by A Schwartz, T Leung; submitted 14.11.23; peer-reviewed by C Asuzu, S Li, N Behn; comments to author 05.04.24; revised version received 09.09.24; accepted 29.11.24; published 09.01.25.

Please cite as:
Cinotti R, Derouin Y, Chenet A, Oujamaa L, Glize B, Launey Y, Dahyot-Fizelier C, Cartron E, Renvoise M, Sautenet B, Sebille V Standardized Outcomes for Randomized Controlled Trials Targeting Early Interventions in Patients With Moderate-to-Severe Traumatic Brain Injury: Protocol for the Development of a Core Outcome Set
JMIR Res Protoc 2025;14:e54525
URL: https://www.researchprotocols.org/2025/1/e54525
doi:10.2196/54525
PMID:

Original Paper

Methodology for the Positive Voices 2022 Survey of People With HIV Accessing Care in England, Wales, and Scotland: Cross-Sectional Questionnaire Study

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Related Article:

This is a corrected version. See correction statement: https://www.researchprotocols.org/2025/1/e72512

Abstract

Background: Due to advances in treatment, HIV is now a chronic condition with near-normal life expectancy. However, people with HIV continue to have a higher burden of mental and physical health conditions and are impacted by wider socioeconomic issues. Positive Voices is a nationally representative series of surveys of people with HIV in the United Kingdom. It monitors the physical, mental, and social health, well-being, and needs of this population so that they can be addressed.

Objective: This paper aimed to describe the methodology, recruitment strategies, and key demographic features of participants recruited for the second national round of Positive Voices (PV2022).

Methods: PV2022 was a national, cross-sectional questionnaire study that included people attending HIV care at 101 of the 178 clinics in the United Kingdom between April 2022 and March 2023. Data from the HIV and AIDS reporting system (HARS), a national surveillance database of people with HIV and attending care that is held at the UK Health Security Agency (UKHSA), was used as a sampling frame. The information collected in PV2022 included demographic and socioeconomic factors, HIV diagnoses and treatment, mental and physical health, health service use and satisfaction, social care and support, met and unmet needs, stigma and discrimination, quality of life, lifestyle factors, and additional challenges experienced due to the COVID-19 pandemic. Data linkage to HARS enabled the extraction of clinical information on antiretroviral therapy (ART), HIV viral load, and CD4 lymphocyte counts. Probabilistic sampling was used to provide a randomly selected, representative sample of people attending HIV care who could be invited to complete a paper or online questionnaire. At the start of 2023, due to under-recruitment mainly due to the impact of the monkeypox (Mpox) outbreak, a separate sequential recruitment strategy was initiated in 14 of the largest clinics to increase participant numbers.

Results: Of the 4622 participants who completed the questionnaire, 3692 were recruited through probabilistic recruitment and 930 through sequential recruitment. The overall response rate (measured as the number of people who completed a questionnaire of those who either accepted or declined) was 50%. Survey respondents represented approximately 1 in 20 people diagnosed with HIV in England, Wales, and Scotland. The median age of participants was 52 years, 3428 of participants were men, 2991 were White, and 1121 were Black.

Conclusions: PV2022 is currently the largest survey of people with HIV in the United Kingdom (as of September 2024). The PV2022 findings will be used to explore the health and well-being of the HIV population and examine associations with demographic, socioeconomic, lifestyle, and other HIV-related factors.

International Registered Report Identifier (IRRID): RR1-10.2196/58531

(JMIR Res Protoc 2025;14:e58531) doi:10.2196/58531

KEYWORDS

HIV care; national survey; quality of life; Positive Voices; transgender population; gender-diverse population; health disparities; health services research; living with HIV; HIV stigma; social determinants of health; longitudinal cohort; access to care; welfare services; health policy; preventive care

Introduction

In the last 2 and a half decades, advances in HIV treatment have greatly reduced the mortality rate among people with HIV [1]. As a result, HIV is now viewed as a chronic condition with near-normal life expectancy [2]. As the population of people with HIV is ageing (half are now aged 50 years and older) [3] and health service delivery models are undergoing continuous change [4], it is essential to understand the types and levels of health needs of people with HIV and to assess long-term outcomes and quality of life [5].

In 2022, there were 94,397 people diagnosed with HIV and accessing care in England [6]. It was estimated that 95% of people with HIV were diagnosed; 98% of those diagnosed were on treatment; and 98% of those on treatment were virally suppressed and therefore unable to transmit HIV [7,8]. Research has indicated that despite substantial improvements in prognosis for people with HIV on treatment and the high coverage of specialist HIV care, there remains a significant level of psychosocial need among people with HIV [9]. They experience higher levels of mental health symptoms [9], with the prevalence of depression and anxiety around twice as much as the general population [10-12]. High levels of perceived and internalized stigma associated with HIV status are experienced by people with HIV, impacting their mental health [13]. Socioeconomic issues, such as poverty, unemployment, unstable housing, lack of social support, and intimate partner violence have also been shown to impact people with HIV, affecting both physical and mental health [14-16]. Understanding these needs is particularly crucial following a period of significant changes in health and social care service provision, due to policies of austerity and the COVID-19 pandemic [17]. Positive Voices (PV) collects and analyses these types of data, providing valuable insights that are used to inform national HIV policy and prevention programs and to evaluate and commission HIV specialist services.

PV is a cross-sectional questionnaire study of people with HIV who receive HIV specialist care in England, Wales, and Scotland, carried out every 3-5 years. In 2014, an extensive pilot phase that included formative research with the HIV community and health care staff facilitated the development of the survey methodology, which was subsequently used for the national roll-out in 2017 (Positive Voices 2017 [PV2017]) [9,18]. Our paper aims to describe the methodology and study design of the second round of the study: Positive Voices 2022 (PV2022).

Methods

Study Design

PV2022 was a national, cross-sectional questionnaire survey of people with HIV attending HIV outpatient care in England, Wales, and Scotland. The questionnaire data were linked to clinical data on antiretroviral therapy (ART), HIV viral load, and CD4 lymphocyte count from the HIV and AIDS reporting system (HARS), a national surveillance database of people with HIV attending care, held at the UK Health Security Agency (UKHSA).

Setting

In December 2020, all HIV clinics that routinely report to HARS were emailed by the PV team and asked whether they wished to express an interest in becoming a PV2022 study site. A total of 101 clinics, over half (57%) of the 178 HIV clinics in the country, returned an expression of interest, 98% of whom were in England (99/101), 1 was in Scotland (1/101), and 1 in Wales (1/101). Sixty-two (61%) clinics had previously participated in the previous round of the study (PV2017). Initially, the recruitment of participants was planned to begin in 2021, but was delayed as patient attendance at clinics was disrupted due to the COVID-19 pandemic restrictions. In April 2022, the recruitment of participants began, as services had started returning to face-to-face consultations. However, following the pandemic, many clinics had adopted a hybrid approach of giving remote telephone or video consultations as well as seeing patients in clinic. Refer to Multimedia Appendix 1 for a list of participating clinics.

In this paper, “clinic staff” has been defined as clinicians (nurses or doctors) and researchers who worked in the participating HIV clinics.

Sample Size

HARS was used as a sampling frame to provide a representative, random sample of people with HIV within each participating clinic who could be approached to participate in the PV2022 survey. HARS is a surveillance database held at the UKHSA that consists of pseudonymized data on the demographic, clinical, and treatment characteristics of people with HIV that is reported each quarter year by all HIV service providers in England [19,20].

The population of patients attending the participating clinics was approximately 74,000. The sample was to include 1 in 5 patients attending each of these clinics. Data from the pilot study and PV2017 indicated a proportion of individuals would be nonrecruitable due to being deceased, no longer attending clinic, being lost-to-follow-up, having been imprisoned or having an incorrect hospital identification number. Therefore, considering this, a sample list of 17,121 patients was created with the assumption that approximately 14,400 would be recruitable. Based on the response rate in PV2017 and observed declines in response rates in other large population-based studies in recent years, the PV2022 response rate was expected to be between 30% and 50%, resulting in 4320 to 7200 participants being recruited. The precision of prevalence estimates of measures such as diagnosed depression, occurring at approximately 30% prevalence, would therefore be ±1.4% and ±1.1% (with 95% confidence) for the response rates of 30% and 50%, respectively. Within a key demographic subgroup comprising 10% of the population, the precision would be ±4.4% and ±3.3%, respectively.

Study Population and Selection

Clinic staff were asked to approach their patients who had been randomly sampled from HARS and included in a list provided by the PV team. Each selected patient was assigned a unique identifier that was displayed on their survey packs or could be used to access their online questionnaire.

The PV team had made efforts to oversample the transgender and gender-diverse HIV population by adding to each clinic's list all patients recorded on HARS who identified as trans or gender-diverse. This was carried out to ensure a sufficient number of participants from this population group were represented, as it had been reported that this cohort was experiencing larger health inequalities in comparison with the general population [8].

Inclusion Criteria

The inclusion criteria were people diagnosed with HIV, aged 18 years or older, residing in the United Kingdom, accessing care at a participating HIV clinic in England, Wales, or Scotland, and able to complete the questionnaire in English either online or on paper.

Exclusion Criteria

There were no set exclusion criteria, however the preselected patients were defined as nonrecruitable if they were unable to take part in the survey for any of the following reasons: moved abroad, transferred care to another clinic, lost contact with the clinic for more than 12 months, had died, had any mental or emotional issue affecting their ability to give implied consent, had a language barrier or literacy difficulties, or were imprisoned or deemed a vulnerable adult.

Study Management

PV2022 was a collaboration between the University College London (UCL) NICHE team, the UKHSA HIV national surveillance team, and a NICHE Patient and Public Involvement representative. "A Person-Centered Needs Informed Model of Care for People with HIV" (NICHE) is a National Institute for Health Research (NIHR) funded program of research to improve the health and well-being of people with HIV. The PV team oversaw all aspects of the research including the study design, the development of the questionnaire and study documents, the oversight of the ethics and governance processes, the monitoring of response rates and recruitment at the participating sites and considered strategies to support and boost recruitment.

Questionnaire Development

Half of the questions in PV2022 were identical to those in PV2017 and were considered core questions to the survey series. These included demographic and socioeconomic factors, HIV related factors, comorbidities, met and unmet health, social and welfare service needs, quality of life measured by EQ-5D-5L, height and weight, smoking and alcohol status by the Alcohol Use Disorders Identification Test-Consumption (AUDIT-C), recreational drug use and general practice (GP), and HIV clinic satisfaction, enabling assessment of trends over time in these factors. New items included in the PV2022 questionnaire included self-reported HIV viral load (whether undetectable or not at last test); questions exploring how well participants understood and trusted the concept of Undetectable equals Untransmittable (U=U), if U=U knowledge and trust impacted on how they felt about their HIV status, a modified version of the Duke-UNC (University of North Carolina) Functional Social Support Questionnaire [21], the 14-item Resilience Scale (RS14) [22], the General Practice Physical Activity Questionnaire (GPPAQ) [23], and questions on the impact of COVID-19 and the uptake of COVID-19 vaccines. In addition, the measure for anxiety and depression in 2017 [24] was replaced with standardized separate measures for depression and anxiety symptoms: the Patient Health Questionnaire-9 (PHQ-9) [25], and the General Anxiety Disorder Questionnaire-7 (GAD-7) [26]. Questions on stigma and discrimination were expanded to take account of internalized and other stigma and included an adapted validated stigma scale [27]. In addition, participants who completed the study online in PV2022 were able to opt-in to complete "Positive Outcomes," an HIV Patient Reported Outcome Measure (PO-PROM), a tool designed for use in clinical settings to assess the needs and concerns of people with HIV [28]. Table 1 details the topics included in PV2017 and PV2022 questionnaires. The PV2022 questionnaire was evaluated online by two groups of people with HIV (up to 10 per group) during November and December 2021. Members of these groups had previously participated in PV2017 and had provided their consent to be contacted again to take part in further research. They provided helpful feedback on the length of the questionnaire, the readability and phrasing of questions,

and the flow and overall order of questions. The questionnaire was modified accordingly.

Table 1. Questionnaire topics, questions, survey tools, and clinical data collected in Positive Voices 2017 and Positive Voices 2022.

Questionnaire topic	PV2017[a]	PV2022[b]
Demographics (age, gender, ethnicity, and sexual orientation)	✓	✓
Socioeconomics (education, employment, housing, financial status, and religion)	✓	✓
HIV diagnosis and treatment (year and country of diagnosis, year started on ART[c], adherence, and side effects)	✓	✓
Self-reported HIV viral load and when last test conducted	—[d]	✓
U=U[e] (understanding of and trust in U=U)	—	✓
Non-HIV diagnosed conditions and treatments (cardiovascular conditions, joint and bone, cancer, mental health, and other long-term conditions)	✓	✓
Mental health and well-being (mental health symptoms [General Health Questionnaire, GHQ-12])	✓	—
Mental health and well-being (depression symptoms [Patient Health Questionnaire, PHQ-9], anxiety symptoms [Generalized Anxiety Disorder questionnaire, GAD-7], modified DUKE-UNC Functional Social Support questionnaire [DUKE-FSSQ], and the Resilience Scale [RS14])	—	✓
Quality of life, life satisfaction and self-rated health (EQ-5D-5L,Office for National Statistics Life Satisfaction and self-rated health questions)	✓	✓
Disclosure and discrimination (disclosure, discrimination in health care settings)	✓	✓
Stigma (internalized stigma and anticipated stigma)	—	✓
Sex and relationships (partner status, sexual behavior, sexually transmitted infections diagnoses)	✓	✓
Women's sexual and reproductive health (pregnancy and contraception)	✓	—
Sexual satisfaction (physical and emotional sexual satisfaction)	—	✓
General health and lifestyle (height, weight, smoking, alcohol [Alcohol Use Disorders Identification Test-Consumption, AUDIT-C] and recreational drug use)	✓	✓
General health and lifestyle (exercise and physical activity [General Practice Physical Activity Questionnaire, GPPAQ])	—	✓
GP[f] and HIV service use and satisfaction (GP and HIV satisfaction, patient experience measures, and use of GP and HIV support services)	✓	✓
Health service use and satisfaction (expanded list of health and social care service use)	—	✓
Impact of COVID-19 pandemic (COVID-19 diagnosis, vaccination status, and access to technology for online appointments)	—	✓
Met and unmet needs (need for HIV related services, health services, social and welfare services)	✓	✓
HIV Positive Outcomes Patient Reported Outcome Measure (PO-PROM[g]) (online questionnaire only, opt-in option)	—	✓
Clinical information from HARS[h]		
Antiretroviral treatment regimen	✓	✓
Laboratory measures (viral load and CD4 lymphocyte count)	✓	✓

[a]PV2017: Positive Voices 2017.

[b]PV2022: Positive Voices 2022.

[c]ART: antiretroviral therapy.

[d]—: not applicable.

[e]U=U: Undetectable=Untransmittable.

[f]GP: general practitioner.

[g]PO-PROM: Positive Outcomes patient-reported outcome measure.

[h]HARS: HIV and AIDS reporting system.

Study Documents

Each participating clinic was provided with electronic copies of the study materials including the protocol, manual of operations, participant information leaflet, privacy notice, waiting room poster, and a password-protected study log that listed each clinic's sample list of randomly selected participants. Study documents such as the protocol were also available on

the study website [29]. Questionnaire packs, 1 for each participant within the clinic's sample, were dispatched by courier to the site. The pack consisted of a sealed envelope labelled with the participant's clinic number, hospital name, and unique identifier displayed on the outside, as well as the patient information leaflet, questionnaire, a freepost envelope, and a signposting sheet detailing community support organizations such as the Terrence Higgins Trust, a British charity that campaigns and provides services relating to HIV and sexual health.

Site Initiation Meetings

Each participating site attended 1 of the site initiation meetings that took place remotely on Microsoft Teams between February and March 2022. A maximum of ten clinic sites attended each meeting. Information on how to identify, contact, and recruit participants was explained, and a demonstration was given on the procedure for completing the study log (refer to Recruitment and Data Collection section). Sites were asked to nominate a PV2022 champion within their clinic who would act as the main contact with the PV team. All the site initiation meetings were completed by March 18, 2022, just before the recruitment of participants commenced in April 2022.

Recruitment and Data Collection

The first participant was recruited on April 11, 2022, and recruitment closed on March 31, 2023. At each site, clinic staff were asked to complete a study log on their recruitment outcomes and return it to the PV team each month. The information they recorded in their study log included the mode (whether in-person, email, text, or post) and date of each participant's initial contact, the survey distribution method (in-person, email, text, or post), the survey distribution date, the recruitment status (whether nonrecruitable, accepted, or declined), and the reason if the status was nonrecruitable.

The PV team provided a brief script for email and text message approaches as a guide for clinic staff. Online questionnaires were sent by a link by email or text message, or patients received their survey pack containing the paper questionnaire at their next clinic attendance. Clinic staff decided on the method of approach used in accordance with each participant's preferred and usual method of communication with their clinics.

Change to the Sequential Recruitment Strategy at Specific London Sites

Reviewing the study logs monthly, it was established that several sites were underrecruiting. Consequently, the recruitment period was extended from 6 to 12 months to allow clinics additional time to reach their recruitment targets. Further email correspondence with clinics revealed that many had resource pressures, fewer face-to-face clinic appointments after the start of the COVID-19 pandemic, and the 2022 Mpox outbreak had been an unanticipated challenge impacting upon recruitment, particularly in London. In response, the PV team designed a sequential recruitment strategy whereby a site could approach any eligible participant attending the clinic sequentially, that is, approach patients as they entered the clinic instead of contacting participants from their preselected sample list. In total, 14 HIV clinics across 7 NHS trusts in London that had recruited less than 10% of their minimum target after 8 months were offered a switch to the sequential recruitment strategy, which they commenced at the beginning of December 2022, having been sent new recruitment packs, survey labels, and a simpler study log that reflected the new strategy.

Participants recruited through the new sequential recruitment strategy were only able to complete the paper questionnaire. Staff were asked to encourage participants to complete their questionnaires in the clinic when they came for their consultation rather than taking them home, as questionnaires sometimes got lost, forgotten, or were not returned to the PV team at UKHSA.

Secure Storage and Transfer of Data

Paper questionnaires and study logs were securely stored within each clinic. The sites were responsible for collecting, storing, and returning the paper questionnaires completed in their clinic to the PV team at the UKHSA by using the Freepost envelopes provided in the participant packs or by courier.

Data Management

When paper questionnaires were received by the PV team, data were double data-entered (entered by 2 separate data input personnel) into Snap Survey software (Snap Survey Ltd) and each questionnaire was scanned. Online responses were extracted from Snap Survey as an electronic csv file. The data from both sources was then imported into Stata (version 15.0, StataCorp) and merged to create a master questionnaire data file. Data discrepancies between the 1st and 2nd date entries of the paper questionnaires were checked and resolved by referring to scanned copies of questionnaires.

Linkage

Data on ART use, the most recent CD4 lymphocyte count, and HIV viral load measurement were linked from HARS to the survey data using the participant's clinic ID number and unique identifier.

Data Security

Paper questionnaires were stored securely in locked cabinets at UKHSA where they will remain for a maximum of 10 years and then be securely destroyed. The online version of the questionnaire was hosted on a secure HTTPS connection and data were encrypted at the point of transmission and stored on a secure, dedicated, virtual server hosted at UKHSA.

All data were securely held at UKHSA, encrypted, and restricted to the PV team. Data collection, storage, and use were consistent with the procedures described in the NHS Information Governance Toolkit. A data-sharing agreement was developed to ensure the secure transfer of pseudonymized data between UKHSA and UCL for data analysis.

All researchers were trained to handle data according to Caldicott guidelines, the General Data Protection Regulation, and Section 60 of the Health and Social Care Act.

Ethical Considerations

The Positive Voices study was granted ethical approval by the London Harrow Research Ethics Committee (13/LO/0279) on March 28, 2013. All the updated documents for PV2022 were

submitted as a substantial amendment and subsequently approved on June 23, 2021. The patient information leaflet provided information on how the patients could participate, the potential risks and benefits of participation, and contact information for the PV team. Clinic staff were advised to tell each eligible participant that participation was voluntary and that their decision to participate would not affect their care. A privacy notice was available online with further information about data security [29]. Consent was implied on voluntary completion of the questionnaire. All participants received a digital gift voucher for 5 GBP (equivalent to US $6.50) as an acknowledgement for their time and consideration. This incentive was chosen based on findings from the formative work undertaken before the survey began, where participants expressed a requirement for an incentive. The PV team provided monthly feedback to sites showing the number of completed questionnaires received either by post or online from participants from their clinic. If a patient agreed to participate in the survey but no questionnaire had been returned, clinic staff were asked to send up to 3 reminders using the preferred method of contact initially used. Participants were not asked to provide identifiable information for the survey. However, at the end of the survey, participants were given the option of providing their personal contact details, either phone number or email address, if they were willing to be contacted for future research. If contact details were given, this personal information was unlinked from their survey data and stored securely on a separate password-protected database at UKHSA.

Results

Overview

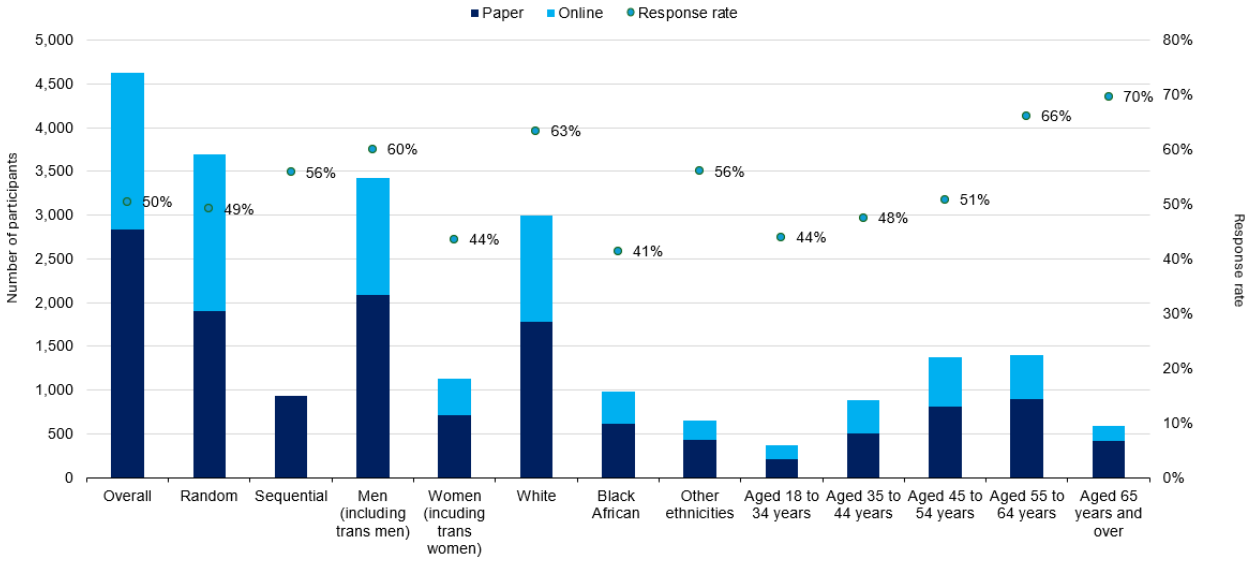
The PV2022 survey was completed by 4622 people diagnosed with HIV, representing approximately one in 20 people living with HIV and accessing care in England, Wales, and Scotland in 2022 [19]. Overall, 4540 participants provided sufficient demographic information to enable linkage to HARS to acquire additional clinical data, which included treatment information, viral load, and CD4 lymphocyte count. The most popular completion method was by paper questionnaires with 2829 (61%) compared with 1793 (39%) online questionnaires. A third (930/2829, 33%) of the paper questionnaires were completed by participants recruited sequentially. Of the 4622 participants, 1737 provided their phone numbers or email addresses as contact details regarding further research, and 897 completed the optional PO PROM questionnaire online.

Response Rate

To calculate the response rate, the number of completed questionnaires (n=4622) was divided by the number of people who accepted (n=8096) or declined to participate (n=1088), which gave an overall response rate of 50%. In addition, 4994 people had been contacted by email or text but had not responded, which may have reflected further declines although may also have been due to messages not being received, read, or being discounted as an unsolicited message. By including these nonresponses in the calculations, it would have given a response rate of 33%. The true response rate likely lies somewhere between 33% and 50%.

A total of 930 (20%) participants were recruited through the sequential recruitment strategy, a higher response rate (55%) compared with the original preselected participant recruitment strategy (49%, Figure 1). Of the 930 sequentially recruited participants, 906 were able to be matched to HARS: 222 (25%) of these had initially been preselected to take part in the survey. Response rates differed by demographic characteristics (taken from HARS) as shown in Figure 1. Men had a higher response rate (60%) (3428 completed out of 5715 accepted or declined) compared with women (1124/2580, 44%) and White people had a higher response rate (2991/4724, 63%) compared with Black African people (983/2380, 41%) or those of other ethnicities (648/1158, 56%). Response rates were also higher in older age groups, with the highest response rate (592/851, 70%) in the people aged 65 years or older (Figure 1). Multimedia Appendix 2 provides the corresponding numbers for all groups shown in Figure 1.

Figure 1. Positive Voices 2022 response rates by recruitment mode, gender, ethnicity, and age among participants of Positive Voices 2022 (N=4622).



Age, Gender, and Ethnic Distribution of PV2022 Participants

The median age of PV2022 participants (n=4620) was 52 (IQR 43-60) years, and about 3 quarters of participants had been diagnosed with HIV more than 10 years ago (Table 2). Nearly a quarter of participants were women (24%) and over a fifth (21%) of participants were Black African people (Table 2).

Gender identity of participants completing PV2022 broadly reflected the gender identity distribution of people accessing HIV care in the United Kingdom. However, there was some overrepresentation of men (6% higher), and underrepresentation of women (8% lower) compared with HARS data (Figure 2). A total of 67 PV2022 participants identified as transgender or gender diverse.

Compared with the national population of people accessing HIV care, Black African individuals were underrepresented in the PV2022 sample (10% lower), and White participants were overrepresented (13% higher; Figure 2).

Participants from the sequential recruitment route were younger compared to the preselected random recruitment strategy (median age 49 (IQR 39-57) years versus 53 (IQR 45-60) years, for sequential versus random recruitment respectively), overrepresented men (85% vs 72%) and White people (67% vs 64%) and underrepresented Black African people (14% vs 23%).

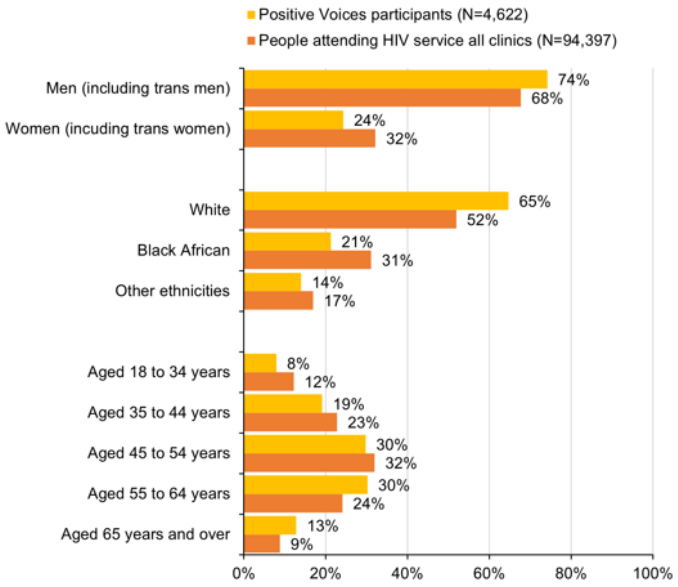
A higher proportion of participants who completed the online questionnaire were White compared to participants who completed the paper questionnaire (67% online vs 63% paper; Figure 1 and Multimedia Appendix 2.

Table 2. Demographics and year of HIV diagnosis among Positive Voices 2022 participants.

Characteristics	Participants (n=4622), n (%)
Age group (years)[a]	
18-34	369 (8)
35-44	885 (19.2)
45-54	1375 (29.8)
55-64	1397 (30.3)
65+	592 (12.8)
Gender	
Man (including trans men)	3428 (74.2)
Woman (including trans woman)	1124 (24.3)
Nonbinary	26 (0.6)
In another way	8 (0.2)
Prefer not to say and unknown	36 (0.8)
Ethnic group	
White	2991 (64.7)
Black African	983 (21.3)
Black other	138 (3)
Asian	189 (4.1)
Mixed	143 (3.1)
Other (including prefer not to say and unknown)	178 (3.9)
Year of diagnosis	
2019-2023	214 (4.6)
2014-2018	801 (17.3)
2009-2013	957 (20.7)
2004-2008	1063 (23)
2003 or earlier	1497 (32.4)
Unknown	90 (1.9)

[a]Age was missing for 2 participants.

Figure 2. Representativeness of Positive Voices 2022 participants compared with the national population of people with HIV who attended HIV services in 2022.



Survey Distribution Method

The survey approach method was available for 4375 of the 4622 responses received. Over half of these participants, 54% (2371/4375), were approached in person, 23% (1001/4375) were contacted by phone, 17% (727/4375) received a text message, 5% (214/4375) were contacted by email, and 1% (62/4375) received the questionnaire by post.

Discussion

Principal Findings

In this paper, we have described the methods, design and sample demographic characteristics of the Positive Voices 2022 study. PV2022 is the largest questionnaire study to date of people with HIV in England, Wales, and Scotland. The outputs from the study will provide a unique insight into the health and well-being of people with HIV, particularly regarding mental health, met and unmet needs, experiences of stigma, and the impact of COVID-19 pandemic [30]. The overall response rate for PV2022 was estimated to be between 33% and 50% compared with 52% for the previous iteration of the survey (PV2017) [9]. Several factors impacted on the response rate in PV2022. In particular, the first 6 months of the recruitment period (between April and September 2022) coincided with the Mpox *clade* IIb outbreak, primarily among gay and bisexual men in London and other large cities in England [31]. The impact of this outbreak on sexual health and HIV services resulted in a significant deployment of clinic staff and resources to manage the outbreak and to provide a vaccination program to contain the infection [31]. Feedback from some of the largest clinics that were open to recruitment for PV2022 over the duration of the Mpox outbreak suggested that recruitment had been challenging to prioritize during this period, particularly as the methodology required considerable clinic staff time commitment.

As a result of a challenging recruitment environment, the switch to sequential recruitment in December 2022 resulted in an improvement to study recruitment. This was mainly because the strategy of sequential recruitment did not require the administration time that had been required for the original strategy. Furthermore, as these participants were only able to complete the paper questionnaire and not the online version, clinic staff recommended questionnaires be completed within the clinic setting and discouraged participants from taking the questionnaires home, where they may have remained uncompleted or unreturned. Although this strategy was not always successful, the proportion that completed and submitted their questionnaire within the clinic was higher in comparison with the original recruitment strategy.

Other potential factors that may have impacted upon the response rate for PV2022 related to the COVID-19 pandemic. The widespread adoption of online health care appointments during the pandemic meant that fewer patients attended regular HIV appointments in person [32,33]. A recent systematic review identified interruption in attendance of in-person clinic consultations, reduced adherence to treatment, and a subsequent increase in mortality among people with HIV, as a consequence of the changes in service delivery due to the COVID-19 pandemic [34]. As the most effective mode of recruitment for PV2022 was in-person with clinic staff, the decreased frequency of participants attending clinic likely contributed to the lower response rate seen in PV2022 in comparison with PV2017. Less personal interaction between patients and clinic staff may also have impacted upon participants' enthusiasm for completing questionnaires when approached. When clinic staff were able to personally hand out the survey packs within the clinic, they were better able to explain the importance of the study and the impact the results would have on policy and service planning. Evidence suggests that initial approach and personal connection greatly impacts on survey completion rates in all populations [35,36] which has implications for future survey planning, particularly as some appointments remain online.

Recent evidence has suggested that survey fatigue and nonparticipation, had increased as a result of the proliferation of online surveys during and following the COVID-19 pandemic

[37]. Whilst the pandemic clearly impacted upon research in terms of recruitment and data collection, evidence suggests that the effects reached far wider. The pandemic exacerbated inequalities in health and access to health care, particularly amongst those living in economic hardship [38] and for Black African individuals and those of other minority ethnic groups [39], and the HIV population consists of a high proportion of these groups.

Strengths of PV2022 include the large sample size, the inclusion of a broadly representative sample of 1 in 20 people with HIV in England, Scotland and Wales (as evidenced by comparison with the national HARS database) and the linkage of participant self-reported questionnaire data to HIV clinical data from HARS. With increasing interest in patient experience and outcome measures, other clinical conditions could use a similar survey method to survey their patient group. PV2022 also has some limitations: as the study was only available to people with HIV in care, it did not represent those people with HIV who were not receiving care in 2022, whose mental and physical health, and experiences of health care, may be different and valuable for informing and improving HIV specialist services. Similarly, nonresponders to participate in the study may differ from responders with respect to health, lifestyle, and other factors. Further efforts to reach these groups and identify their needs are crucial. In addition, the sampling frame for the initial recruitment method was based on those attending care in 2020, and therefore our data are unable to represent those who have been newly diagnosed in the interim. Future work by the PV team will examine the recruitment challenges to PV2022 and will involve participant and public involvement groups and clinic staff. This will inform future rounds of the Positive Voices survey and optimize response rates.

PV2022 formed part of the formative work of the NIHR funded NICHE program of research led by UCL. NICHE aims to improve the mental and physical well-being of people with HIV by designing and evaluating a targeted psychosocial intervention as part of routine HIV care [29]. Findings from PV2022 informed the development of the intervention for the "Psycho-Social Intervention for People With HIV – Evidence From a Randomised Evaluation" (SPHERE) trial, which commenced in United Kingdom HIV clinics in August 2024. Results from Positive Voices 2022 have been published in a government report [30] that has directly informed the HIV action plan for England which aims to end stigma and inform interventions to improve patient-centered care and the provision of HIV clinical and support services. Further analysis of the data will be presented at HIV conferences, published in peer-reviewed journals and disseminated through the extensive NICHE PPI network.

Acknowledgments

The authors would like to thank all the PV2022 study participants who generously participated in this research. The authors would also like to thank the clinic staff in all the 101 participating sites for their hard work and dedication. PV2022 was conducted by the UK Health Security Agency and University College London and represents independent research funded by the National Institute for Health Research (Program Grants for Applied Research, A person-centered Needs Informed model of Care for people with HIV, to improve well-being, mental health and reduce socioeconomic disadvantages and stigma, (NICHE; NIHR202038). The views expressed in this publication are those of the authors and not necessarily those of the NHS, the National Institute for Health Research, or the Department of Health and Social Care. Funding was also received from the UK Health Security Agency and Gilead Sciences Ltd.

Data Availability

The data sets generated during this study are not publicly available due to ongoing analysis and dissemination plans by the NICHE and UKHSA teams. However, data may be available from the corresponding author on reasonable request.

Authors' Contributions

CK, AA, VM, AB, MK, VD, FL, CS, and AR contributed to conceptualization. CK, AA, VM, AB, MK, VD, FL, and AR managed methodology. CK, AA, VM, AB, CH, HK, AF, APM, AR, FL, JS, AS, and APM handled investigation. JS, CK, MK, FL, and AR wrote the original draft. JS, CK, AA, HK, APM, VM, AF, CS, AB, AS, VD, AR, FL, and MK contributed to review and editing. AR, FL, CS, VD, and MK managed funding acquisition. AR, FL, and MK handled supervision.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Full list of participating clinics and clinic teams.
[DOCX File , 18 KB - resprot_v14i1e58531_app1.docx]

Multimedia Appendix 2

Table of Positive Voices 2022 (PV2022) Response rates* by recruitment mode, gender, ethnicity, and age among participants of PV2022 linked to HARS* (N=4622).
[DOCX File , 17 KB - resprot_v14i1e58531_app2.docx]

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Abbreviations

ART: antiretroviral therapy
AUDIT-C: Alcohol Use Disorders Identification Test-Consumption
GAD-7: Generalized Anxiety Disorder questionnaire-7
GP: general practice
GPPAQ: General Practice Physical Activity Questionnaire
HARS: HIV and AIDS reporting system
NICHE: A Person-Centered Needs Informed Model of Care for People with HIV
NIHR: National Institute for Health Research

PHQ-9: Patient Health Questionnaire-9
PV: Positive Voices
PV2017: Positive Voices 2017
PV2022: Positive Voices PV2022
PO-PROM: Positive Outcomes Patient Reported Outcome Measure
RS14: 14-item Resilience Scale
SPHERE: Psycho-Social Intervention for People With HIV–Evidence From a Randomised Evaluation
UKHSA: UK Health Security Agency
U=U: Undetectable equals Untransmittable
UCL: University College London
UNC: University of North Carolina

Edited by T Leung; submitted 02.04.24; peer-reviewed by JM Wiginton, M Mousnad; comments to author 22.07.24; revised version received 07.08.24; accepted 30.09.24; published 10.01.25.

Please cite as:
Sewell J, Kelly C, Aghaizu A, Kitt H, Pelchen-Matthews A, Martin V, Farah A, Smith C, Brown A, Humphreys C, Sparrowhawk A, Delpech V, Rodger A, Lampe F, Kall M
Methodology for the Positive Voices 2022 Survey of People With HIV Accessing Care in England, Wales, and Scotland: Cross-Sectional Questionnaire Study
JMIR Res Protoc 2025;14:e58531
URL: https://www.researchprotocols.org/2025/1/e58531
doi:10.2196/58531
PMID:

Protocol

Assessment of Geriatric Problems and Risk Factors for Delirium in Surgical Medicine: Protocol for Multidisciplinary Prospective Clinical Study

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Abstract

Background: An aging population in combination with more gentle and less stressful surgical procedures leads to an increased number of operations on older patients. This collectively raises novel challenges due to higher age heavily impacting treatment. A major problem, emerging in up to 50% of cases, is perioperative delirium. It is thus vital to understand whether and which existing geriatric assessments are capable of reliably identifying risk factors, how high the incidence of delirium is, and whether the resulting management of these risk factors might lead to a reduced incidence of delirium.

Objective: This study aimed to determine the frequency and severity of geriatric medical problems in elective patients of the Clinics of Oral and Maxillofacial Surgery, Vascular Surgery, and Orthopedics, General Surgery, and Trauma Surgery, revealing associations with the incidence of perioperative delirium regarding potential risk factors, and recording the long-term effects of geriatric problems and any perioperative delirium that might have developed later the patient's life.

Methods: We performed both pre- and postoperative assessments in patients of 4 different surgical departments who are older than 70 years. Patient-validated screening instruments will be used to identify risk factors. A geriatric assessment with the content of basal and instrumental activities of daily living (basal activities of daily living [Katz index], instrumental activities of daily living [Lawton and Brody score], cognition [6-item screener and clock drawing test], mobility [de Morton Mobility Index and Sit-to-Stand test], sleep [Pittsburgh Sleep Quality Index and Insomnia Severity Index/STOP-BANG], drug therapy [polypharmacy and quality of medication, Fit For The Aged classification, and anticholinergic burden score], and pain assessment and delirium risk (Delirium Risk Assessment Tool) will be performed. Any medical problems detected will be treated according to current standards, and no intervention is planned as part of the study. In addition, a telephone follow-up will be performed 3, 6, and 12 months after discharge.

Results: Recruitment started in August 2022, with 421 patients already recruited at the time of submission. Initial analyses of the data are to be published at the end of 2024 or the beginning of 2025.

Conclusions: In the current study, we investigate whether the risk factors addressed in the assessment are associated with an increase in the delirium rate. The aim is then to reduce this comprehensive assessment to the central aspects to be able to conduct targeted and efficient risk screening.

Trial Registration: German Clinical Trials Registry DRKS00028614; https://www.drks.de/search/de/trial/DRKS00028614

International Registered Report Identifier (IRRID): DERR1-10.2196/59203

(JMIR Res Protoc 2025;14:e59203) doi:10.2196/59203

KEYWORDS

delirium; older patients; perioperative assessment; age-related surgical risk factors; geriatric assessment; gerontology; aging; surgical medicine; surgical care; surgery; multidisciplinary; prospective study; perioperative; screening; palliative care; health informatics

Introduction

Background

From the advances in surgical medicine with the development of less stressful surgical and anesthetic procedures, more and more older people are receiving surgical care who would not have been treated surgically a decade ago [1]. However, older age is associated with numerous additional problems, such as frailty [2], cognitive impairment [3,4], sleep disorders [5,6], and polypharmacy [7,8]. These age-associated problems are not routinely recorded but make older patients vulnerable. Perioperative delirium of vulnerable older patients is a major problem. Delirium is distressing for the individual, increases the burden of care, and has long-term negative consequences in terms of cognition, self-care ability, and prognosis [9].

Thus, incidences of perioperative delirium in older people are reported to be as high as 50% [10,11]. Factors influencing the incidence of delirium include duration and depth of anesthesia, the size of the surgical procedure, the duration of the preoperative fasting period, preoperative blood pressure, and frailty, brain disorders, hearing impairment, or history of sleep disturbances [12].

Perioperative delirium is a relatively common and serious complication after surgery [13-15]. The *DSM-5* (*Diagnostic and Statistical Manual of Mental Disorders* [Fifth Edition]) includes delirium into the broader category of neurocognitive disorders, which include acquired cognitive dysfunction [16,17]. Delirium is defined as an attention deficit disorder that develops over a short period of time, with additional cognitive impairment that cannot be explained by other preexisting neurocognitive impairments [18]. According to the *DSM-5*, the typical symptoms that characterize delirium are (1) “disturbance in attention,” (2) “disturbance develops over a short period of time,” (3) “additional disturbance in cognition,” (4) “disturbances in the first 2 criteria are not better explained by another preexisting disorder,” and (5) “disturbance is a direct physiological consequence of another medical condition, substance intoxication, or withdrawal” [19,20]. In general, the incidence of delirium in surgical procedures is 2%-3%, and in high-risk patients, it is even much higher at 50%-70% [11,21]. Nevertheless, precise causes as well as risk factors and incidences for the development of postoperative delirium are not yet known or deciphered [10].

In the literature, several potential risk factors for postoperative delirium are indicated. Among these are the duration and depth of anesthesia [22,23], the extent of the surgical procedure, the duration of the preoperative fasting period [10,24], the preoperative blood pressure, as well as frailty, brain disorders, hearing disorders, or sleep disorders in the history [2,25]. Delirium with its multifactorial genesis is a major challenge in risk stratification and diagnosis. Validated screening tools exist for many of the risk factors [26-32]. However, recording all risk factors is not effective in everyday clinical practice and is difficult to implement in terms of time. It is therefore necessary to compile a specialist assessment in order to identify patients at risk of delirium as effectively and reliably as possible.

Some of these risk factors are captured by validated screening instruments. Identifying risk factors allows better preoperative management [10]. Still, the regular recording of dementia, the need for assistance in daily life, or the accumulation of several diseases by geriatric screening to determine geriatric care needs is practically not established. Comorbid geriatric problems leading to functional limitations are therefore often overlooked, although they represent a major social and economic problem [33,34].

Aim of This Research

We aim to analyze which parameters of our comprehensive geriatric assessment are associated with the occurrence of delirium depending on the specialty, and what parameters are to be included in a time-effective, target-oriented, and implementable assessment.

Methods

Study Design and Setting

This prospective clinical observational study analyzes the frequency and risk factors for perioperative delirium in patients after surgical treatment in the Department of Orthopedics and Trauma Surgery, the Department of Vascular and Endovascular Surgery, General Surgery, and the Department of Oral and Maxillofacial Plastic Surgery of the University Hospital of Düsseldorf in the intensive care unit and normal ward. The University Hospital of Düsseldorf is the largest hospital in the state capital of North Rhine-Westphalia, Germany. It houses more than 50,000 in-patients per year [35].

Study Population

Inclusion criteria will be patients (aged 70 years and older) presenting for elective and emergency surgery at the Departments of Oral and Maxillofacial Surgery, Orthopedics and Trauma Surgery, General Surgery, and Vascular Surgery. In addition, we will also contact the included patients by telephone 3, 6, and 12 months after discharge to ask about their health status in a standardized way. No interventions are planned as part of this study, and any medical problems uncovered will be treated according to standard medical practice.

A case number calculation is hardly possible due to the sparse data. Therefore, one goal of this study is to collect robust data on the incidence of delirium and to be able to plan further studies on the basis of this solid data. Initially, we will offer participation in this study to all consecutive presenting patients who meet the inclusion criteria (Textbox 1). The initial recruitment period is planned to be 6 months. The goal is to enroll at least 100 patients per discipline, in total over 400

patients. If this number is not reached within this period, the recruitment period will have to be extended accordingly. Solid incidence figures are to be determined within the framework of this pilot study, so further studies can then be planned with possible case number calculation.

Textbox 1. Inclusion and exclusion criteria.

Inclusion criteria

- Patients presenting for elective surgery at the Clinic for Oral and Maxillofacial Plastic Surgery, Orthopedics and Trauma Surgery, General Surgery, and Vascular Surgery.
- Age 70 years.
- Consent of the patient or caregiver.

Exclusion criteria

- No consent to participate.
- Unstable clinical situation.
- Patients requiring palliative care.
- Very advanced dementia (Reisberg VI-VII).

Recruitment

Patient recruitment starts in August 2022. We have been in negotiations with other surgical disciplines for almost a year, aiming to include as many different surgical specialties as possible. We are therefore submitting this study protocol during ongoing recruitment. After inpatient admission in the respective disciplines, the eligible patients are informed about the clinical examination by the study doctor. The patients are given sufficient time to think about their participation and to discuss it with their caregivers. They can also clarify any questions with the study doctor. After the patient has given and signed his or her consent, he or she takes part in the study (Figure 1).

Figure 1. Study procedure overview. Timeline including recruitment, pre- and postoperative assessment, surgery, discharge assessment, and the assessment by phone after 3,6, and 12 months.

Measures and Parameters

In the context of this study, in addition to routine preoperative preparation in elective and emergency older patients, a geriatric assessment (Textbox 2) with the content of basal and instrumental ADL (basal ADL: Katz index [26]; instrumental ADL: Lawton and Brody score [27]; emotion: World Health Organization-5 scale [28]; cognition: 6-item screener and clock drawing test; mobility: de Morton Mobility Index and Sit-to-Stand test [29]; sleep: Pittsburgh Sleep Quality Index, Insomnia Severity Index, and STOP-BANG [30-32]; drug therapy: polypharmacy and quality of medication, Fit For The Aged classification, and anticholinergic burden score), pain assessment, and delirium risk (Delirium Risk Assessment Tool) is to be performed. The Fit For The Aged list evaluates drugs in terms of their benefit-risk profile when used in older patients. The aim is to reduce the number of potentially inadequate medications in patients aged over 65 years old [36]. In an emergency setting, the tests to record the acute status were carried out directly preoperatively. Tests such as sleep quality and well-being, which cover a longer period before the operation, were carried out postoperatively if not otherwise possible. Through this, the study gains a broad spectrum of possible risk factors while using validated and clinically approved assessment tools.

Textbox 2. Depiction of the pre- and postoperative parameters.

Preoperative parameters

- Age (years), gender, and BMI
- American Society of Anesthesiologists classification
- Comorbidities, risk factors, previous radio and chemotherapy
- Preoperative medication and calculation of anticholinergic load (anticholinergic burden score)
- Delirium Risk Assessment Tool
- Routine laboratory values

Geriatric assessment

- Katz index
- Instrumental activities of daily living score according to Lawton and Brody
- Mobility and strength
- de Morton Mobility Index
- Handgrip strength (Hydraulic hand dynamometer)
- Sit-to-stand test
- Emotion World Health Organization-5 scale
- Nutritional status
- Mini Nutritional Assessment Short-Form
- Skinfold thickness over the triceps muscle
- Brain performance
- 6-Item-Screener
- Clock-Drawing-Test
- Hearing ability
- Hearing Handicap Inventory for the Elderly-Short Form
- Sleep disorders or sleep quality
  - Pittsburgh Sleep Quality Index
  - Insomnia Severity Index
  - STOP-BANG–Risk score for obstructive sleep apneas
- Pain assessment

Postoperative parameters

- Nursing Delirium Screening Scale (routinely performed in the recovery room by anesthesia)
- Confusion Assessment Method
- Confusion Assessment Method-Intensive Care Unit
- Alertness, Abbreviated Mental Test 4, Attention, Acute Chance or Fluctuating Course
- postoperative pain assessment
- Mobility (de Morton Mobility Index, instrumental activities of daily living, and Katz index) before discharge

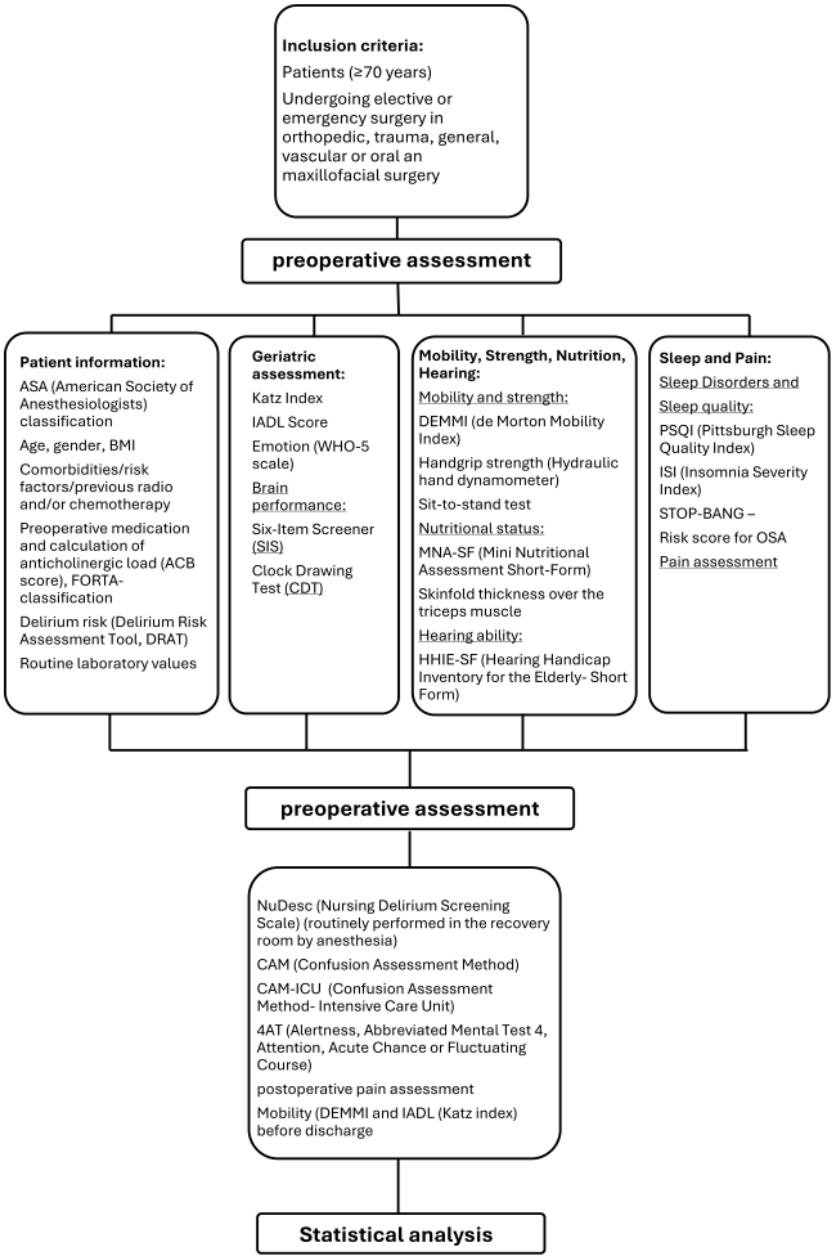
Follow-up

- Instrumental activities of daily living
- Katz index
- G8 screening test
- Pain assessment
- World Health Organization-5 scale

Testing is done every 8 hours in the Intensive Care Unit Confusion Assessment Method-Intensive Care Unit and twice daily in the normal ward (Confusion Assessment Method and Alertness, Abbreviated Mental Test 4) until postoperative day 7 or discharge [37]. Further testing is done as needed or after revision, operation, and so on.

Patients are assessed perioperatively during the daily ward rounds with a focus on their general condition and the presence of delirium. The instruments NuDesc, Confusion Assessment Method, which are routinely recorded in-house, and the Alertness, Abbreviated Mental Test 4, which was introduced in 2020, are used for this purpose [38]. The simultaneous use of these instruments also allows their comparison regarding their quality criteria and may lead to a reduction in monitoring effort in the medium term if one of these instruments proves to be superior (Figure 2).

Figure 2. Overview of preoperative evaluation, pre- and postoperative assessment, and analysis. 4AT: Alertness, Abbreviated Mental Test 4, Attention, Acute Chance or Fluctuating Course; ACB: anticholinergic burden; ADL: activities of daily living; ASA: American Society of Anesthesiologists; CAM: Confusion Assessment Method; CAM-ICU: Confusion Assessment Method-Intensive Care Unit; DEMMI: de Morton Mobility Index; DRAT: Delirium Risk Assessment Tool; FORTA: Fit For The Aged; HHIE-SF: Hearing Handicap Inventory for the Elderly-Short Form; IADL: instrumental activities of daily living; ISI: Insomnia Severity Index; MNA-SF: Mini Nutritional Assessment Short-Form; Nu-Desc: Nursing Delirium Screening Scale; OSA: obstructive sleep apnea; PSQI: Pittsburgh Sleep Quality Index; WHO: World Health Organization.



Follow-Up

We plan to contact patients by telephone 3, 6, and 12 months after discharge to inquire about their current health status. Here the patients are asked about changes in sleeping behavior, changes in medication, changes in mobility, and possible rehabilitation treatment. Furthermore, ADL and Katz, G8 Screening Test, a pain assessment, and the World Health

Organization–5 scale are recorded. Bellera et al [39] created the G8 geriatric screening test, which evaluates drug use, general health, age, mobility, nutritional state, and cognitive status.

Evaluation Outcomes

We aim to determine the frequency of perioperative delirium in patients after surgical treatment in the Clinic for Orthopedics and Trauma Surgery, in the Clinic for Vascular and Endovascular Surgery, and in the Clinic for Oral and Maxillofacial Facial Plastic Surgery at the University Hospital Düsseldorf in the intensive and normal care unit. We want to use the comprehensive assessment to create a risk profile for patients with delirium. The individual risk factors are to be evaluated with regard to their use in the context of a specialized geriatric assessment.

Statistical Analysis

The evaluation is performed as descriptive statistics with the listing of the frequencies of geriatric problems and perioperative delirium. To investigate the correlation between perioperative delirium and clinical and geriatric parameters, the correlation is determined. The parameters that correlate significantly with the incidence of delirium are examined in a further step in the context of logistic regression analysis for their concrete and independent influence on delirium incidence. Calculations are performed using the statistical program SPSS (version 28.0; IBM Corp) and Jamovi [40]. A *P* value of <.05 is considered significant. If the normal distribution of the dependent variables was confirmed by the Shapiro-Wilk test, homoscedasticity was confirmed by the Levene test and significant outliers were eliminated by boxplots, the mean differences were analyzed using the independent *t* test. The Mann-Whitney *U* test is used to analyze the mean differences of the dependent variables that were not regularly distributed. Chi-square tests are used to analyze bivariate correlations between relevant variables and the occurrence of delirium (delirium vs no delirium). The odds ratios of the relationships are calculated with 95% CIs. Two-sided statistical tests are used, and the α level of .05 is used to determine significance. Significance is defined as a *P* value of less than .05, very significant as a value of less than .01, and highly significant as a value of less than .001. To reduce the possibility of a type I error in repeated testing, Bonferroni correction is used [41]. The factors that cause delirium and that are classified as statistically significant at a significance level of *P*=.05 are determined using binomial logistic regression analysis.

Ethical Considerations

The study was approved by the Ethics Committee of the Medical Faculty of the Heinrich Heine University Düsseldorf (2022-1810). This study is registered in a publicly accessible database according to DvH2013, § 35 (DRKS-ID; DRKS00028614 [42]). Meeting the requirements for data protection and confidentiality, the data are pseudonymized. It is not possible to identify individual participants or users in figures and illustrations of the manuscript or supplementary materials. No compensation is provided to participants for research.

This study was approved by the ethics review board of the University Hospital of Düsseldorf (2022-1810_2) and all the participants provided written informed consent.

Results

The comprehensive preoperative geriatric assessment was developed to capture as many potential risk factors for delirium as possible. The findings aim to assist in the development of a specialist and condensed preoperative assessment. Recruitment started in August 2022, with 421 patients already recruited at the time of submission. Initial analyses of the data are to be published at the end of 2024 or the beginning of 2025. Recruitment will continue until August 2025. A final analysis will be issued in a subsequent publication.

Discussion

We intend to determine the frequency of delirium in the aforementioned specialist disciplines. Furthermore, a specialist risk profile is to be created using a comprehensive geriatric assessment in order to specifically identify patients at risk in the future.

Relevance of This Study

Delirium occurs particularly in older patients where (1) patients aged 65 years account for up to 40% of all surgical procedures, (2) 50% undergo emergency surgeries, and (3) 75% are affected by surgical mortality [43]. Also, prevalence is particularly increased in those patients who are older, neurocognitively impaired, or emergency-associated patients [44,45]. The reason why delirium is gaining increasing importance in the age group of older patients becomes clear against the background of 2 facts: first, because the total population is getting older, and second, because this group of patients is being operated more and more frequently [46].

Despite the clinical relevance of delirium, there is still no established screening that considers the risk factors of the older patient group in particular so far. This deficiency was the decisive criterion for the establishment of a screening system in the current study, which focuses on the special needs of these older patients. Building on this, the current screening system is therefore intended to create further prevention options in order to meet the needs of the older patient group.

Further on, the need for a new screening system arises from the fact that the presence of delirium is not only a patient-specific problem: postoperative delirium places an additional burden on hospital care in that the average hospital stay is prolonged by an average of 48-72 hours due to postoperative delirium. It is also associated with a 30-day mortality rate of 7%-10% [9,10,47]. The prolonged hospital stays that result, combined with the need for more intensive therapy, lead to increasing costs for the hospital and ultimately for the entire population [48]. A sound assessment that can act preventively on emerging problems and thus prevent the development of delirium, if necessary, would be of both individual and economic benefit.

Limitations

As described above, predisposing discipline-specific risk factors for the development of postoperative delirium have not yet been thoroughly investigated. The current screening system is intended to circumvent precisely this deficiency and to identify potential risk factors to prevent the development of such delirium in older patients.

Focus was placed on the extraction of clinically relevant examination procedures for the diagnosis of delirium and the elimination of irrelevant procedures, as there is often insufficient time in daily clinical practice to perform comprehensive examinations. General assessments that address the classification of postoperative delirium have already found their way into clinical practice [13,49,50]. However, these do not place a separate focus on the existing risk factors of the group of older patients, who should be given a separate status against the background of the problems described above. What has so far complicated the breakdown of such risk factors is the fact that it is insufficiently possible to distinguish between the normal aging process, the associated increasing physical degradation, and existing medical diseases that accelerate such a decay.

Method Criticism

The screening system presented here is intended to identify risk factors that can be used for regular screening of older patients. The findings of this study assist in preventing postoperative delirium in the future and reduce the frequency of perioperative problems and mortality in these patients [51,52].

The potential risk factors for the development of postoperative delirium already described above had an influence on the structuring of the screening system presented here. Therefore, the following examination parameters have also found their way into the present screening, which are (1) preoperative history, (2) geriatric assessment, (3) mobility and strength, (4) emotion, (5) nutritional status, (6) brain performance, (7) hearing ability, (8) sleep disorders and sleep quality, (9) pain symptomatology, and (10) postoperative evaluations. They are intended to help extract and further eliminate several different potentially delirium-inducing elements.

Further Questions

Recording systems have not yet been significantly established, that would be needed for determining dementia, the need for assistance in everyday life, or multimorbidity. These would also be important for determining geriatric care needs.

It has been shown that a geriatric assessment could make perioperative risks more understandable, also in the case of delirium [53]. Marcantonio et al [54] have already elaborated that such a geriatric assessment would reduce delirium by over 30% and severe delirium by over 50%. In this context, the question arises which parameters of such a geriatric screening system could be related to the reduction of delirium frequency.

Conclusions

We want to investigate whether the risk factors addressed in the assessment are associated with an increase in the delirium rate. The aim is then to reduce this comprehensive assessment to the central aspects to be able to conduct targeted and efficient risk screening.

Many of the known risk factors cannot be easily translated into risk prevention strategies comprehensively in everyday clinical practice. Since each discipline poses different challenges to patients, it is necessary to develop assessments that can be implemented in the individual disciplines.

Acknowledgments

We acknowledge all the people who participated in this study. All authors collected and analyzed the data and read and approved the final manuscript. HLM and HF designed the study. HLM, EA, PO, and HF wrote the paper. All authors read and approved the final manuscript. This work was financed with institute funds and the Paul Kuth Foundation (file number: 310, administrative district: Düsseldorf, registered office: Wuppertal, contact (c/o): Deutsche Bank AG Private Wealth Management Region Wuppertal, Friedrich-Ebert-Str.1-11, 42103 Wuppertal). The funder of the study has no role in study design, data collection, data analysis, data interpretation, or writing the manuscript.

Data Availability

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Conflicts of Interest

None declared.

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Abbreviations

ADL: activities of daily living
DSM-5: Diagnostic and Statistical Manual of Mental Disorders (Fifth Edition)

Edited by A Schwartz; submitted 05.04.24; peer-reviewed by J Bartussek, S Heinemann; comments to author 16.07.24; revised version received 19.08.24; accepted 15.11.24; published 22.01.25.

Please cite as:
Möllmann HL, Alhammadi E, Boulghoudan S, Kuhlmann J, Mevissen A, Olbrich P, Rahm L, Frohnhofen H
Assessment of Geriatric Problems and Risk Factors for Delirium in Surgical Medicine: Protocol for Multidisciplinary Prospective Clinical Study
JMIR Res Protoc 2025;14:e59203
URL: https://www.researchprotocols.org/2025/1/e59203
doi:10.2196/59203
PMID:39841510

Protocol

Harnessing Big Heterogeneous Data to Evaluate the Potential Impact of HIV Responses Among Key Populations in Sub-Saharan Africa: Protocol for the Boloka Data Repository Initiative

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Abstract

Background: In South Africa, there is no centralized HIV surveillance system where key populations (KPs) data, including gay men and other men who have sex with men, female sex workers, transgender persons, people who use drugs, and incarcerated persons, are stored in South Africa despite being on higher risk of HIV acquisition and transmission than the general population. Data on KPs are being collected on a smaller scale by numerous stakeholders and managed in silos. There exists an opportunity to harness a variety of data, such as empirical, contextual, observational, and programmatic data, for evaluating the potential impact of HIV responses among KPs in South Africa.

Objective: This study aimed to leverage and harness big heterogeneous data on HIV among KPs and harmonize and analyze it to inform a targeted HIV response for greater impact in Sub-Saharan Africa.

Methods: The Boloka data repository initiative has 5 stages. There will be engagement of a wide range of stakeholders to facilitate the acquisition of data (stage 1). Through these engagements, different data types will be collated (stage 2). The data will be filtered and screened to enable high-quality analyses (stage 3). The collated data will be stored in the Boloka data repository (stage 4). The Boloka data repository will be made accessible to stakeholders and authorized users (stage 5).

Results: The protocol was funded by the South African Medical Research Council following external peer reviews (December 2022). The study received initial ethics approval (May 2022), renewal (June 2023), and amendment (July 2024) from the University

of Johannesburg (UJ) Research Ethics Committee. The research team has been recruited, onboarded, and received non–web-based internet ethics training (January 2023). A list of current and potential data partners has been compiled (January 2023 to date). Data sharing or user agreements have been signed with several data partners (August 2023 to date). Survey and routine data have been and are being secured (January 5, 2023). In (September 2024) we received Ghana Men Study data. The data transfer agreement between the Pan African Centre for Epidemics Research and the Perinatal HIV Research Unit was finalized (October 2024), and we are anticipating receiving data by (December 2024). In total, 7 abstracts are underway, with 1 abstract completed the analysis and expected to submit the full article to the peer-reviewed journal in early January 2024. As of March 2025, we expect to submit the remaining 6 full articles.

Conclusions: A truly "complete" data infrastructure that systematically and rigorously integrates diverse data for KPs will not only improve our understanding of local epidemics but will also improve HIV interventions and policies. Furthermore, it will inform future research directions and become an incredible institutional mechanism for epidemiological and public health training in South Africa and Sub-Saharan Africa.

International Registered Report Identifier (IRRID): DERR1-10.2196/63583

(JMIR Res Protoc 2025;14:e63583) doi:10.2196/63583

KEYWORDS

HIV, key populations; Sub-Saharan Africa; big heterogeneous data; Boloka data repository

Introduction

In 2024, the world is at a critical juncture in the HIV response, counting down 6 years toward the global goal of ending AIDS as a public health threat by 2030 [1,2]. Despite the investment and focus on addressing HIV/AIDS, it remains a significant public health threat with persistent prevention and treatment challenges globally, regionally, in Sub-Saharan Africa, and in South Africa [1-3]. South Africa has the largest HIV epidemic in the world, with about 8 million people living with HIV, which represents approximately 1 in 5 of the estimated 38.4 million people living with HIV globally in 2022 [1,4]. While there has been a steady decline of 30.5% (n=198,311) in new infections in the last 5 years, the country still has an unacceptably high HIV incidence (South African National HIV, Prevalence, Incidence, Behaviour, and Communication Survey) [3-5]. South Africa has the largest HIV treatment program in the world to meet the treatment needs of the highest proportion of people living with HIV [1].

Key populations (KPs), including female sex workers and their clients, gay men and other men who have sex with men, transgender people, people who use and inject drugs, and incarcerated persons, face a disproportionate risk of HIV acquisition and onward transmission [6]. As a result of unmet prevention and treatment needs, 51% of new HIV infections are acquired by key populations and their sexual partners despite making up approximately 1.5% of the total adult population in Sub-Saharan Africa [1]. The estimated prevalence of HIV was 59.5% among female sex workers and 29.7% among men who have sex with men in South Africa in 2020 [3,4]. Given social network dynamics, the overall impact of the unmet needs of key populations on onward transmission may be even greater. Other modeling studies have a higher risk of onward transmission due to the unmet prevention and treatment needs among key populations using the transmission population attributable fraction over time ($tPAF_t$) [7]. This demonstrates the need for the specificity of the HIV response in characterizing and addressing heterogeneity in onward transmission for a more significant impact in the reduction of new infections. This disproportionate risk of HIV is driven by discrimination, stigma, and criminalization of behavior [8,9]. These same factors, alongside social network dynamics, make collecting data on HIV burden and specific HIV prevention and treatment needs challenging due to distrust of institutions and fear of poor treatment, arrest, or violence [10-12].

In South Africa, where there is robust HIV surveillance compared with other Sub-Saharan African countries, there is no specific mechanism or centralized system to gather and monitor key population data. The existing HIV surveillance systems include the district health information system (DHIS) and the integrated electronic registers, which both collect patient-level HIV data but have no identifiers for KPs, making it difficult to disaggregate data by these subpopulations [13]. The inability to disaggregate information among KPs can lead to misallocation of resources and services, perpetuating health inequities. This lack of adequate data can also lead to underestimation of the disproportionate risk of onward transmission and ultimately missed opportunities for targeted approaches that can lead to a significant reduction of new HIV cases [7,14,15]. Despite this lack of a centralized system, data on KPs are being collected on a smaller scale by numerous stakeholders, including program implementers, the government, academic partners, and others. There exists an opportunity to harness these different data sources for integration and in-depth analyses.

In generalized epidemic settings, there has been a tendency to focus the HIV response on the general population rather than KPs [16-18]. The scientific justification for the project presented here is that continued reliance on nonspecific population-based approaches to guide programs has limited the broader impact of the HIV response in a generalized epidemic setting like South Africa. At the same time, there is limited data to determine the extent to which a KP-tailored HIV response could reduce HIV incidence in South Africa [6,7,19-21]. A more specific HIV response will likely optimize the use of limited resources [7,20]. The proposed work can support program implementers, funders, and policy makers in making well-informed choices as to where, what, and whom to prioritize and how to deliver effective HIV

control programs to maximize health benefits at a population level. An effective control of the HIV epidemic in South Africa requires a focus on KPs [22].

To address the identified gaps in the field, we are in the process of designing and developing a big data platform called "The Boloka data repository" and harmonization of disparate data from multiple data sources. The Boloka data repository seeks to store a diverse range of data, including empirical, observational, and programmatic data, to improve understanding of HIV acquisition and transmission among KPs. In addition, the Boloka data repository seeks to evaluate the potential impact of HIV responses in South Africa in the context of a generalized epidemic setting. Boloka is a South African Sepedi, Sesotho, and Setswana word that means to "store or keep." In this case, we will store or keep big heterogeneous data. These data, including HIV-related and relevant data for KPs from the year 2000 onward in South Africa, can be used to inform policy and programming. By harnessing big heterogeneous data, more data-driven and ultimately more effective HIV response strategies can be generated.

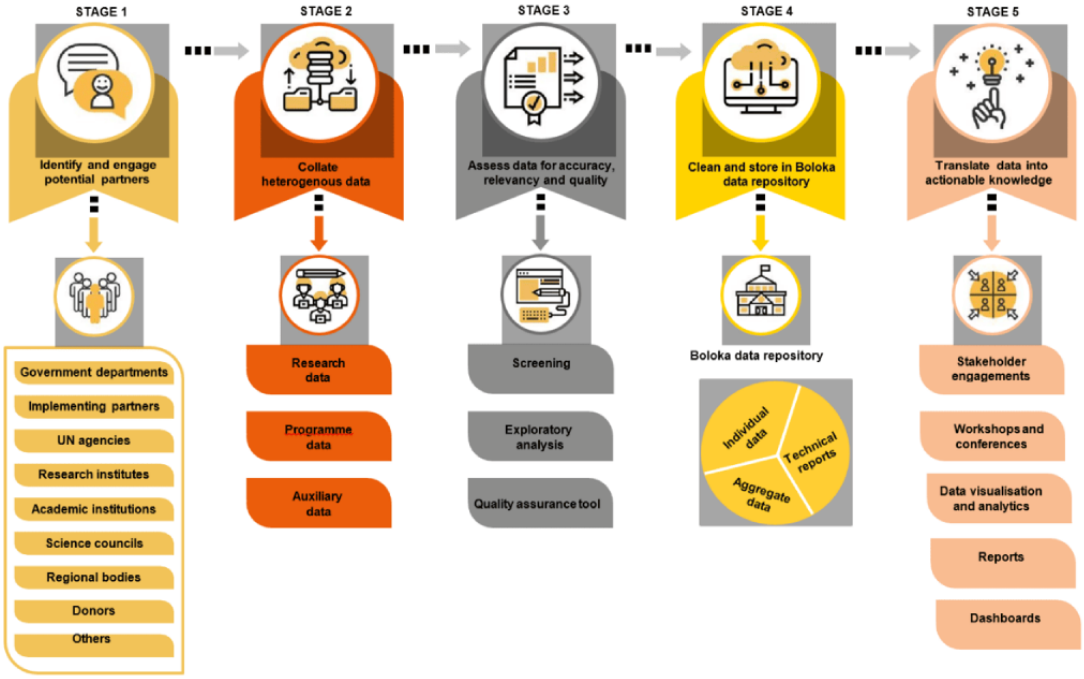
In this protocol paper, we describe the process for developing the Boloka data repository for South Africa. It is envisaged that once the Boloka data repository has been developed, it can be adapted to other countries throughout Sub-Saharan Africa. This study has 3 specific objectives: First, to build a Boloka data repository to handle data on KPs. Second, to collate available HIV-related data for KPs in South Africa from 2000 onwards. Third, to make the data user-friendly for use by stakeholders and authorized users.

Methods

Overview

To achieve the stated objectives, this study project will be developed in the following 5 key stages (Figure 1) [23].

Figure 1. The 5 stages of the Boloka data repository initiative [23], with permission from RNPM. UN: United Nations.



Stage 1: Engage Key Stakeholders to Develop Meaningful Data Partnerships

A range of stakeholders (potential data partners) will be engaged to explore data sharing partnerships and facilitate the collation as well as the organization of the diverse data sources (Table 1). A list of current and potential data sharing partners and the nature of data they are in possession of is being developed (Multimedia Appendix 1 shows the list of potential and current data partners as well nature of data).

A key stakeholder in this work is the South African National AIDS Council (SANAC), which will act as a partner in both the sharing of data and the facilitation of connections to additional potential data sharing partners. A transdisciplinary participatory approach will be adapted to develop meaningful partnerships ensuring collaboration between researchers and data partners, buy-in, project performance, co-ownership, and sustainability [24-26] guided by key principles of mutual trust, sharing, transparency, and responsibility [25,26]. Stakeholders will be given an opportunity to give input at all stages about various components of the Boloka data repository, including which data are collected, how they are stored, data confidentiality, data privacy, and data security, as well as how others may access them using the approved data management processes of the respective data partners. The Boloka research team will also engage with stakeholders regarding priority research questions that will be answered using the data (January 2024 to December 2026). This will ensure that the questions asked have use for those directly involved in the HIV response.

The data processing agreement (DPA) and data partnership or user and related agreements will be signed between the University of Johannesburg and the respective data partners

[27]. These documents will govern the rights and duties of the parties in line "Protection of Personal Information (POPI) Act number 4 of 2014," henceforth referred to as the POPI Act, and any other applicable data protection, security, storage, regulation, and legal requirements [28]. Through these agreements, it will be ensured that the collection, storage, use, disclosure, transfer, disposal, and other processing of any personal information is in line with the prescribed data protection law. The signed agreements will be stored at the University of Johannesburg records management unit.

The Boloka data repository initiative will be executed in the South African Medical Research Council/ UJ (SAMRC/UJ) Pan African Centre for Epidemics Research (PACER) Extramural Unit, which is part of over 40 research centers and institutes, and 20 prestigious national research and industry-funded chairs that the University of Johannesburg is hosting. The South African Medical Research Council/ UJ (SAMRC/UJ) Pan African Centre for Epidemics Research Extramural Unit is one of the flagship initiatives that is supported under the Global Excellence and Stature strategic initiative [29].

Table 1. List of current and potential Boloka Project data partners.

Partner category	Examples of data partners
Country coordinating mechanism	SANAC (South African National AIDS Council)
International and Regional UN Agencies	Centers for Disease Control and Prevention (CDC), UNICEF, United Nations Development Programme, UNAIDS, WHO, United Nations Population Fund.
Government Departments	National Departments of Health, Social Development, Correctional Services, Basic Education.
Nongovernmental organizations (NGOs), nonprofit organizations (NPOs), and other	Beyond Zero (BZ), Networking HIV & AIDS Community of Southern Africa (NACOSA), Sex Workers Education and Advocacy Taskforce (SWEAT), Aurum, TB/HIV Care, Right to Care, Sisonke, U.S. President's Emergency Plan for AIDS Relief (PEPFAR) funded organizations.
Science Councils	Human Sciences Research Council (HSRC), South African Medical Research Council, Council for Scientific and Industrial Research.
Research Institutes in Universities	Desmond Tutu HIV Foundation, Centre for the AIDS Programme of Research in South Africa, Perinatal Health Research Unit.
Local and international donors	Global Fund, President's Emergency Plan for AIDS Relief (PEPFAR), UNAIDS, European Union (EU), Department for International Development (DFID), Canadian International Development Agency (CIDA), Directorate-General for International Cooperation (DGIS), Bill and Melinda Gates Foundation (BMG).
National Universities	All South African Universities.
Regional economic communities	Southern Africa Development Community.

Stage 2: Acquire and Collate Heterogeneous Data

Overview

The Boloka data repository will leverage and collate available and diverse data from various sources across places, times, and populations (Multimedia Appendix 1 shows the list of potential or current data partners and data types). The inclusion and exclusion criteria (Textbox 1), as well as the Boloka data indicator tool (Multimedia Appendix 2), will guide the eligibility of the data source. The inclusion of HIV-related data from the period 2000 and onwards will enable the capturing of the developments that took place over time in the HIV field. The use of reliable and granular data collected over time is essential for improving population health, setting targets as well as developing strategies for targeted HIV response.

The team reviewed the Joint United Nations Programme on HIV/AIDS global monitoring tool and the National Department of Health (NDoH) national indicator dataset form used for global, regional, and national HIV reporting to identify primary and secondary indicators in line with global, regional, and national priorities. The team also reviewed existing validated questionnaires or instruments from various data partners to further refine priority indicators; from this, broader categories of HIV-related interest areas were formed (Figure 2). Accordingly, each potential data partner is required to indicate the primary and secondary indicators that they have collected data on the Boloka data indicator tool (Multimedia Appendix 2).

Where possible, data will be disaggregated at individual, facility, district, or sub-district levels to enable advanced analyses that are not possible with higher-order aggregated data. This will help us develop an in-depth understanding of various subsets of the populations within the larger datasets. Where data are aggregated, we will seek data disaggregated by sex, gender, age groups, socioeconomic status, geo-location, facility type, and temporal factors to understand a range of HIV indicators, including heterogeneity of HIV risk and burden, engagement in HIV services (treatment cascade, pre-exposure prophylaxis uptake and continuation), and population size estimates, among others. The process for requesting and accessing data varies based on the data type and institution. As such, the process of acquiring and collating the data for the different data types is discussed below.

Textbox 1. Inclusion and exclusion criteria.

Inclusion criteria:

- Study topic: HIV, key populations, HIV prevention and treatment.
- Study area: South Africa.
- Language: English.
- Time frame: Collected in the year 2000 or later.
- Data type: Research and program data.
- Data regulation: Secondary dataset or study with primary consent, specifying that the original consent or ethics approval covers secondary analysis without additional consent from participants.

Exclusion criteria:

- Study topic: Non-HIV.
- Study area: Non–South Africa.
- Language: Non-English.
- Time frame: Collected before the year 2000.
- Data type: Social media data.
- Data regulation: In circumstances where primary consent is needed from the participants, such datasets or studies will be excluded as it may not be feasible to go back to the participants for reconsent.

Figure 2. Boloka HIV-related indicator list.

Research Data

For open access data, which is typically aggregated or deidentified individual data, we will adhere to procedures set by the respective institutions to obtain access in line with the POPI Act. This may require the submission of designated data access request forms before gaining direct access to the dataset. For data that are only available upon request, we will contact the data partner to understand their specific procedures for accessing data. This typically requires the completion of a data access request form and the sharing of relevant information, such as the project proposal, ethics approval, and timelines for analysis. For institutions such as the NDoH, district health information data is made available for public use upon request and completion of their data user agreement (DUA) forms. The data or indicators requested should be aligned with the approved National indicator dataset, which outlines the data elements and indicators collected by the NDoH. In such cases, the request and DUA forms will be completed to access data. For institutions in possession of data that are not typically available for public access (eg, implementing partners), we will seek to develop formal partnership agreements and additionally use the University of Johannesburg DPA to ensure adherence to the Protection of Personal Information Act in terms of data privacy and security before any data sharing. Once agreed upon, a formalized partnership agreement will be approved by the legal team of both parties. These agreements will be reviewed in accordance with the policies of the respective organizations.

Program Data

For institutions in possession of data that is not typically available for public access, we will seek to develop formal partnership agreements and additionally use the University of Johannesburg DPA to ensure adherence to the POPI Act in terms of data privacy and security before any data sharing. Once agreed upon, a formalized partnership agreement approved by the legal team of both parties will be signed. These agreements will be reviewed in accordance with the policies of the respective organizations.

Stage 3: Screen Data for Relevance and Quality

Overview

Once data are acquired and determined to be eligible according to the inclusion and exclusion criteria (Textbox 1), they will go through a process of screening and assessment for accuracy, relevance, quality, completeness, and consistency before inclusion in the Boloka data repository. Due to limited information and validated tools on how to specifically check for relevance and quality for some of the data types [30], we will adopt the Framework for Data Quality developed by the Federal Committee on Statistical Methodology (FCSM) [31] and the Information Quality Assessment Framework [32]. Below are further details on the data screening process by the different data types.

Research Data

For research data, a multistep quality assessment process will be carried out using the Global HIV Quality Assessment Tool (Multimedia Appendix 3) [33]. This tool will be used to review and verify the suitability and quality of research data sources in terms of study design and implementation, along with criteria for HIV indicators, specifically prevalence, incidence, engagement in the HIV care continuum, and population size estimates [33]. There will be close supervision and checks to minimize errors by using an honest data broker mechanism to manage and maintain datasets. In addition, 2 individuals (research assistants) will perform the initial quality assessment. Any discrepancies identified will be addressed by a third assessor (Project Manager and Principal Investigator [PI]). Exploratory analyses will be conducted to understand the nature of the data and identify outliers and missing data that will be cleaned for data quality and accuracy. This will be an iterative process to ensure that we leverage and assemble the best available data.

Program Data

It is important to highlight that program data present unique data quality challenges. Program data are typically aggregated to administrative units, and information on individuals is generally not available. Hence, it is not always feasible to link program exposure directly to an outcome [34]. In terms of screening the program data for inclusion into the Boloka data repository, the World Health Organization's "Data quality review: a toolkit for facility data quality assessment—Module 1: Framework and metrics" will be adapted for use [35]. This framework is made up of 4 dimensions. For this study, dimensions 1 and 2 will be used: completeness and timeliness of the data (dimension 1) and internal consistency of reported data (dimension 2). Dimension 1 focuses on the data elements and indicators collected. For example, the NDoH and implementing partners' data elements and indicators will be assessed and checked for completeness [35]. Dimension 2, that is, the internal consistency of the data, relates to the coherence of the evaluated data. In this regard, 4 metrics of internal consistency will be used [35]: (1) presence of outliers, (2) consistency over time, (3) consistency between indicators, and (4) consistency of reported data.

In this initial screening, articles, reports, and datasets will be excluded if their scope does not adhere to the inclusion criteria mentioned in Textbox 1. Data that focuses on the general population will be included in addition to data with a focus on KPs, as the general population provides important KP contextualization. Furthermore, data that have been empirically collected will be prioritized. Estimates and modeled data will be included but carefully reviewed to ensure they meet quality standards and are deduplicated within the datasets.

A report detailing the results of the quality assessment will be written. The report will include the recommendations for data quality improvement plans considering the context and existing constraints. A feedback loop will be used to engage with stakeholders on the potential data quality issues and anomalies, such as completeness of data, discrepancies, and inaccuracies. In addition, the data quality results will be available and stored alongside the data in the repository as part of the metadata.

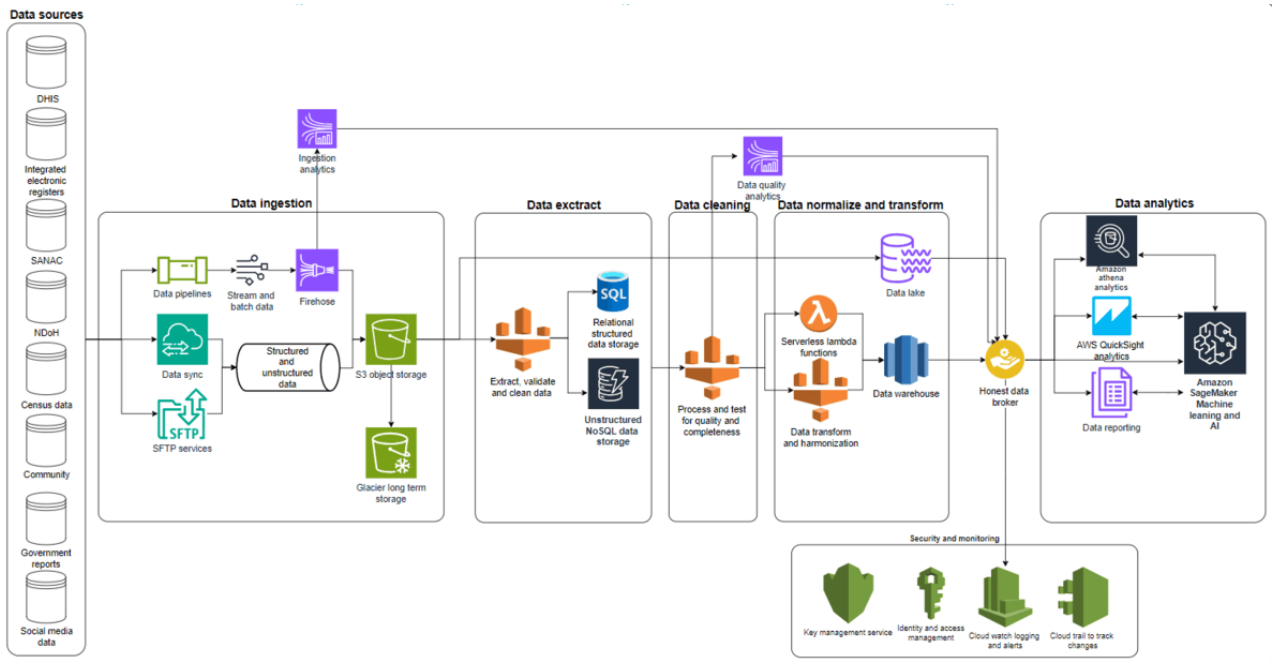
Stage 4: Clean and Store Data In A Data Repository

Overview

Data will be extracted from data sources and put into a staging area before being transformed and loaded into the data repository (Figure 3). We will use the Data Intensive Research Initiative of South Africa (DIRISA) platform, which will enable the provision of much-needed timely information at a level and scale that will improve understanding of HIV heterogeneities. Structured data will be preprocessed and normalized into a standardized format using the Boloka Data Harmonization Tool (Multimedia Appendix 4). The repository will be flexible and updatable for structured data by design [36]. Unstructured data will be stored in the NoSQL data store. Preprocessing will entail data cleaning, transformation, and integration to make the data complete for analysis. Data management will involve assembling multiple big, existing HIV data sources and datasets, capturing, preprocessing, cleaning, integrating, and building them into the Boloka data repository.

For disaggregated data, personal identifiable information will be encrypted and hashed to ensure anonymity and protect privacy. This role is also performed by the appointed honest data broker. Ideally, the Boloka data repository will not store any identifiable personal information, but a procedure in accordance with the POPI Act will be put in place for handling this issue if such information comes with the data. The honest data broker mechanism will be set up to screen the data for compliance in terms of the latter before it passes to the Boloka data repository. The resulting data repository will be responsive to the size and scope of the collected data. It will be dynamic and flexible to accommodate diverse data that has a high number of dimensions.

Figure 3. Envisaged Boloka data storage process flow. AI: Artificial Intelligence; AWS: Amazon Web Service; DHIS: District Health Information System; NDoH: Nation Department of Health; S3: Simple Storage Service; SANAC: South African AIDS Council; SFTP: Secure File Transfer Protocol; NoSQL: Not Only Structured Query Language.



Data Security and Access

The access to the data repository will be secured with login credentials (username and password) in conjunction with multifactor authentication (MFA) to ensure compliance with the POPI Act and avoid any confidentiality breaches as well as contravention of human rights. Access to the repository will be made to the PI and Project Manager through a formal and written request. Login credentials (password) will be updated on a 3-month basis to enhance layers of security and reduce the risk of unauthorized access.

Stage 5: Translate Data Into Actionable Knowledge

Knowledge created from available data will be applied to address real-world challenges. To ensure that findings are incorporated into program and policy decisions promptly, the study will establish a feedback loop with stakeholders and authorized users throughout the project lifespan. Knowledge sharing will be done through dissemination workshops, consultative meetings, reports, dashboards, data visualization, and other methods deemed appropriate. This will support open communication and 2-way feedback between researchers and stakeholders (Multimedia Appendix 5). This participatory process will contribute towards improved use of available data and narrowing the gap between science and practice. Various forms of analysis will be planned in partnership with stakeholders to answer research questions that are relevant to their respective organizations and national priorities. Ultimately, the translation of research will seek to strengthen health systems and, therefore, improve health outcomes throughout South Africa, specifically for KPs and other vulnerable populations. Our goal is to make the Boloka data repository an accessible tool that can be used by local, regional, and international stakeholders for more effective and efficient health care management, prevention, and programming.

The University of Johannesburg Strategic Communication Department designated official will promote and market the initiative using the University of Johannesburg's communication technologies, media, and platforms. They will promote public understanding of the study and research outputs throughout. This will include articles in the daily press, magazines, and other popular media, public lectures, and interviews or programs on television or print media.

Ethical Considerations

Ethics approval (May 2022), renewal (June 2023), and amendment (July 2024) have been secured from the University of Johannesburg, Faculty of Health Sciences, Research Ethics Committee for conducting secondary analysis of data (REC-1504-2022) (Multimedia Appendix 6). Data partners will only share deidentified secondary datasets, and no personal information of the participants will be retrieved as per the POPI Act and the University of Johannesburg DPA, which governs the sharing, storage, and use of personal information. For example, in cases of NDoH, the routine data is aggregated and not at an individual level. The South Africa National HIV Prevalence, Incidence, Behavior and Communication Surveys (SABSSM) data is open access and unique identifiers were used. Data handling, processing, and analysis will be guided by the University of Johannesburg DPA, POPI Act, and data partnership agreement or request form. There is no monetary compensation for the data partners for being part of the Boloka project.

Results

As of December 2022, the protocol was funded by the South African Medical Research Council following external peer reviews. Subsequently, the study received ethics approval from the University of Johannesburg, Faculty of Health Sciences,

Research Ethics Committee. The research assistants, students, and postdoctoral fellows who will partake in the creation of the data repository and subsequent analyses were recruited, onboarded, and received online training and resources in research ethics evaluation (TRREE), management and analysis of data in epidemiology (MADE), data types, and structures. The team will continue to tap into opportunities for professional development training, including sensitivity training for KPs and training on data privacy, specifically regarding the POPI Act and DIRISA functionalities for the duration of the study (January 2024-February 2027). The progress as of September 2024 is described below according to the 5 stages.

Stage 1: Identify and Engage Key Stakeholders to Develop Meaningful Data Partnerships

Overview

The stakeholder engagement is ongoing using the data partner tracking tool (Multimedia Appendix 7) listing potential and current stakeholders and their level of engagement with data (eg, district, provincial, and national) is in place.

Research Data

The research team secured open access data from 5 (2002, 2005, 2008, 2012, and 2017) South Africa National HIV Prevalence, Incidence, Behavior and Communication Surveys from the Human Sciences Research Council (HSRC) on January 5, 2023. Since the data is open access, no signing of DPA was required to access and secure the data. Engagement with stakeholders is expected to conclude in December 2026 in terms of finalizing data sharing agreements, and an example of the University of Johannesburg DPA has been shared for consideration by the potential data partners. An engagement with NDoH was done in 2022, and HIV-related routine data was secured (April 2024).

Program Data

The research team had a series of meetings with SANAC regarding the Boloka data repository. These meetings have established a strong partnership and system for the coordination of data-sharing partnerships. The partnership with SANAC is essential in ensuring that the Boloka data repository is used to guide national HIV strategy related to KPs. This strong relationship will ensure the complementarity of the Boloka data repository rather than duplication of SANAC's efforts to develop "The Situation Room," a central HIV data repository for program data in South Africa. The Situation Room, still in its infancy stages, seeks to enable data checks and balances, dynamic visualization, and sharing of the national, provincial, and district HIV data in the general population to monitor progress toward reaching set targets. The Boloka data repository will be a resource for KP data toward SANAC's efforts. SANAC introduced the research team to its implementation partners to acquire potential data partners, namely Beyond Zero [37], Networking HIV and AIDS Community of Southern Africa (NACOSA) [38], Sex Worker Education Advocacy Taskforce (SWEAT) [39], Sisonke [40], and AIDS Foundation South Africa (AFSA) [41] as well as Perinatal HIV Research Unit (PHRU) [42].

A series of engagements have been carried out with the respective organizations; the engagements are at different stages. Beyond Zero has been engaged since September 2022, and a final copy of the University of Johannesburg and Beyond Zero data-sharing agreement is under review by the Beyond Zero legal team before it is signed by both parties. A data partnership agreement with PHRU is expected to be finalized by the end of December 2024. For this partnership, the PHRU data-sharing agreement is being developed by their legal department. With AFSA, the agreement is in the early stages of communication. In addition to engagements with SANAC and its implementing partners, the research team has consulted with other community leaders who work or worked with community-based organizations, such as treatment action campaigns.

Stage 2: Acquire and Collate Heterogeneous Data

Overview

Significant progress has been made in securing program data, published research data, and technical reports. The security of the acquired data is prioritized during this interim period; thus, the data have been stored in a secure staging area and will later be moved to appropriate data storage software.

Research Data

Open access data from 5 cycles (2002, 2005, 2008, 2012, and 2017) of the population-based multistage cluster cross-sectional of up to 85,000 randomly selected households in South Africa has been secured from the HSRC (January 5, 2023). The South African HIV Behavioural, Sero-status and Media data is within the restricted access level. The data was accessed by completing a non–web-based internet data request form detailing the name of the project, a brief description of the intended use, and the expected date of project completion. The surveys provide data on HIV incidence, prevalence, antiretroviral therapy (ART), viral load suppression, drug resistance, risk behaviors, and HIV care, among others. The Key Population Implementation Science (KPIS) data on HIV testing and engagement in care was secured at Emory University (May 16, 2022) for the degree purpose of postgraduate students. Further, data on HIV testing proficiency was generated by a postgraduate student from the health care facilities in Eastern Cape Province (May 2023).

Data from the Demographic Health Surveys Program has been secured (August 2022). This required registration and submission of a data access request form along with the justification of the request. The demographic health survey collects indicators such as HIV prevalence, prevention and treatment, stigma, and discrimination, as well as sexual behavior. We also secured HIV-related data from the NDoH, and the data includes the following HIV indicators: HIV testing and HIV prevention; ART (ie, ART initiation, ART rate, viral load & CD4 T lymphocyte count testing, ART type, ART adherence); sexually transmitted infections; maternal and neonatal (antenatal HIV test, ART initiation, ART adherence, live birth, infant HIV test); management of inpatients and management of primary health care facility.

There are plans to use data from the 1173 NDoH High Transmission Area sites across South African provinces based in communities that function like clinics and provide services

to KPs. The NDoH's High Transmission Area program reaches key and vulnerable populations with HIV, tuberculosis, and sexually transmitted infections prevention and management services in key hotspots across the country.

Program Data

This protocol will also leverage a partnership with the largest HIV service provider for key populations in South Africa, TB HIV Care, a nonprofit organization, building on a decade-long period of dynamic and exciting work; preliminary discussions have already taken place with the Chief Executive Officer. TB HIV Care focuses on preventing, finding, and treating HIV and TB across 7 provinces and 22 districts in South Africa [43]. Its KP program provides services to sex workers and people who use drugs. Furthermore, data-sharing agreements are being drafted and checked for Beyond Zero, NACOSA, and AFSA, as detailed above.

Stage 3: Assess Data for Accuracy, Relevance, And Quality

Overview

The data received in stage 2 went through screening and assessment for accuracy, completeness, and consistency before its placement in the staging area. The data received was screened and filtered for relevance and inclusion by a member of the research team using the FCSM and the Information Quality Assessment Framework [32] where applicable.

Research Data

South African HIV Behavioural, Sero-status and Media data has undergone a quality check to assess the completeness of the data received. Using the Needs Assessment Form, the DHIS data received has been checked to assess the relevance of the data to the project aims. The assessment checked that the data included the relevant indicators and if the data was complete. This process has been done by 2 researchers on the team.

Stage 4: Clean and Store Data in The Boloka Data Repository

The data have been placed in the staging area before being stored in the data repository. South African Medical Research Council/UJ (SAMRC/UJ) Pan African Centre for Epidemics Research Extramural Unit secured cloud-based storage on the DIRISA platform on June 14, 2024. DIRISA is a "component of the National Integrated Cyberinfrastructure System that coordinates and promotes sound research data management practices and supports data-intensive research" [44]. The access will grant the University of Johannesburg permission to use the DIRISA platform, along with access to the support tools and resources. The resources have been shared to provide access to DIRISA training materials. Through this platform, KP data will be harmonized into a centralized storage area that is managed and protected. All data is to be cleaned and converted into a standardized format to create a structured, flexible, and updatable data repository. The designing of the Boloka data repository will be completed by December 2026. Multimedia Appendix 8 shows the summary of planned and executed milestones for this project.

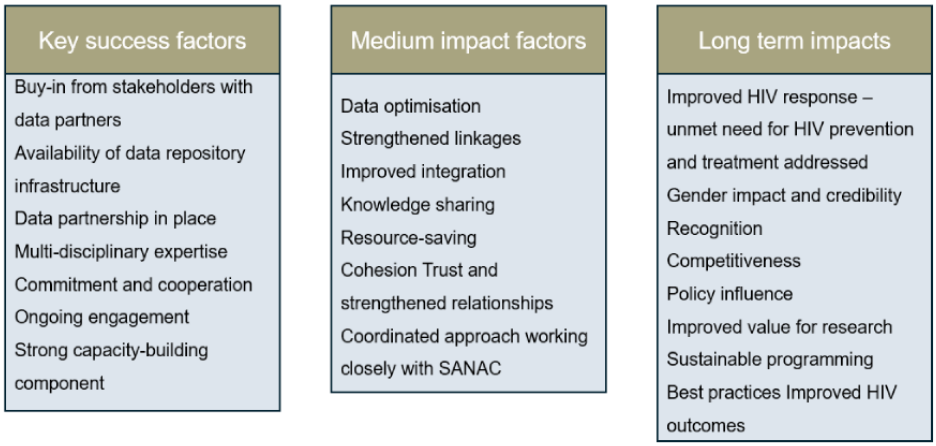
Stage 5: Translate Data Into Actionable Knowledge

Authorized users and stakeholders will have the capability to generate customized reports and export the data to applications such as Stata software (StataCorp) for further dissemination. Authorized users and stakeholders will submit a data request before receiving log-in credentials to access the data repository. Initial secondary data analyses using analytic methods attuned to the structure of available data, including cross-sectional and longitudinal analyses, are being conducted to improve our understanding of HIV among KPs for a targeted response. The proposed analyses will be a transdisciplinary collaborative effort to enable joint application of theories and methods to share conceptual frameworks, innovations, and best practices for solving public health problems. In this regard, the proposed analyses will be jointly finalized with program partners to identify priority research questions that will measure program progress, guide programmatic decision-making, and ultimately improve the response to HIV.

Data synthesis and initial analyses are being planned with a transdisciplinary team of infectious disease epidemiologists, public health scientists, statisticians, data scientists, data analysts, implementing partners, and data partners who will bring complementary expertise on global key populations insights, key population modeling, epidemiology, human rights, and the development of a sustainable data platform. We have already worked with some of the data partners to determine the research agenda that targets policy and practice outcomes, that is, determining common research questions, models, and methods to improve South Africa's HIV response. The doctoral students who will use the Boloka data repository for their dissertations have begun writing their research proposals and seeking ethical approval.

Some factors are critical for the success of this project in achieving the envisaged medium- and long-term impacts, as shown in Figure 4.

Figure 4. Key success factors for Boloka data repository and envisaged impacts. SANAC: South African National AIDS Council.



Discussion

Principal Findings

It is anticipated that there will be data challenges that are common across projects of this nature due to the POPI Act. The University of Johannesburg has already established a mechanism to address these. Potential POPI Act–related challenges have been highlighted in the University of Johannesburg DPA, which is standard for all data-driven projects.

The Boloka data repository will be a lasting resource for the country to guide regional policies and strategies to address HIV, particularly among KPs. Therefore, in addition to traditional research dissemination led by the research team and the proposed feedback loop (Multimedia Appendix 4), the data repository will be widely accessible to all data partners and stakeholders. This co-ownership with stakeholders will enable alternative possibilities for analyses and translation of data to real-world settings. The knowledge, historical context, and applied understanding that stakeholders possess provide opportunities for transformative change. The protocol will provide the opportunity to document lessons learned into a knowledge base, which may be applied to other countries in Sub-Saharan Africa.

The Boloka data repository will contribute to improved storage, retrieval, and access to KP data; linkages of surveillance data collection systems and other data collection efforts; integrated data reporting for monitoring national trends and patterns; recommendations for research, policy, and planning; as well as changes in current and future research. The Boloka data repository will provide a richer empirical basis for policy and program debates in a relatively neglected area of health research in the country. The data, along with its analyses and research outcomes, can form the basis of regularly reported statistics by stakeholders. The Boloka data repository will be maintained up to date to serve as a real-time sustainable resource to guide HIV planning, resource allocation, policy formulation, and programming.

Strengths and Limitations

The Boloka project seeks to build a complex data repository to house and analyze big heterogeneous data from KPs to guide the HIV response in South Africa and, ultimately, SSA. This initiative is crucial in developing policy recommendations for innovative methods towards ending the HIV epidemic in 2030. The Boloka initiative is a novel approach that has the potential to enhance knowledge translation. It will also provide opportunities for capacity-building among academic trainees and stakeholders. Furthermore, the Boloka repository will contribute to the optimization of the HIV data systems necessary for epidemic control. Various data types will be used through integrated analysis to uncover latent outcomes. However, the use of secondary data has limitations as no changes can be made toward improving internal validity. The data requested are from cross-sectional surveys that lack the ability to establish causality. Mitigation of data security, integrity, and confidentiality issues has been described in the relevant sections.

Conclusions

We posit that a truly “complete” data infrastructure that systematically and rigorously integrates empirical, contextual, observational, and programmatic data for KPs will not only improve our understanding of local epidemics but will also improve HIV interventions and policies. Furthermore, it will inform future research directions and become an incredible institutional mechanism for epidemiological and public health training. Achieving epidemic control in South Africa necessitates moving beyond HIV data silos, harnessing underused heterogeneous data, and conducting unconventional analyses. Creating a comprehensive and accessible data infrastructure inclusive of heterogeneous data will improve our understanding of HIV among KPs and accelerate the production of high-quality evidence. Empowered with this evidence, scientists, program leaders, community stakeholders, and policy makers will be able to tailor and optimize HIV service delivery to the most vulnerable populations, thus making the South African National Strategic Plan goal possible. The amassed evidence will provide opportunities for comprehensive and innovative analyses that seek to address priority research questions to improve our understanding of HIV among KPs, assist in setting program targets, guide programmatic decision-making, and ultimately improve the response to HIV in South Africa and other Sub-Saharan African countries. Efforts will be made to incorporate the findings from this study into the South African HIV response strategy.

Acknowledgments

The work reported herein was made possible through funding by the South African Medical Research Council (SAMRC; Project Code #57035; SAMRC File ref no: HDID8528/KR/202) through its Division of Research Capacity Development under the Mid-Career Scientist Programme through funding received from the South African National Treasury. The content hereof is the sole responsibility of the authors and does not necessarily represent the official views of the SAMRC." This research is also funded, in part, by the US National Institute of Allergy and Infectious Diseases (award R01AI170249). The content hereof is the sole responsibility of the authors and does not necessarily represent the official views of the funders.

Authors' Contributions

RNPM and SB conceptualized the protocol and initial draft of the manuscript and provided overall leadership for executing the review to completion. RNPM, EP, AR, KW, KR, KAV, AB, CS, BS, MS, MJ, LLO, KJ, HIS, XL, BO, NH, PD, FW, YAS, LM, MR, and SB contributed to the introduction, methodology, and progress updates of the study. RNPM, EP, KAV, AB, CS, BS, MS, MJ, LLO, KJ, and HS were responsible for engaging with key stakeholders and initiating the data-sharing process. RPNM and EP were responsible for engaging with the legal team and finalizing data-sharing agreements. LM and MR were responsible for the facilitation and linkage to key stakeholders. NH and PD provided insights into the Boloka Data Storage Process Flow. HS and KJ drafted the Boloka Indicator list; KAV and AB drafted the Boloka Harmonization Tool—and the rest of the team reviewed the tools for further input. RNPM was responsible for the management and coordination of review activities. All authors discussed the results and contributed to the final manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
List of potential and current data partners as well as nature of data.
[DOCX File , 15 KB - resprot_v14i1e63583_app1.docx]

Multimedia Appendix 2
Boloka Data Indicator Tool.
[DOCX File , 59 KB - resprot_v14i1e63583_app2.docx]

Multimedia Appendix 3
Global HIV Quality Assessment Tool.
[DOCX File , 129 KB - resprot_v14i1e63583_app3.docx]

Multimedia Appendix 4
Boloka Harmonization Tool.
[DOCX File , 223 KB - resprot_v14i1e63583_app4.docx]

Multimedia Appendix 5
Proposed feedback loop.
[DOCX File , 289 KB - resprot_v14i1e63583_app5.docx]

Multimedia Appendix 6
Ethics approval letter.
[DOCX File , 147 KB - resprot_v14i1e63583_app6.docx]

Multimedia Appendix 7
Data Partners Tracking Tool.
[DOCX File , 153 KB - resprot_v14i1e63583_app7.docx]

Multimedia Appendix 8
Summary of planned and executed milestones for this project.
[DOCX File , 14 KB - resprot_v14i1e63583_app8.docx]

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Abbreviations

AFSA: AIDS Foundation South Africa
ART: antiretroviral therapy
DHIS: District Health Information System

DIRISA: Data Intensive Research Initiative of South Africa
DPA: Data Processing Agreement
DUA: Data User Agreement
FCSM: Federal Committee on Statistical Methodology
HSRC: Human Sciences Research Council
KP: key population
KPIS: Key Population Implementation Science
MADE: management and analysis of data in epidemiology
MFA: multifactor authentication
NACOSA: Networking HIV and AIDS Community of Southern Africa
NDoH: National Department of Health
PACER: Pan African Centre for Epidemics Research
PHRU: Perinatal HIV Research Unit
PI: Principal Investigator
POPI: Protection of Personal Information
SABSSM: South Africa National HIV Prevalence, Incidence, Behavior and Communication Surveys
SAMRC: South African Medical Research Council
SANAC: South African National AIDS Council
SWEAT: Sex Worker Education Advocacy Taskforce
tPAFt: transmission population attributable fraction over time
TRREE: training and resources in research ethics evaluation

Edited by A Schwartz; submitted 25.06.24; peer-reviewed by RL Anderson, MCC Lavoie; comments to author 30.08.24; revised version received 19.09.24; accepted 30.09.24; published 22.01.25.

Please cite as:
Phaswana Mafuya RN, Phalane E, Rao A, Willis K, Rucinski K, Voet KA, Abdulrahman A, Siyamayambo C, Sebati B, Seloka M, Jaiteh M, Olifant LL, Journeay K, Sisel H, Li X, Olatosi B, Hikmet N, Duhoon P, Wolmarans F, Shiferaw YA, Motsieloa L, Rampilo M, Baral S
Harnessing Big Heterogeneous Data to Evaluate the Potential Impact of HIV Responses Among Key Populations in Sub-Saharan Africa: Protocol for the Boloka Data Repository Initiative
JMIR Res Protoc 2025;14:e63583
URL: https://www.researchprotocols.org/2025/1/e63583
doi:10.2196/63583
PMID:

Protocol

Estimating the Effect of Adhering to the Recommendations of the 2019 Canada's Food Guide on Health Outcomes in Older Adults: Protocol for a Target Trial Emulation

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Abstract

Background: The 2019 Canada's Food Guide provides universal recommendations to individuals aged ≥2 years. However, the extent to which these recommendations are appropriate for older adults is unknown. Although ideal, conducting a large randomized controlled trial is unrealistic in the short term. An alternative is the target trial emulation framework for causal inference, a novel approach to improve the analysis of observational data.

Objective: This study aims to describe the protocol for a target trial emulation in older adults, with an emphasis on key aspects of a hypothetical sustained diet and physical activity intervention.

Methods: To emulate the target trial, nonexperimental data from the Quebec Longitudinal Study on Nutrition and Successful Aging (NuAge; N=1753 adults aged ≥67 years) will be used. NuAge includes 4 yearly measurements of dietary intakes, covariates, and outcomes. The per-protocol causal contrast will be the primary causal contrast of interest to account for nonadherence. The sustained intervention strategy will be modeled using the parametric g-formula. In the hypothetical trial, participants will be instructed to meet sex-specific minimal intakes for vegetables and fruits, whole grains, animal- and plant-based protein foods, milk and plant-based beverages, and unsaturated fats. The eligibility criteria, follow-up, intervention, outcomes, and causal contrast in the emulation will closely align with those of the target trial, with only minor modifications. We will attempt to emulate the randomization of treatment by adjusting for baseline covariates and prebaseline dietary habits.

Results: Data collection for NuAge was completed in June 2008. For this study, the main analysis was started in May 2024. Submission of the manuscript is expected by February 2025.

Conclusions: Emulating a target trial will provide the first evidence of the adequacy of the 2019 Canada's Food Guide recommendations for older adults in relation to health outcomes.

International Registered Report Identifier (IRRID): DERR1-10.2196/65182

(JMIR Res Protoc 2025;14:e65182) doi:10.2196/65182

KEYWORDS

aged; Canada's Food Guide; diet; dietary guidelines; target trial emulation; hypothetical trial; Healthy Eating Food Index-2019; HEFI-2019

Introduction

Background

The latest edition of Canada's Food Guide (CFG) was published in 2019 [1]. Compared with the previous edition, key changes include the removal of the prespecified number of servings to consume each day, a shift toward qualitative (eg, "eat plenty of...") instead of quantitative recommendations, and the provision of universal recommendations instead of age- and sex-specific recommendations. In addition, CFG recommendations primarily aim to reduce chronic disease risk. The evidence supporting CFG recommendations focuses on reducing the risk of cardiovascular disease, cancer, and type 2 diabetes risk [2]. However, evidence from a nationally representative survey of adults aged ≥65 years from Canada suggested that greater adherence to recommendations was insufficient to meet calcium, vitamin D, and folate requirements [3]. In Canada, one-third of community-dwelling older adults are at high nutrition risk [4,5], highlighting the importance of maintaining adequate nutritional status in this stratum of the population. Similarly, in the absence of specific recommendations on the amount of protein foods to eat, older adults may be eating less protein than required to maintain muscle mass [6-8]. CFG also provides brief physical activity recommendations but without explicit acknowledgment of the importance of these recommendations for older adults [1]. Indeed, performing a minimal amount of physical activity is paramount to maintaining muscle mass [6,7]. Thus, the universal recommendations in CFG may not be appropriate for older adults because they face unique challenges in consuming a healthy diet [9] and may require specific nutritional strategies [10].

Ideally, a randomized controlled trial (RCT) should be conducted to investigate the adequacy of CFG recommendations in older adults. However, such an RCT is unlikely to be conducted in the short term. An alternative is the target trial emulation framework for causal effect estimation using observational data [11-14]. Informally, the target trial emulation framework aims to emphasize and resolve design challenges in observational data analysis by explicitly emulating a hypothetical trial to estimate a causal effect [11]. In nutritional epidemiology, common issues with design and analyses can yield results that are largely inconsistent with those of randomized trials [15]. For example, the lack of consideration of the compositional nature of diet can dramatically influence effect estimates, that is, increasing the intake of one food must be compensated by decreasing the intake of another food in substitution modeling [15-17]. Furthermore, diet is a lifelong sustained exposure. In an observational study, the effect of diet assessed at a given time may actually reflect the cumulative exposure to previous dietary habits. In turn, ignoring previous dietary habits may result in a misalignment of "time zero" [18], as dietary habits are not randomly assigned at the beginning of the observational study. In other words, ignoring previous dietary habits makes it impossible to distinguish the effect of prospective or hypothetical dietary modification from the effect of retrospective dietary habits. The target trial framework is a helpful tool to highlight and address common issues in nutritional epidemiology. Ultimately, a successful emulation of the target trial based on observational data could yield effect estimates that more closely align with those of a hypothetical future RCT. Example applications of the target trial framework include the emulation of interventions on diet [19-22], physical activity [23], or both [24].

Objectives

To the best of our knowledge, a target trial framework has not been used to assess the effect of adhering to CFG recommendations. Accordingly, this study aims, first, to describe the protocol for the emulation of a target trial using observational data from the Quebec Longitudinal Study on Nutrition and Successful Aging (NuAge [25]), which includes a cohort of 1753 adults aged 67 to 84 years at baseline, and, second, to address key aspects of the target trial emulation in the context of a sustained lifestyle intervention strategy involving diet and physical activity. Key aspects are the description of the sustained lifestyle intervention strategy, the attempt to emulate randomization, as well as assumptions and limitations specific to diet intervention. Notably, more general introductory texts to the target trial framework are available elsewhere [11,12,14].

Methods

Research Question and Hypothesis

Explicitly acknowledging the causal nature of a research question is a prerequisite to causal effect estimation using observational data [26-28]. This study aims to examine the adequacy of the universal dietary recommendations provided by CFG for older adults. Expressed as a counterfactual statement, we aim to answer the following question: What would be the difference in a given health outcome at the end of the follow-up if all eligible participants had increased their adherence to CFG recommendations on healthy food choices, compared to if they had maintained their habitual diet?

Specifically, among adults aged 67 to 84 years followed for 3 years, and compared with maintenance of habits, we aim to (1) estimate the causal effect of adhering to CFG dietary recommendations on markers of muscle health (eg, physical function and muscle strength), general health (eg, waist circumference, blood pressure, and glucose), and cognitive health (ie, Modified Mini-Mental State Examination) and (2) estimate the causal effect of adhering to a *reformulation* of CFG dietary recommendations, including more protein foods and a minimal physical activity recommendation, to amplify the positive health effects.

Accordingly, we hypothesize the following:

- *Hypothesis 1: adhering to recommendations positively influences general and cognitive health but does not influence muscle health.*
- *Hypothesis 2: increasing the consumption of protein-rich foods positively influences muscle health, and meeting minimal physical activity recommendations (≥30 min per day) further amplifies positive health effects.*

Study Design and Sample

Data from the NuAge prospective cohort will be used to emulate the target trial [25]. The NuAge cohort comprised 1753 generally healthy community-dwelling adults aged 67 to 84 years at baseline and followed for 3 years. The baseline and each annual follow-up evaluation included a comprehensive assessment of sociodemographic data, diet, physical activity, functional status, as well as physical and mental health status [25].

The NuAge sample is relevant to our research question. The target population of CFG recommendations comprises all individuals aged ≥2 years, which is compatible with the NuAge target sample of generally healthy older adults from the greater Montreal, Sherbrooke, and Laval areas of the province of Quebec, Canada.

Target Trial

The target trial framework has been suggested as a potential solution to improve the analysis of nutritional epidemiology studies aiming at causal inference [13]. Informally, the target trial framework helps to align the observational data analysis with that of a hypothetical trial. This framework is appropriate for the research question in this study, as we aim to estimate the effect of adhering to a hypothetical diet and physical activity intervention using observational data. The first step of a target trial emulation is the description of the target trial, that is, the protocol for the hypothetical RCT we wish to conduct [11,14]. The second step is the emulation, that is, describing how the target trial is emulated and conducting the study described in this protocol.

Table 1 presents the target trial and its emulation using observational data from NuAge. Key differences between the target trial and its emulation are that participants will be required to provide complete dietary assessment and covariate data at baseline (ie, eligibility component) and that we will attempt to emulate the randomized assignment by adjusting for dietary intakes before baseline as well as baseline covariates (ie, assignment component). Each part of the target trial and its emulation are described in the subsequent sections.

Table 1. Emulation of a dietary intervention target trial using observational data from the Quebec Longitudinal Study on Nutrition and Successful Aging (NuAge [25]).

Trial component	Target trial specification	Target trial emulation
Eligibility criteria	• NuAge inclusion criteria: individuals aged 67-84 years; living in Montreal, Laval, or Sherbrooke; not cognitively impaired; and free of disabilities in activities of daily living • Exclusion criteria: class II heart failure, chronic obstructive pulmonary disease requiring home oxygen therapy or oral steroids, inflammatory digestive diseases, and cancer treatment in the past 5 years	• The inclusion and exclusion criteria are the same as those specified in the target trial. • Furthermore, participants will be required to have complete baseline dietary assessment (at least one 24-hour recall with ≥500 kcal and FFQ[a]) and provide baseline covariate data.
Interventions[b]	• Each individual would be assigned to 1 of the 4 following strategies: • Control group (habitual diet, ie, typical North American diet) • Adherence to Canada's Food Guide recommendations on healthy food choices • Adherence to Canada's Food Guide recommendations on healthy food choices and including a high-protein reformulation • Adherence to Canada's Food Guide recommendations on healthy food choices, including a high-protein reformulation and a minimal physical activity component • Each strategy is followed until the end of follow-up. Participants assigned to a lifestyle strategy are expected to maintain their dietary intake or amount of physical activity at or above the prespecified threshold by the corresponding intervention strategy.	• The intervention component will be the same as that specified in the target trial. • Furthermore, we will assume that each dietary assessment period (ie, within 2 months beginning at each time point) accurately reflects the average diet in the interval between follow-ups.
Assignment	• Participants are randomly assigned to a dietary strategy but are not blinded to their assignment.	• We will attempt to emulate randomized assignment by adjusting for dietary intakes before baseline and baseline covariates.
Outcomes	• The outcomes are physical function and muscle strength, general health indicators, and cognitive health.	• The outcomes will be physical function and muscle strength, general health indicators, and cognitive health.
Time zero and follow-up	• The study starts at baseline and ends at incomplete follow-up or 3 years after baseline, whichever occurs first.	• The study will start at baseline and end at incomplete follow-up or 3 years after baseline, whichever occurs first. • An incomplete follow-up is defined as missing data for questionnaires (nonresponse or loss to follow-up) or missing outcome data at the end of follow-up.
Causal contrast[c]	• Intention-to-treat effect • Per-protocol effect	• Observational analog of both contrasts: • Secondary: intention-to-treat effect • Primary: per-protocol effect
Statistical analysis	• Intention-to-treat analysis: apply inverse probability weighting with adjustment for prebaseline and baseline factors associated with incomplete follow-up to account for study dropouts • Per-protocol analysis: apply the parametric g-formula algorithm to compare postintervention outcomes between groups receiving each treatment strategy, adjusting for pre- and postbaseline factors associated with adherence to intervention strategies and incomplete follow-up.	• Analysis will be the same as that specified in the target trial for both contrasts. • However, the observational analog will require additional adjustments for confounding at baseline and before baseline due to previous dietary pattern.

[a]FFQ: food-frequency questionnaire.

[b]Refer to the *Hypothetical Interventions* section for detailed intervention.

[c]The observational analog of the intention-to-treat contrast corresponds to the baseline values of the intervention, which are assigned and initiated at the same time.

Eligibility Criteria

The inclusion criteria for the target trial are the same as those for NuAge [25]. In the emulation, participants will be required to have at least one 24-hour dietary recall completed at baseline with ≥500 calories, as well as complete covariate data at baseline, as identified in the *Assignment* section.

Hypothetical Interventions

Overview

The hypothetical intervention strategies evaluated will be as follows:

1. No change in dietary habits or physical activity (similar to a control intervention)
2. Adherence to CFG recommendations
3. Adherence to CFG recommendations, including reformulation (ie, higher intake of protein foods)
4. Adherence to CFG recommendations, including reformulation (ie, higher intake of protein foods) and performing at least 30 minutes of aerobic physical activity

Physical activity recommendations are not traditionally at the forefront of CFG recommendations. However, CFG does mention that "at least 150 minutes of moderate-to vigorous-intensity aerobic physical activity per week ... is recommended to achieve health benefits" [1]. Thus, recognizing the key role of exercise in maintaining health and muscle for older adults, the fourth hypothetical intervention includes a formal physical activity recommendation. In the target trial, the physical activity corresponds to performing aerobic exercise of light to vigorous intensity for at least 30 minutes per day [6].

The Challenge of a Well-Defined Nutritional Intervention

Emulating a well-defined dietary intervention for CFG recommendations is challenging. First, recommendations in the latest edition of CFG are qualitative and flexible (eg, "eat plenty of vegetables and fruits" [1,29]). Thus, various suitable yet distinct dietary patterns can align with the recommendations. Second, CFG recommendations target both food intakes (eg, vegetables and fruits) and nutrients (eg, saturated fats). The nutrient-based recommendations can be met by modifying the consumption of various foods. For example, to achieve the hypothetical intervention of "decreasing consumption of calories from saturated fats," one could decrease saturated fats from dairy, nuts, and low nutritive value foods altogether. Arguably, the relationship between these food categories and a given health outcome may vary greatly.

To estimate a causal effect using observational data, the hypothetical interventions must be clearly defined to the point where "no meaningful variation" in the intervention remains [30,31]. In other words, the hypothetical diet interventions should be elaborated until no additional dietary characteristics are deemed impactful regarding the outcome of interest. Another consideration is that the modeling of hypothetical interventions should ideally be conducted with dietary intakes expressed using the same units. For example, mixing food intakes expressed in servings and grams in a statistical model may cause poor estimation of causal effects [17]. Finally, the statistical approach used to account for total energy or total food intake also affects the causal effect of interest and should be consistent with the research question [17,31-33].

Diet Simulations

For this study, adherence to CFG recommendations was defined based on simulated diets generated by Health Canada [34] and summarized in Multimedia Appendix 1 [34]. The simulated diets were designed to meet CFG recommendations on healthy food choices and nutrient requirements (Dietary Reference Intake).

These diets achieve near-perfect Healthy Eating Food Index (HEFI)-2019 scores (>78/80) through relatively high intake of recommended foods (ie, vegetables and fruits, whole grain foods, protein foods, and unsweetened milk and plant-based beverages with protein) and null intakes of foods not recommended (ie, non–whole grain foods; other low nutritive value foods; juice, sugary drinks and alcohol; and fatty foods rich in saturated fats). The HEFI-2019 score indicates the extent to which dietary intakes are consistent with CFG recommendations on healthy food choices [29,35].

Notably, the HEFI-2019 could have been used as a main exposure to measure adherence to CFG. However, the use of a composite score metric would not completely satisfy the criterion of a well-defined intervention to estimate a causal effect. First, high HEFI-2019 scores and high adherence to CFG recommendations can be achieved through many different strategies or dietary patterns. In the context of observational data, the specific strategies through which individuals achieve a high HEFI-2019 score would be based on dietary habits and patterns self-selected by the participants. This approach is similar to asking hypothetical trial participants to modify their intakes without clearly specifying how, which would obscure the estimated causal effect. Second, the HEFI-2019 score includes recommendations on foods and nutrients. As described earlier, mixing servings and grams in statistical models may cause poor estimation of causal effects [17].

We stress that the diets simulated by Health Canada were not actually consumed by older adults. Therefore, the simulated values for vegetables and fruits, whole grain foods, and plant-based protein foods *exceed* the 99th percentile of the distribution of usual intakes of these food categories, as estimated in adults aged ≥65 years from the Canadian Community Health Survey 2015–Nutrition [3]. In Table 2, the target intakes for vegetables and fruits, whole grains, and plant-based protein foods in the adherence to the 2019 CFG recommendations intervention were revised to correspond, at most, to the 90th percentile of the distribution of usual intakes among Canadians aged ≥65 years in 2015 [3].

Table 2. Emulation[a] of hypothetical diet and exercise interventions by sex in the Quebec Longitudinal Study on Nutrition and Successful Aging (NuAge) cohort [25].

Sex	Recommended foods (RA[b]/d)						Dietary supplement[c]	Foods and beverages not recommended (RA/d)[d]			Physical activity (min/d)[e]
	Vegetables and fruits	Whole grains	Plant-based protein foods	Animal-based protein foods	Milk and plant-based beverages with protein	Unsaturated oils and fats		Other foods	Sugary drinks and alcohol	Non–whole grains	
Control (no change)[f]											
Male individuals	—[g]	—	—	—	—	—	—	—	—	—	—
Female individuals	—	—	—	—	—	—	—	—	—	—	—
Adhering to the 2019 Canada's Food Guide recommendations on healthy food choices[h]											
Male individuals	6	1.5	1.0	2.0	1.0	1	No change	Minimum	Minimum	Minimum	No change
Female individuals	5	1.5	0.8	1.5	1.0	1	No change	Minimum	Minimum	Minimum	No change
Adhering to the 2019 Canada's Food Guide recommendations on healthy food choices, including extra protein[i]											
Male individuals	6	1.5	1.5	3.5	1.5	1	No change	Minimum	Minimum	Minimum	No change
Female individuals	5	1.5	1.3	3.0	1.5	1	No change	Minimum	Minimum	Minimum	No change
Adhering to the 2019 Canada's Food Guide recommendations on healthy food choices, including extra protein and physical activity											
Male individuals	6	1.5	1.5	3.5	1.5	1	No change	Minimum	Minimum	Minimum	30 or more
Female individuals	5	1.5	1.3	3.0	1.5	1	No change	Minimum	Minimum	Minimum	30 or more

[a]The emulation of all hypothetical interventions will be implemented using a substitution approach in statistical models. In all models, 1 variable for total food intake and 1 variable for total beverage intake will be included, and foods not recommended will be left out from the models (ie, non–whole grain foods; other low nutritive value foods; juice, sugary drinks and alcohol; and fatty foods rich in saturated fats).

[b]RA: reference amount.

[c]Dietary supplements were not intervened on but were, nonetheless, excluded from foods and beverages not recommended to avoid being considered in the substitution. In other words, participants would not be instructed to modify their dietary supplements in the hypothetical trial.

[d]Minimum indicates that consumption would be set at the smallest amount, permitting a concomitant increase in recommended foods to meet Canada's Food Guide targets. Portions for foods not recommended may vary on an individual basis.

[e]Physical activity corresponds to aerobic exercise of moderate or higher intensity [6].

[f]Values will be the averages observed at baseline in the NuAge cohort. In other words, values will be the observed intakes for the food categories or amount of physical activity when no change is applied.

[g]Not applicable.

[h]Values are derived from Health Canada's simulated composite diets of adults aged ≥71 years. Participants would be expected to meet these targets for each food category. The specific food choices within these categories would be at the participants' discretion. Values for vegetables and fruits, whole grain foods, and plant-based protein foods were truncated to correspond, at most, to the 90th percentile of the distribution of usual intakes among Canadians aged 65 years in 2015.

[i]Extra protein foods were added as follows: +0.5 RA of plant-based protein foods (eg, 25 g of nuts), +1.5 RA of animal-based protein foods (eg, 150 g of cooked unprocessed red meat, fish, or poultry or 3 small eggs), +0.5 RA of milk or plant-based beverage with protein (eg, 125 mL of milk or plant-based beverages with sufficient protein).

Because the 2019 CFG does not have a portion size system, reference amounts (RAs) were used as a proxy for servings. RAs are regulated quantities of foods that reflect the portion size typically consumed at 1 sitting in Canada. RAs were used by Health Canada to simulate a diet consistent with the 2019 CFG recommendations and dietary reference intake (Multimedia Appendix 1 [34]); therefore, RAs are adequate for this study.

Implementation

In the target trial, the sustained intervention strategy could be implemented as follows:

- Step 1: the participants' usual dietary intake and physical activity would be assessed by research dietitians at each study visit.
- Step 2: if reported food intakes and duration of physical activity were equal to or above the prespecified thresholds (Table 2), no change would be suggested to the participants' diet or physical activity. If food intakes or duration of physical activity were below the prespecified thresholds, participants would be instructed to increase food consumption to exactly the prespecified portions or increase physical activity duration to 30 minutes per day (when applicable).
- Step 3: if changes are required, participants would be instructed to decrease consumption of foods not recommended by the same amount as the increase in step 2. For example, if a 2-serving increase in vegetables and fruits is required to meet the prespecified intervention thresholds, participants would be instructed to substitute 2 servings of vegetables and fruits for non–whole grain foods; other low nutritive value foods; juice, sugary drinks and alcohol; and fatty foods rich in saturated fats.

In the emulation, for all hypothetical interventions, substitution will be implemented by including total intakes as a covariate and excluding foods not recommended from the models. More precisely, a variable reflecting total food intake (in RA/d) and a variable reflecting total beverage intake (in RA/d) will be included in all models. Hence, total food and beverage intakes will be constant across hypothetical diet interventions. In this approach to account for total energy, all model coefficients reflect the action of increasing intakes of recommended foods and a concomitant decrease in *any* of the foods not recommended [32]. On one hand, this approach can be potentially confusing [17,33], as the default interpretation of model coefficients assumes increasing the intake of each *food included in the model* while simultaneously decreasing the intake of foods *excluded from the model* [32]. On the other hand, the standard model is generally consistent with the implementation of dietary intervention in feeding trials [16,36,37]. The standard model also reduces the number of variables to be considered as intervention variables. Otherwise, 4 additional dietary components would have to be modeled for foods not recommended (ie, non–whole grain foods; other low nutritive value foods; juice, sugary drinks and alcohol; and fatty foods rich in saturated fats). Finally, the explicit description of the intervention strategies in the target trial protocol clarifies the estimand of interest, as done in an earlier study [19,31].

Notably, nutrient-based recommendations in CFG (ie, saturated fats, free sugars, and sodium intake) are not explicitly modeled to avoid the problems associated with mixed-unit models [17]. In the target trial, we assume that nutrient-based targets would be met by reducing consumption of foods not recommended (ie, non–whole grain foods; other low nutritive value foods; juice, sugary drinks, and alcohol; and fatty foods rich in saturated fats). In that regard, food-level substitution analyses in Canadians support this assumption for saturated fats [38,39].

The extra protein intervention consists of increasing the intake of both animal-based and plant-based protein foods by 1.5 and 0.5 RA per day, respectively, as well as milk and plant-based beverages with sufficient protein by 0.5 RA per day. Regarding the amount of food, this corresponds to adding 150 g of cooked unprocessed red meat, fish, or poultry or 3 small eggs; 25 g of nuts and seeds; and 125 mL of milk or plant-based beverages with sufficient protein while proportionally decreasing the intake of foods not recommended. In a previous RCT [40], older women aged 60 to 90 years were able to consume an additional 160 g of cooked lean red meat without substitution, thereby supporting the feasibility of the protein intervention in this hypothetical study.

Assignment

We will attempt to emulate random allocation or randomization by adjusting for dietary intakes in the year before the intervention, as well as adjusting for covariates at the start of the study. Covariates were identified using the causal diagrams depicted in Figure 1, based on background knowledge of the relationship between the hypothetical lifestyle intervention and outcomes.

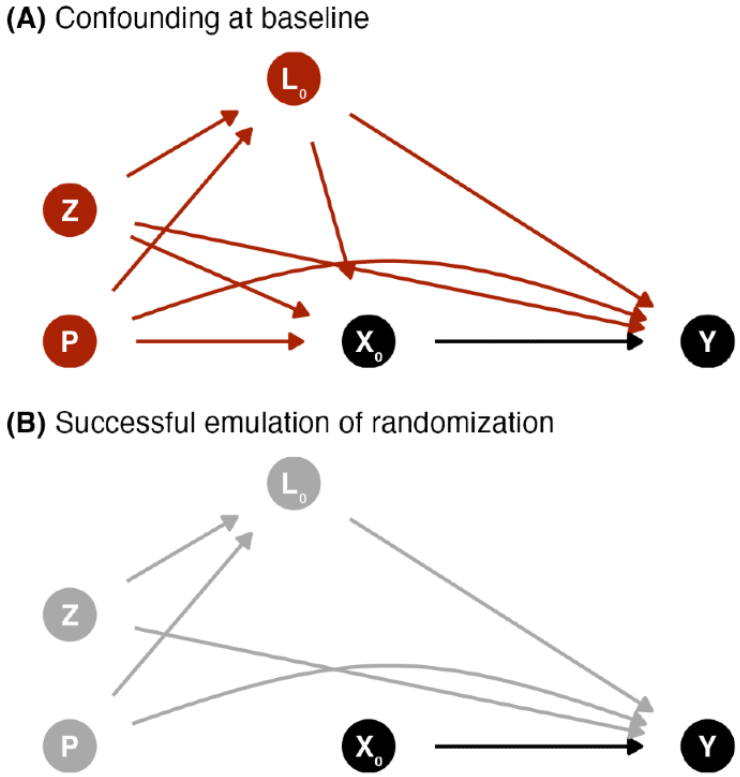
Dietary components that are the foundation for healthy eating in CFG include intakes of vegetables and fruits, whole grains, protein foods (plant- and animal-based protein foods, milk, and plant-based beverages with protein), and unsaturated oils and fats [1].

Covariates, including age at baseline, biological sex, region, education, living alone, smoking and drinking (alcohol) habits, major chronic diseases (ie, hypertension, diabetes, cancer, and heart disease), the number of medications, supplement use (eg, vitamins and minerals), and height and weight, are as follows:

1. *Z*, baseline covariates: age, sex, region, education, history of smoking, height, and former cancer history
2. *P*, previous exposure (ie, exposure of time-varying intervention before baseline): dietary habits before baseline
3. *L*, (time-varying) covariates: weight, number of medications, supplement use, living alone, major chronic diseases (eg, hypertension, diabetes, cancer, and heart disease), and smoking and alcohol habits
4. *X*, (time-varying) treatment: diet and physical activity habits
5. *Y*, end of follow-up outcome: muscle health, general health, and cognitive health

Contrary to dietary habits, data on physical activity habits before baseline were not collected in NuAge. In this case, the potential effect of previous physical activity habits will not be accounted for in the models that aim to emulate the sustained physical activity intervention strategy. For the models emulating the sustained diet intervention strategy only, physical activity habits during the study will be used as a covariate, hence mitigating the confounding of previous physical activity, at least to some extent.

Figure 1. Causal directed acyclic graph (DAG) depicting (A) confounding and (B) successful emulation of randomization using g-methods at baseline between the intervention strategy (X) and outcome (Y). Baseline covariates (both time-invariant [Z] and time-varying [L]) and previous diet and physical activity habits (P) must be considered to emulate randomization. Time-varying treatment and covariates are not shown in this DAG to focus on randomization emulation. Subscripts indicate the time points, where 0 represents baseline.



A successful emulation of randomization requires that there is no unmeasured confounding. However, this is never guaranteed with observational data. Thus, we emphasize our assumptions that (1) the causal graph accurately depicts the relationship under study and (2) the covariates included are a sufficient set of covariates to address confounding.

Outcomes

The primary outcomes will be the mean end of follow-up values for muscle strength (ie, handgrip using vigorimeter, elbow flexor, and knee extensor) and physical function (ie, normal and fast walking and "timed up-and-go"). Outcome values were measured according to a standardized protocol in NuAge [25].

For secondary outcomes, mean end of follow-up values for a set of relevant variables will be considered by domains:

- *General health:* waist circumference, blood pressure (systolic and diastolic), blood glucose, and estimated glomerular filtration rate
- *Cognition:* the modified Mini-Mental State Examination score

Time Zero and Follow-Up

In the target trial of a sustained lifestyle intervention, participants would be met at baseline and then regularly to ensure that diet and physical activity habits are consistent with the intervention assigned by the random allocation. The hypothetical diet and physical activity intervention would be assigned and initiated at baseline. In the emulation, annual follow-ups with comprehensive diet, physical activity, and covariate data collection are available to emulate the hypothetical intervention. Hence, participants would be followed from the study baseline (time point 0; ie, the time at which the intervention strategy would also be assigned and would begin), at each year (ie, time points 1 and 2), and until the end of the study (time point 3). We also assume that the diet and physical activity habits measured at each follow-up time adequately reflect the habits during the entire year.

The end of follow-up outcome measurements will be used to estimate the effect of the sustained lifestyle intervention strategy. Measures of dietary intake and physical activity throughout the study (ie, time point 0 to time point 3) will be used to emulate the sustained lifestyle intervention. Dietary intakes in the year preceding the intervention will be estimated using the frequency questionnaire completed at baseline (ie, time point 0). Missing covariate data at a given follow-up will be carried forward once, after which participants will be considered as having incomplete follow-up.

Causal Contrast

The estimand of interest in this study, the target causal effect of a sustained lifestyle intervention strategy, is

$$E(Y^{1,1,1,1}|C = 0) - E(Y^{0,0,0,0}|C = 0) \quad \textbf{(1)}$$

that is, the expected value of a given health outcome Y at the end of follow-up if all participants had increased their adherence to CFG recommendations on healthy food choices and physical activity, when applicable, at all 4 time points ($X_k=1$, *always intervene*) versus if all participants had maintained their habitual diet and physical activity ($X_k=0$, *never intervene*). The estimand

(equation 1) also indicates that all participants completed the intervention (C=0), that is, in the absence of incomplete follow-up.

The causal contrasts of interest are the observational analogs of intention-to-treat and per-protocol analyses [11]. Given the observational design, participants are not expected to have followed a treatment strategy unknown to them at the time of data collection. Therefore, the primary analysis will be the per-protocol contrast of a sustained lifestyle intervention strategy. In the per-protocol analysis, nonadherence to the hypothetical interventions can be accounted for. In the target trial, participants with a condition after baseline that would have prevented or limited participation in a hypothetical lifestyle intervention would be allowed to discontinue the intervention (eg, lengthy hospitalization, prolonged bed rest, and incident cancer). In the emulation, if such conditions occur in a sufficiently large number of participants, these participants will be "excused" from following the hypothetical intervention [23]. In other words, participants who would have been unable to pursue the study due to major events will not be considered as having incomplete follow-up if they attended the annual assessment. Allowing participants to discontinue adhering to the hypothetical intervention strategy mitigates confounding by the disease burden [23].

The intention-to-treat analysis will be a secondary analysis of a hypothetical point intervention, for example, dietary counseling at baseline only. Notably, it will not be possible to conduct an intention-to-treat analysis identical to that of a controlled study where the interest is to estimate the effect of being *assigned* to an intervention [11]. However, it is possible to conduct an observational analog of the intention-to-treat analysis. In the observational analog, the intention-to-treat analysis aims to estimate the impact of a hypothetical intervention in which adherence is measured at baseline only.

Statistical Analysis

Modeling of Hypothetical interventions

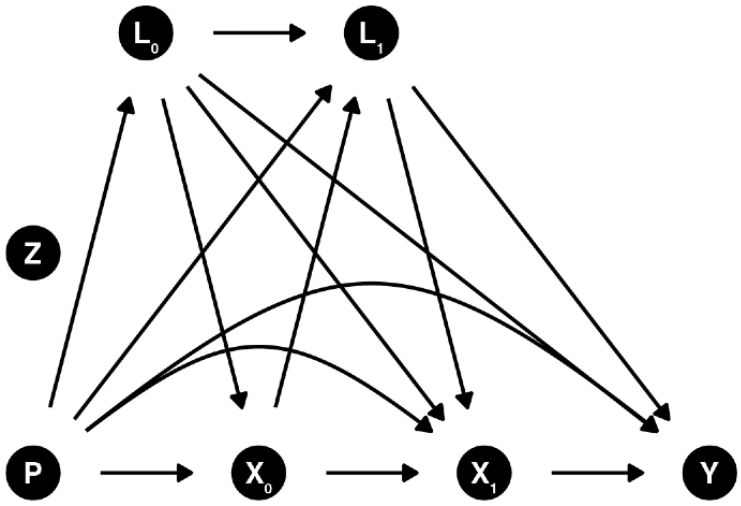
Stratification and multivariable regression (ie, covariate adjustment) are conventional statistical approaches to address confounding in nutritional epidemiology. However, the conventional approaches are not adequate to estimate cumulative treatment effects (eg, diet over time) in the presence of time-varying confounding (eg, weight status over time) and treatment (eg, previous diet) [41,42]. In this study, nonadherence to the hypothetical interventions and incomplete follow-up will be considered using general g-methods for the per-protocol analysis [11,42]. Among g-methods, the parametric g-formula provides the most flexibility for analyses involving hypothetical dietary interventions, as used in previous studies [19,22,43]. Briefly, in the context of an observational study, the parametric g-formula and its implementation into an R package (R Foundation for Statistical Computing) [44] use parametric models to predict the joint history of previous diet and physical activity habits (ie, the hypothetical sustained intervention strategy) and confounding variables. For example, linear regression models are used to predict continuous covariates (eg, body weight), while logistic regressions are used to predict binary or categorical variables (eg, indicator variable for dietary supplement use). The per-protocol causal contrast of the hypothetical intervention presented in Table 2 is then emulated based on Monte Carlo simulated data generated using the g-formula algorithm [44]. The parametric g-formula correctly accounts for time-varying confounding in the presence of feedback between the intervention and the confounding variables, as confounding is addressed using standardization [41,42]. Furthermore, standardization allows for estimating an average causal effect (ie, marginal effect) consistent with the estimand of interest (equation 1) rather than a conditional effect. In summary, "threshold interventions" that depend on the reported dietary intakes or amount of physical activity [43,45] and the parametric g-formula [44,46] will be used to emulate the intervention of *consuming at least x servings of food* and *doing at least x minutes of light to vigorous physical activity.*

Figure 2 presents the causal directed acyclic graph (DAG) of the hypothesized relationship between a sustained lifestyle intervention strategy (X_0, X_1) and an end of follow-up outcome Y for 1 follow-up after baseline (year 1). The model is limited to year 1 for clarity, but the hypothesized causal structure extends to additional follow-ups. The exposure of interest X_k is the joint and cumulative effect of a sustained diet and physical activity intervention strategy measured at baseline and follow-ups.

In the context of this target trial emulation (Figure 2), P includes dietary habits before the baseline assessment. P can have an effect on baseline dietary habits (eg, previous healthy habits increase the likelihood of baseline healthy habits) and dietary habits throughout the target trial emulation (eg, previous healthy habits increase the likelihood of adhering to healthy habits). Furthermore, P influences baseline and time-varying confounding. Finally, given the long-term effect of chronic exposure, P potentially affects Y directly.

The intention-to-treat analysis is similar to the per-protocol analysis. However, only baseline diet and physical activity habits and covariates are considered, as well as prebaseline diet and physical activity. In both the per-protocol and intention-to-treat analyses, loss to follow-up (eg, nonresponse or missing follow-up and health outcomes not measured) will be accounted for using g-methods such as inverse probability weighting.

Figure 2. Directed acyclic graph depicting the hypothesized relationship among previous dietary exposure, time-varying interventions (diet and physical activity), and covariates. Arrows from the Z node are not shown for clarity but would point toward all baseline and time-varying nodes, as well as the outcome. Only 1 follow-up is shown for visualization purposes, but the hypothesized causal structure extends to additional follow-ups. Subscripts indicate the time points, where 0 represents baseline and 1 represents time point 1.



Dietary Assessment

In NuAge, diet during the year before baseline was assessed using 1 semiquantitative food-frequency questionnaire [47]. Dietary intakes at baseline (ie, time point 0) and each annual follow-up (ie, time points 1, 2, and 3) were assessed using 3 repeated face-to-face interviewer-administered 24-hour dietary recalls.

Dietary intakes measured using 24-hour dietary recall are more accurate (ie, have less systematic error or bias) than food-frequency questionnaire [48-50] but are particularly affected by random measurement error (ie, within-individual random error) [50]. When several variables measured with errors are considered simultaneously in a regression model, the regression coefficients may be biased in any direction [51]. To account for random measurement error, the National Cancer Institute Markov Chain Monte Carlo (NCI MCMC) multivariate method could be applied [52]. However, the combination of the parametric g-formula and multivariate measurement error correction using the NCI MCMC method is not feasible. The NCI MCMC method estimates time-invariant measurement error–corrected intakes, while the g-formula algorithm is designed for time-varying exposures.

Recognizing the importance of accounting for measurement error, the correction for measurement error will be reserved for the secondary intention-to-treat analysis. For the intention-to-treat contrast, the time-varying values of exposure and the time-varying values of confounding are not considered. Thus, the NCI MCMC method will be used to obtain measurement error–corrected estimates of the relationship between dietary intakes measured at baseline and outcome at the end of follow-up. Notably, the three 24-hour dietary recalls collected at each time point contribute to reducing random errors, at least to some extent, even in the absence of measurement error correction.

Sensitivity Analysis to Assess the Impact of Measurement Error

For the secondary intention-to-treat analysis, results based on the measurement error–corrected and –uncorrected dietary intakes will be compared. The difference between the estimated relationships will allow to extrapolate the impact of not accounting for random errors in the primary *per-protocol* analysis.

Physical Activity Assessment

Physical activity throughout the study will be assessed using the Physical Activity Scale for the Elderly questionnaire [53,54]. Rather than the total Physical Activity Scale for the Elderly score, specific questions estimating the total time of physical activities will be used to be consistent with the intervention strategy.

Covariates and Subgroups

To the extent permitted by the number of observations for each outcome, continuous covariates will be modeled using restricted cubic splines with 3 to 5 knots (at percentiles 10-50-90, 5-35-65-95, or 5-27.5-50-77.5-95) [55]. Categorical covariates will be modeled to ensure a sufficient sample size at each level.

The effect of dietary changes will be estimated for the entire sample. The sample will also be stratified by biological sex to reflect both potential biological differences and, to some extent, gender differences (although not reported).

Variance Estimation

The variance will be estimated using a minimum of 200 bootstrap sample replicates to consider uncertainty at each step of the estimation [56].

Software and Code

The main statistical analyses will be conducted using R software (version 4.3.1 or greater) and the *gfoRmula* package [44,57]. The manuscript results will be generated using Quarto markdown (Posit PBC). Codes for main analyses and generation

of manuscript results will be shared in a publicly available code repository.

Ethical Considerations

The original NuAge protocol was approved by the research ethics boards of the *Institut universitaire de gériatrie de Montréal* and the *Institut universitaire de gériatrie de Sherbrooke* (Quebec, Canada). The NuAge Database and Biobank [58] has received approval by the *Centre intégré universitaire de santé et de services sociaux de l'Estrie—Centre hospitalier universitaire de Sherbrooke* Research Ethics Board. Secondary analyses of data from the NuAge Database and Biobank for the study described in this protocol are approved by the McGill University Research Ethics Board Office (#22-11-041).

All participants of NuAge provided informed consent. From the initial cohort of 1793 participants, 1753 (97.77%) agreed to the integration of their data and biological samples into the NuAge Database and Biobank for future studies.

Secondary analyses based on the NuAge Database and Biobank use deidentified data, which do not allow participants to be identified by the investigators.

NuAge participants voluntarily consented to participate and were not provided with monetary compensation.

Results

Data collection for NuAge was completed in June 2008. For this study, the main analysis based on the final curated data started in May 2024. The manuscript will be written according to the Strengthening the Reporting of Observational Studies in Epidemiology statement. We anticipate the submission of the manuscript to a peer-reviewed academic journal by February 2025.

Discussion

Principal Findings

In this study protocol, we have described a target trial to assess the effect of adhering to CFG recommendations on healthy food choices. The emulation will be performed using data from the NuAge Database and Biobank [58]. Benefiting from the flexibility of observational data, we also aim to compare adherence to multiple reformulations of CFG recommendations, including the effect of increasing the intake of protein-rich foods and the amount of aerobic physical activity on selected health outcomes. Furthermore, we have outlined the rationale for using simulated diets to emulate adherence to CFG recommendations, the process of selecting covariates to attempt to emulate randomization with causal diagrams, and the challenges of addressing random measurement error.

We emphasize that the purpose of emulating a target trial using observational data is to improve the quality of observational analysis [11,14]. In other words, the target trial framework aims to support the coherence between the causal research question and the observational data analysis [26]. However, estimating causal effects with nonexperimental observational data depends on strong assumptions. The key assumptions are that there are no unmeasured confounders, no measurement errors, and no model misspecifications (eg, functional form of covariates and model outcome distribution) [19]. We first recognize that the absence of residual or unmeasured confounding cannot be guaranteed. The extent to which this assumption is sufficiently satisfied depends on the appraisal of covariates considered. In that regard, we have used graphical tools, DAG, to explicitly describe our analytical assumptions and to identify confounding variables [59-61]. Second, the absence of measurement error assumption will not be satisfied considering the use of dietary intake data measured with 24-hour dietary recalls. On one hand, 24-hour dietary recalls have the least systematic error or bias compared with other common instruments, such as food-frequency questionnaires [48,49]. On the other hand, 24-hour dietary recalls are largely affected by within-individual random errors [50], which can cause bias in any direction in multivariable models [51], as in this study. This issue is mitigated, at least to some extent, by using average data from 3 repeated 24-hour dietary recalls at each follow-up. Sensitivity analyses comparing estimates based on measurement error–corrected and –uncorrected baseline dietary intakes will be used to assess the impact of random measurement errors. Third, the absence of model misspecification will be assessed by examining differences between the observed value of time-varying covariates and the predicted value of time-varying covariates as modeled with the g-formula.

Limitations

The strengths of this study and protocol include the explicit emulation of a hypothetical trial, the thorough description of the emulation of the sustained dietary intervention, and the use of background knowledge and DAG to derive a sufficient set of confounders. Limitations must be addressed. First, the NuAge sample size is relatively limited (N=1753), although comprehensive nutrition and covariate data were collected. Second, the target food intakes based on diet simulations from Health Canada *exceeded* the 99th percentile of the usual intake distribution of Canadians aged ≥65 years from Canada in 2015 [3]. A revision of the dietary intervention targets may be needed if observed dietary intakes in NuAge deviate significantly from targets (Table 2), as was done in a previous nutrition target trial emulation [22]. Third, the presence of random measurement error associated with 24-hour dietary recalls may bias estimates. Finally, the target trial emulation cannot replace an actual RCT. Evidence from an RCT will be required to confirm the value of either CFG recommendations or the enhanced CFG recommendations.

Conclusions

In conclusion, the target trial framework is useful for estimating the causal effect of adhering to CFG recommendations using nonexperimental data when an RCT is impractical [11,19]. Coupled with key assumptions, including the absence of unmeasured confounding, the absence of measurement error, and no model misspecification, we believe that the emulation will provide timely evidence regarding the effect of adhering to CFG recommendations in older adults and inform on the added value of a reformulation.

Acknowledgments

This work was supported by a Canadian Institutes of Health Research Fellowship award (MFE-181852) granted to DB.

Data Availability

The datasets analyzed during this study are available in the GitHub repository [62].

Authors' Contributions

The study was conceptualized by all authors. DB and SC were involved in the methodology. DB was involved in data curation, formal analysis, visualization, and writing of the original draft, and SC supervised the study. All authors reviewed and edited the paper.

Conflicts of Interest

DB was a casual employee of Health Canada (2019 to 2020) and held a doctoral training award from the Fonds de recherche du Québec - Santé (2019 to 2021). DB has no conflicts of interest. SC receives research funding from the Canadian Institutes of Health Research, Fonds de recherche du Québec, Canadian Foundation for Dietetics Research, Canadian Foundation for Innovation, and Canadian Cancer Society. None of these agencies has funded or been involved in this study. NP is the NuAge database administrator; NP and SC serve as NuAge steering committee members. NuAge was supported by a research grant from the Canadian Institutes of Health Research (MOP-62842). The NuAge Database and Biobank is supported by the Fonds de recherche du Québec (2020-VICO-279753); the Quebec Network for Research on Aging, a thematic network funded by the Fonds de recherche du Québec - Santé; and the Merck-Frosst Chair funded by La Fondation de l'Université de Sherbrooke.

Multimedia Appendix 1
Healthy Eating Food Index-2019 dietary constituents and score among simulated diets by Health Canada, by age and sex group.
[DOCX File , 20 KB - resprot_v14i1e65182_app1.docx]

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Abbreviations

CFG: Canada's Food Guide
DAG: directed acyclic graph
HEFI: Healthy Eating Food Index
NCI MCMC: National Cancer Institute Markov Chain Monte Carlo
NuAge: Quebec Longitudinal Study on Nutrition and Successful Aging
RA: reference amount
RCT: randomized controlled trial

Edited by A Schwartz; submitted 07.08.24; peer-reviewed by JM Hutchinson; comments to author 12.11.24; revised version received 27.11.24; accepted 29.11.24; published 23.01.25.

Please cite as:
Brassard D, Presse N, Chevalier S
Estimating the Effect of Adhering to the Recommendations of the 2019 Canada's Food Guide on Health Outcomes in Older Adults: Protocol for a Target Trial Emulation
JMIR Res Protoc 2025;14:e65182
URL: https://www.researchprotocols.org/2025/1/e65182
doi:10.2196/65182
PMID:39847422

Protocol

Clozapine for Treatment-Resistant Disruptive Behaviors in Youths With Autism Spectrum Disorder Aged 10-17 Years: Protocol for an Open-Label Trial

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Abstract

Background: Autism Spectrum Disorder (ASD) is a complex neurodevelopmental condition emerging in early childhood, characterized by core features such as sociocommunicative deficits and repetitive, rigid behaviors, interests, and activities. In addition to these, disruptive behaviors (DB), including aggression, self-injury, and severe tantrums, are frequently observed in pediatric patients with ASD. The atypical antipsychotics risperidone and aripiprazole, currently the only Food and Drug Administration–approved treatments for severe DB in patients with ASD, often encounter therapeutic failure or intolerance. Given this, exploring pharmacological alternatives for more effective management of DB associated with ASD is essential. Clozapine, noted for its unique antiaggressive effects in schizophrenia and in various treatment-resistant neuropsychiatric disorders, independent from its antipsychotic efficacy, remains underexplored in youths with ASD facing severe and persistent DB.

Objective: This study aimed to evaluate the efficacy, tolerability, and safety of clozapine for treatment-resistant DB in youths with ASD.

Methods: This is a prospective, single-center, noncontrolled, open-label trial. After a cross-titration phase, 31 patients with ASD aged 10-17 years and with treatment-resistant DB received a flexible dosage regimen of clozapine (up to 600 mg/day) for 12 weeks. Standardized instruments were applied before, during, and after the treatment, and rigorous clinical monitoring was performed weekly. The primary outcome was assessed using the Irritability Subscale of the Aberrant Behavior Checklist. Other

efficacy measures include the Clinical Global Impression Severity and Improvement, the Swanson, Nolan, and Pelham questionnaire-IV, the Childhood Autism Rating Scale, and the Vineland Adaptive Behavior Scale. Safety and tolerability measures comprised adverse events, vital signs, electrocardiography, laboratory tests, physical measurements, and extrapyramidal symptoms with the Simpsons-Angus Scale. Statistical analysis will include chi-square tests with Monte Carlo simulation for categorical variables, paired *t* tests or Wilcoxon tests for continuous variables, and multivariate linear mixed models to evaluate the primary outcome, adjusting for confounders.

Results: Recruitment commenced in February 2023. Data collection was concluded by April 2024, with analysis ongoing. This article presents the protocol of the initially planned study to provide a detailed methodological description. The results of this trial will be published in a future paper.

Conclusions: The urgent need for effective pharmacological therapies in mitigating treatment-resistant DB in pediatric patients with ASD underscores the importance of this research. Our study represents the first open-label trial to explore the anti-aggressive effects of clozapine in this specific demographic, marking a pioneering step in clinical investigation. Adopting a pragmatic approach, this trial protocol aims to mirror real-world clinical settings, thereby enhancing the applicability and relevance of our findings. The preliminary nature of future results from this research has the potential to pave the way for more robust studies and emphasize the need for continued innovation in ASD treatment.

Trial Registration: Brazilian Clinical Trials Registry RBR-54j3726; https://ensaiosclinicos.gov.br/rg/RBR-54j3726

International Registered Report Identifier (IRRID): DERR1-10.2196/58031

(JMIR Res Protoc 2025;14:e58031) doi:10.2196/58031

KEYWORDS

neurodevelopmental disorders; clozapine; psychopharmacology; antipsychotic medication; autism spectrum disorder; youth

Introduction

The autism spectrum disorder (ASD) comprises a continuum of neurodevelopmental disorders that manifest in early childhood [1], characterized by impaired communication and social interaction, restricted and repetitive behavioral patterns, and occasionally impaired cognition or verbal language [2]. In the United States, the prevalence of ASD in 8-year-old children is 27.6/1000 (1 in 36 children) and 3.8-fold higher in boys than girls [3]. The diagnosis of ASD is an integrative process that includes the collection of current and developmental histories, direct observation, and clinical evaluation. Various standardized instruments may also support and substantiate the diagnosis [1]. Patients with ASD frequently present comorbid psychiatric conditions including, but not limited to, obsessive-compulsive disorder, intellectual disability, oppositional defiant disorder, mood and anxiety disorders, sleep disturbances, eating disorders, and attention-deficit/hyperactivity disorder [4].

The management of ASD involves a multidisciplinary approach, using behavioral and educational strategies to improve the patient's quality of life and promote independence. First-line behavioral treatments comprise applied behavior analysis, cognitive behavioral therapy, and social skills training [5]. While pharmacological treatments do not directly address the core symptoms of ASD, they are used to manage psychiatric comorbidities and severe disruptive behaviors (DB) associated with autism (ie, irritability, hetero-aggression, self-injury, tantrums, and severe oppositional defiant symptoms) [6]. DB are common and can be observed in up to 1/4 of children with ASD [7]. Thus, pharmacotherapy can be pivotal in protecting the physical well-being of both autistic individuals and their caregivers, mitigating social exclusion, and enhancing overall quality of life [8]. The atypical antipsychotics risperidone and aripiprazole are the only drugs approved by the United States Food and Drug Administration for the treatment of irritability associated with ASD, and they are commonly used to treat DB in this population [9]. However, many patients do not respond adequately: approximately 30% of patients fail to respond to risperidone and 50% to aripiprazole [10].

It is essential to highlight that there are other psychosocial therapeutic resources (eg, behavioral therapies) and pharmacological treatments (eg, antidepressants and mood stabilizers) for managing DB. However, some patients, with a pronounced treatment resistance to these approaches, require the use of antipsychotics for the management of more severe symptoms. For those who do not respond adequately to the antipsychotics commonly used in clinical practice, clozapine emerges as a "last-resort" therapeutic alternative, as these patients still demand alternatives.

Clozapine, the first atypical antipsychotic developed, is the treatment of choice for treatment-resistant early-onset schizophrenia (EOS) and is noted for its anti-aggressive effects across several mental disorders [11]. Observational studies have also demonstrated its benefits in reducing treatment-resistant DB in ASD [12]. For instance, Beherec et al [13] analyzed medical records of 6 patients with ASD with refractory DB receiving clozapine, noting a reduction in the number of days with aggressive episodes and concomitant antipsychotic dosing. In addition, Rothärmel et al [14] reported maintained long-term benefits and favorable tolerability in their initial 6-patient cohorts. They corroborated these findings with a replication study involving an additional sample of 13 patients who exhibited a significant reduction in DB (65.2%, *P*=.003), leading to improved quality of life.

Clozapine therapy requires caution and rigorous monitoring during treatment due to its potential health risks, which include severe neutropenia [15], myocarditis [16], and seizures [17]. However, for some children and adolescents with ASD, the

balance of risks and benefits is favorable, particularly when intense and treatment-resistant aggression leads to significant impairments [18]. Although preliminary and exploratory studies showed positive results, no prospective interventional studies with objective measures investigated the efficacy and tolerability of clozapine for treatment-resistant DB in pediatric patients with ASD, highlighting the need to explore it as a potential treatment for this subset of patients.

In this sense, this study aims to evaluate the efficacy, tolerability, and safety of clozapine in treating patients with ASD aged 10 to 17 years with DB resistance or intolerance to conventional antipsychotics. In addition, the study evaluates changes in adaptive functioning among patients and the impact of clozapine on caregivers' quality of life. Drawing on prior evidence regarding clozapine's specific anti-aggressive effects, this study explores its potential as a viable treatment for intractable cases. Accordingly, the hypothesis is that clozapine will prove efficacious and tolerable, with a safety profile acceptable for this clinical population. This article outlines the study protocol, which was initially drafted before the study's completion. Recruitment began in February 2023, and data collection concluded in April 2024. This protocol is now published to provide a comprehensive methodological description. Trial results will be reported in a future publication.

Methods

Study Design

This open-label, noncontrolled trial administers clozapine to all participants. The rationale for this study design, instead of a randomized controlled investigation, was based on the logistical and ethical challenges inherent in conducting a study within a pediatric ASD subpopulation characterized by refractoriness and severe DB. The study's framework facilitates direct observation of adverse events and potentially severe risks related to clozapine use in vulnerable patients. Independent evaluators carry out baseline and follow-up assessments.

Participants

The estimated sample consists of 30 patients aged 10 to 17 years who have been diagnosed with ASD and exhibit treatment-resistant DB.

Eligibility

Inclusion Criteria

This study includes patients of both sexes aged between 10 and 17 years with a confirmed diagnosis of ASD according to the *DSM-5* (*Diagnostic and Statistical Manual of Mental Disorders* [Fifth Edition]) [19] criteria. Also, they must present DB (eg, psychomotor agitation, angry outbursts, oppositional defiant behavior, property destruction, self-injury behavior, or hetero-aggression) that are not caused by a coexisting medical or psychiatric condition, which could act as a trigger for the onset of these symptoms. Individuals must exhibit severe symptoms, impairing different function domains, reflected by a score of 5 or higher (markedly ill) on the Clinical Global Impression-Severity (CGI-S) scale, specifically anchored to DB. Treatment resistance, as defined by the research team, refers to the continued presence of severe DB despite adequate treatment (therapeutic failure) or intolerance to at least 2 antipsychotic agents, with at least 1 being atypical.

Exclusion Criteria

Patients who present the following conditions are excluded: unstable clinical illness or condition preventing the use of clozapine (eg, refractory epilepsy and heart or hematological diseases); insufficient psychosocial resources to follow the study protocol strictly (eg, correct drug administration and weekly attendance to the research center for clinical evaluations and blood testing); previous failure to clozapine treatment due to inadequate response after sufficient duration and dosing (a minimum of 400 mg/day for 6 weeks) or due to intolerable adverse events, such as leukopenia or cardiotoxicity; or pregnant, breastfeeding, or fertile patients not using an adequate contraceptive method.

Recruitment

Our protocol uses a convenience sampling strategy. The study is disclosed in services for university hospitals, integral health of childhood and adolescence, and specialized assistance services for patients with neurodevelopmental disorders through informative material prepared by our research team, inviting patients, who meet the criteria for our study, to participate. Furthermore, we contact child and adolescent psychiatry outpatient clinics, special education institutes and ASD support groups in the metropolitan region of Porto Alegre in the state of Rio Grande do Sul (Brazil), disseminating our research and asking them to refer patients who could benefit from the intervention. It is also disclosed using traditional media (television, newspaper, and radio) and the Hospital de Clínicas de Porto Alegre (HCPA) social media website and institutional email. Legal guardians who intend to participate in the study contact the research team by phone or email.

Screening

Caregivers interested in participating are invited to a screening assessment with a child and adolescent psychiatrist experienced in ASD to determine the patient's eligibility for the study. During the evaluation, the psychiatrists verify the ASD diagnosis according to *DSM-5* criteria [19] and with the support of the Childhood Autism Rating Scale, Brazilian version (CARS-BR) [20]. Clinical features on the presence of severe DB and psychopharmacological treatment history are assessed. The research team informs caregivers about the study's objectives, procedures, potential benefits, and risks associated with clozapine therapy, including side effects, and the mandatory requirement for weekly blood tests. Selected patients undergo a baseline evaluation, which includes data collection, laboratory tests, an electrocardiogram, and a physical examination. The psychiatrist confirms cardiometabolic and hematological stability as part of this initial assessment.

Measures of Evaluation

Trained evaluators apply the following questionnaires and instruments before, during, and after the intervention:

Baseline Sociodemographic and Clinical Data

Data on age, sex, ethnicity, education level, socioeconomic status, clinical, and therapeutical history (eg, comorbidities, previous interventions, gestational and neonatal history, neurodevelopmental milestones, ASD diagnosis and support level, characteristics of DB, family psychiatric history, and response to previous and ongoing pharmacological treatments) are collected at the beginning of the study.

The CARS-BR

This scale comprises 14 items that help diagnose ASD in children and differentiate it from other developmental disorders [20]. It is fast to apply, suitable for all ages, and has objective and quantifiable scores through direct observation. The CARS-BR is used before and during the intervention to evaluate the central symptoms of ASD.

Schedule for Affective Disorders and Schizophrenia for School-Age Children–Present and Lifetime Version, DSM-5 Update

This semistructured interview evaluates the presence and severity of psychiatric disorders in children and adolescents in the present and throughout life [21]. In this study, it is used to assess psychiatric comorbidities.

CGI-S and Clinical Global Impression-Improvement

The Clinical Global Impression Severity (CGI-S) scale evaluates the global severity of the patient at baseline through an increasing score (1 to 7) considering the last 7 days [22]. The patient must score ≥ 5 (markedly ill) to meet the inclusion criteria. Also, the Clinical Global Impression–Improvement (CGI-I) compares the level of improvement or impairment of the patient every week after starting the pharmacological treatment through a score ranging from 1 (very much improved since the initiation of treatment) to 7 (very much worse since the initiation of treatment).

Aberrant Behavior Checklist, Irritability Subscale

Irritability is 1 of the 5 Aberrant Behavior Checklist (ABC) subscales with 15 items; it is easy to use and reliable [23]. This subscale is widely used in clinical trials to evaluate the efficacy of pharmacological treatments for irritability and DB in ASD, assessing several DB and changes over time. The ABC, Irritability (ABC-I) score change following clozapine treatment is the primary outcome of this open-label trial.

The Swanson, Nolan, and Pelham Questionnaire, Version IV

This questionnaire has 26 items to evaluate inattention, hyperactivity, impulsivity, and oppositional defiant behavior and is a complementary instrument to diagnose attention-deficit/hyperactivity disorder [24]. Our protocol uses this tool for additional assessment of DB.

Vineland Adaptive Behavior Scales, Third Edition

The Vineland Adaptive Behavior Scale, Third Edition (VABS-3) is a semistructured interview to evaluate adaptive behaviors divided into domains, such as communication (receptive, expressive, and written), daily living skills (personal, domestic, and community), socialization (interpersonal relationships, play and leisure, and coping skills), motor skills (gross, fine, and advanced motor coordination), and maladaptive behavior (internalizing, externalizing, and critical items) [25]. In our protocol, this tool evaluates how clozapine treatment impacts patients' adaptive behaviors.

Side Effects Questionnaire Based on the Ugvalg for Kliniske Undergelser Side Effect Rating Scale for Psychotropic Drugs

The Ugvalg for Kliniske Undergelser Side Effect Rating Scale for Psychotropic Drugs (UKU) scale is divided into 4 sections, with 48 items evaluating the physical, psychological, neurological, and autonomic side effects of psychotropic drugs [26]. Each item is scored from 0 to 3, reflecting the intensity of the side effects. The scale has been specifically adapted for this study to monitor clozapine's side effects comprehensively.

Simpsons-Angus Scale for Extrapyramidal Side Effects

This widely used scale consists of 10 items that evaluate the presence and severity of extrapyramidal side effects [27]. Each item is rated on a scale from 0 to 4, and the total score is obtained by summing the items and dividing them by 10, with scores up to 0.3 considered within the normal range. The Simpsons-Angus Scale for Extrapyramidal Side Effects (SAS) is a standard tool for evaluating drug-induced movement disorders.

Europe Health Interview Surveys Quality of Life, Abbreviated Instrument

The Europe Health Interview Surveys Quality of Life, Abbreviated Instrument (EUROHIS-QOL 8-item) assesses the quality of life across 4 domains, with 2 items per domain: physical, psychological, environmental, and social [28]. This study uses it to evaluate the caregivers' quality of life, thus monitoring the potential effects of clozapine treatment on this aspect.

Intervention

Throughout the study, a team of child and adolescent psychiatrists skilled in managing clozapine undertakes weekly evaluations of patients at the research facility. Out of 2 different evaluators assesses each patient. The first evaluator conducts the baseline assessment, and the second evaluator conducts all subsequent evaluations while following the same patient throughout the study protocol. This includes monitoring the therapeutic response of clozapine and managing any associated adverse effects. In addition, evaluators receive training to apply the evaluation measures accurately. Patients with significant medical comorbidities undergo specialist physician evaluation to confirm clinical suitability for the study. Eligible patients are prescribed clozapine therapy through a flexible titration regimen. Dose adjustments are made gradually over weeks to achieve a personalized dose. Implementing CGI scales during the titration phase facilitates the determination of an individualized fixed dose for each patient. Once the dosing has been stabilized, the clozapine intervention spans 12 weeks, during which the dose should remain constant. However, if necessary, minor changes may be made to ensure optimal patient outcomes. Blood tests

follows the schedule outlined in Table 1. In addition, physical evaluations, including measurements of blood pressure, heart rate, abdominal and pelvic circumferences, weight, and BMI, are carried out weekly.

Table 1. Study timeline and measures of evaluation. From the beginning of the intervention to a stable clozapine dose, the titration duration varies to determine the most appropriate therapeutic dose for each individual patient.

	Baseline	DP[a]	V1[b]	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12
Physical evaluation[c]	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
CBC[d]	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Monitoring of severe adverse events	N/A[e]	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Adverse events[f]	N/A	✓	✓	N/A	N/A	✓	N/A	✓	N/A	N/A	✓	N/A	N/A	✓
CGI-S[g]	✓	✓	✓	N/A	N/A	N/A	N/A	✓	N/A	N/A	N/A	N/A	N/A	✓
CGI-I[h]	N/A	✓	✓	N/A	N/A	N/A	N/A	✓	N/A	N/A	N/A	N/A	N/A	✓
Metabolic panel[i]	✓	N/A	✓	N/A	N/A	N/A	N/A	✓	N/A	N/A	N/A	N/A	N/A	✓
ABC-I[j], CARS-BR[k], and SNAP-IV[l]	✓	N/A	✓	N/A	N/A	N/A	N/A	✓	N/A	N/A	N/A	N/A	N/A	✓
VABS-3[m]	✓	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	✓
EUROHIS-QOL 8-item[n]	✓	N/A	✓	N/A	N/A	N/A	N/A	✓	N/A	N/A	N/A	N/A	N/A	✓
ECG[o]	✓	N/A	✓	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
K-SADS-PL[p]	✓	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
AST[q], ALT[r]	✓	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A

[a]aDP: Dose progression with a flexible titration schedule to reach a stable clozapine dose for each patient.

[b]V: visit.

[c]Weight, height, BMI, blood pressure, heart rate, and abdominal and pelvic circumference.

[d]CBC: Complete blood count.

[e]N/A: not applicable.

[f]Application of the Simpson-Angus Scale for extrapyramidal side effects and side effects questionnaire based on the Ugvalg for Kliniske Undergelser side effect rating scale for psychotropic drugs.

[g]CGI-S: Clinical Global Impression-Severity.

[h]CGI-I: Clinical Global Impression--Improvement.

[i]Fasting blood glucose, total cholesterol, high- and low-density lipoprotein, and triglycerides.

[j]ABC-I: Aberrant Behavior Checklist, Irritability Subscale.

[k]CARS-BR: Childhood Autism Rating Scale–Brazilian version.

[l]SNAP-IV: Swanson, Nolan, and Pelham questionnaire, version IV.

[m]VABS-3: Vineland Adaptive Behavior Scales-third edition.

[n]EUROHIS-QOL8: Europe Health Interview Surveys Quality of Life Abbreviated Instrument.

[o]ECG: electrocardiogram.

[p]K-SADS-PL: Schedule for Affective Disorders and Schizophrenia for School-age Children, present and lifetime version.

[q]AST: aspartate aminotransferase.

[r]ALT: alanine aminotransferase.

The initial dose of clozapine is 12.5 mg or 25 mg, divided into once or twice-daily doses. The starting dose of clozapine will be determined using an initial dose reference of approximately 0.3 mg/kg, rounded to the nearest multiple of 6.25 mg, with a maximum initial dose not exceeding 25 mg daily. Dose titration is tailored to the patient's response and tolerability, up to 600 mg daily. Clinical management of clozapine considers individual conditions and comorbidities. The therapeutic range for most patients is expected to be between 200 and 400 mg/day. After the clozapine dosage reaches 100 to 200 mg per day, gradual discontinuation of other antipsychotics commences using plateau cross-titration. While the study does not mandate clozapine monotherapy, it aims the reduction of other psychotropics, particularly antipsychotics.

Clinical Monitoring and Adverse Event Management

Patients and caregivers receive educational materials on clozapine treatment and psychoeducational guidance from psychiatrists. Also, they can contact the researchers via phone in case of emergency symptoms (eg, fever, flu-like symptoms, sore throat, dyspnea, chest pain, and seizures). Caregivers are instructed to search for emergency services in case of severe symptomatology. Moreover, the team of psychiatrists is available to other physicians as required.

The study follows guidelines for clozapine treatment in EOS [29]. During all visits, psychiatrists proactively manage side effects to alleviate patients' discomfort and optimize treatment adherence. If needed, side effects are treated symptomatically. Also, a consultant pediatrician and other specialists may be consulted whenever required. Advice on diet control and exercise is emphasized, and metformin may be used to mitigate weight gain and metabolic abnormalities from the beginning of treatment [30]. Prophylactic measures must be discussed with all caregivers to prevent constipation, and early prescription of stool softeners (ie, polyethylene glycol) might be used to avoid obstruction and ileus [31].

An electrocardiogram is performed before and after the clozapine treatment to assess the pharmacological impact on cardiac electric activity. Also, blood testing is performed before and during the treatment to monitor the risk of blood dyscrasias. To start clozapine therapy, patients must display the following hematological criteria: neutrophil >1500/µL and leukocyte >3000/µL [32]. Lithium carbonate may be prescribed to increase the neutrophil count in case of benign neutropenia [33], and the clozapine treatment must be suspended if neutrophil reduces under 1000/µL. Metabolic parameters (eg, fasting glucose, triglycerides, and cholesterol).

Data Collection and Management

Initial data is collected upon obtaining caregiver consent and confirming patient eligibility. Subsequently, qualified patients commence with clozapine therapy, marking the beginning of the treatment study and systematic clinical data acquisition. Measures of evaluation are applied as delineated in Table 1. Per the methodology of our study, we make provisions for remote consultations through video call using Google Meet, but only in exceptional circumstances in which patients cannot attend the research center personally. It is important to note that all participants must strictly adhere to the protocol of weekly blood sample collections, regardless of the consultation modality.

All evaluations are registered in HCPA's electronic medical record system, and data is collected and managed using the Research Electronic Data Capture (REDCap) hosted at the HCPA. REDCap [34,35] is a secure web-based software to support data capture for research studies. It provides an intuitive interface for validated data capture, audit trails for tracking manipulations and data export, automated export procedures for continuous data downloads in common statistical packages, and procedures for data integration and interoperability with external sources.

Outcome Measures

The study will assess the efficacy of clozapine in reducing DB, as measured by ABC-I scores. Secondary measures include the CGI-S and Clinical Global Impression Improvement scales, ASD symptoms (CARS-BR), adaptive behaviors (Vineland Adaptive Behavior Scale - third edition), hyperactivity, impulsivity, and oppositional defiant behaviors (the Swanson, Nolan, and Pelham questionnaire), and quality of life of caregivers (EUROHIS-QOL 8-item). The safety and tolerability of the treatment are evaluated using an adverse effects inventory, the SAS, physical evaluation parameters, and blood testing (Table 1).

Statistical Analysis

Overview

Qualitative variables will be presented as absolute and relative frequencies, and quantitative as mean and SD or median and IQR, as appropriate. The distribution of quantitative variables will be assessed using the histogram and quantile-quantile graph. Categorical variables will be compared using the chi-square test of independence with Monte Carlo simulation (when any cell in the contingency table presents an expected frequency < 5), and continuous variables before and after treatment will be compared using the paired *t* test or Wilcoxon signed rank test. The multivariate linear mixed model will assess the primary outcome to reduce possible confounding variables. The magnitude and direction of the association for quantitative secondary outcomes will be evaluated using the robust Poisson regression for binary variables and the generalized linear model for gamma-distributed variables. Multiple comparisons will be performed using the Bonferroni post hoc when needed. The significance level of 5% will be adopted for all analyses, which will be assessed using the PASW [Norman H. Nie] Statistics software (version 18.0 or higher) [36] and R [R Core Team] (version 4.3 or higher) [37].

Sample Size Calculation

The sample size was calculated to detect a reduction in the ABC-I score using the PSS Health tool (version 0.3.1) based on a relevant mean difference of 10 points [38]. Given a power of 99%, a significance level of 1%, and a SD of the expected difference of 9.7 [39], the calculation yielded a required sample size of 27 patients. Anticipating a 10% attrition due to losses and refusals, the sample size was adjusted to include 30 patients. Considering the vulnerable population and the demanding protocol, an over-enrollment strategy can be used to mitigate the impact of potential attrition further and ensure robustness.

Ethical Considerations

This study fully complies with the Regulatory Standards and Guidelines for Research with Human Beings (Resolution 466/12) and upholds the ethical principles of the Declaration of Helsinki. Informed consent is obtained from legal guardians, who may choose to withdraw the patient from the study at any time without consequences. Whenever possible, patient assent is sought. In cases where it is not feasible, the legal guardian decides on the patient's behalf. The study has received approval from the Research Ethics Committee of Hospital de Clínicas de Porto Alegre (CAAE 54677821.0.0000.5327), and its

protocol is registered in the Brazilian Registry of Clinical Trials (RBR-54j3726). The research team continuously supports the patients and their caregivers throughout the study, especially regarding the emergence of alert signs associated with clozapine use. The Brazilian pharmaceutical company Cristália supplied the clozapine (Pinazan) for the participants. However, the company does not influence the study design, intervention, data analysis, or publication of the results. This ensures that the research team can make independent decisions.

Results

Recruitment for the study commenced on February 10, 2023. A total of 33 patients were initially enrolled in the study. However, before the commencement of the intervention, 2 patients were withdrawn from the study due to their guardians' decision not to participate further, and 3 patients discontinued treatment due to adverse events. Data collection was completed by April 2024. No primary or secondary outcomes are being reported in this manuscript, as it focuses solely on describing the study design and methods. The results of the study are expected to be published by June 2025.

Discussion

It is anticipated that clozapine will demonstrate efficacy in reducing DB resistant to conventional treatments in youths with ASD. In addition, we expect to observe an acceptable safety profile by using rigorous monitoring in a pragmatic outpatient setting. In our view, this is the first quasi-experimental study to investigate the use of clozapine for this specific purpose and population. We foresee that our findings will align with several observational studies that have also highlighted clozapine as a valuable tool in similar cases.

Clozapine is recognized as a potential therapeutic alternative for addressing refractory aggressive behaviors in various neuropsychiatric disorders [12]. This study will explore the possibility that clozapine use may also extend to alleviating severe DB in children and adolescents with ASD. Regarding clozapine use to reduce aggression in young patients, a prospective open-label study showed a significant reduction of aggressive behavior in children and adolescents with treatment-resistant EOS during clozapine treatment for 12 to 24 weeks, reducing the need for emergency drugs and isolation [40]. In addition, observational studies suggested the efficacy of clozapine in patients with ASD and severe DB not responsive to conventional treatments [11,13,14]. However, only a small-scale, prospective intervention study explored the potential of clozapine in 3 children with ASD. In this study, Zuddas et al [41] evaluated 2 boys (8 years old) and 1 girl (12 years old) with DB resistant to haloperidol before and after the clozapine treatment. All children improved over 3 months, with a reduction in the Children's Psychiatric Rating Scale scores from 99 to 60, 99 to 80, and 81 to 53. Although the boys demonstrated gradual improvement until 8-month follow-up (from 60 to 50 and 80 to 53), the girl had a complete relapse of symptoms after 5 months, with similar scores to baseline [41].

Considering that other studies examining the role of clozapine in ASD with treatment-resistant DB have maintained an observational design, prospective clinical studies with objective metrics and larger samples are needed to evaluate its efficacy. Thus, the present study aims to investigate the efficacy of clozapine in mitigating treatment-resistant DB in pediatric patients with ASD. The treatment of DB in ASD may improve adaptive behavior, which could favor the development of socialization, communication, cognition, daily activities, and the quality of life of patients and caregivers [8,42]. Also, behavioral improvement and clinical stabilization could allow patients to engage in other therapeutic modalities or actively participate in community activities or programs.

This study's assessment of clozapine safety and tolerability in the pediatric ASD population is essential, particularly as these factors have been understudied in this group, unlike in patients with EOS [43]. A recent naturalistic study on clozapine in youth with neurodevelopmental disorders (ASD and/or ID) and treatment-resistant aggression showed significant improvements in clinical severity, functioning, and aberrant behaviors. Of the 26 patients, 61.5% were responders. Common side effects included increased appetite, sialorrhea, and repetitive behaviors, with 2 cases of seizures. This study supports clozapine's potential in managing aggression in this population [44]. In contrast to the recently published study, our approach adopts a more interventional design. We also emphasize early detection and management of clozapine-induced side effects and serious adverse events. This includes intensive clinical monitoring through weekly evaluations by child and adolescent psychiatry specialists, pediatric support, regular laboratory tests, and close collaboration between doctors and caregivers. Furthermore, our study will evaluate the acceptability of clozapine outpatient treatment in this population, with a particular focus on adherence, considering the drug's complex side effect profile, the frequency of required medical visits and blood tests, and the level of caregiver involvement. This approach aims to assess a practical framework for real-world clinical practice.

Regarding the limitations, the study features a small sample size and an uncontrolled open-label design, which introduces the possibility of biases, such as expectancy bias from both families and investigators. Nevertheless, this study constitutes an important initial step in clinical investigation, laying the groundwork for future controlled clinical trials with larger sample sizes. Furthermore, follow-up studies are necessary to evaluate the long-term efficacy and safety of clozapine.

Our dissemination plan involves publishing the results of this open-label trial in a high-impact international scientific journal, with the aim of providing evidence for the potential efficacy and safety of clozapine in managing DB in youths with ASD. Following this open-label clinical trial, our research team will conduct a longitudinal follow-up study with the same cohort to assess the sustained efficacy and safety of clozapine. In addition, a qualitative study is proposed to examine the caregivers' experiences with clozapine therapy. Therefore, this trial is envisaged as a foundational step informing subsequent research endeavors.

Acknowledgments

The authors thank the Brazilian pharmaceutical company Cristália for the generous donation of clozapine (Pinazan). We emphasize that this contribution will not influence any aspect of the study. This study was financed in part by the Coordenação de Aperfeiçoamento de Pessoal de Nível Superior – Brasil – Finance Code 001 and the Research Incentive Fund /HCPA). In addition, Luis Augusto Rohde receives a productivity-based grant from CNPq.

Data Availability

The dataset collected and examined in this study will be accessible through the lead author upon adequate request.

Authors' Contributions

ALST and MRBC collaborated on the conceptualization of the initial protocol, with GS, FM, LOC, EBB, LD, and ABF contributing to writing the original draft of the manuscript. RBB was responsible for formal analysis. The final writing with review and editing of the text was performed by ALST and OSB, with FM and GS handling the visualization of the manuscript. ASGM and LAR were responsible for supervision on all steps of the study design and manuscript editing.

Conflicts of Interest

LAR has received grant or research support and served as a consultant to the bureau of the speakers from Abbott, Adium, Apsen, Abdi-Ibrahim, Aché, Bial, Medice, Novartis/Sandoz, Upjohn/Viatris, and Shire/Takeda in the last 3 years. The ADHD and Juvenile Bipolar Disorder Outpatient Programs chaired by LAR have received unrestricted educational and research support from the following pharmaceutical companies in the last 3 years: Novartis/Sandoz and Shire/Takeda. LAR has received authorship royalties from the Oxford Press and ArtMed. Other authors declare no conflicts of interest.

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Abbreviations

ABC: Aberrant Behavior Checklist
ABC-I: Aberrant Behavior Checklist, Irritability Subscale
ASD: autism spectrum disorder
CARS-BR: CARS-BR: Childhood Autism Rating Scale, Brazilian version
CGI-I: Clinical Global Impression-Improvement
CGI-S: Clinical Global Impression-Severity
DB: disruptive behavior
DSM-5: Diagnostic and Statistical Manual of Mental Disorders (Fifth Edition)
EOS: early-onset schizophrenia
EUROHIS-QOL8: Europe Health Interview Surveys Quality of Life, Abbreviated Instrument
HCPA: Hospital de Clínicas de Porto Alegre
REDCap: Research Electronic Data Capture
SAS: Simpsons-Angus Scale
UKU: Ugvalg for Kliniske Undergelser Side Effect Rating Scale for Psychotropic Drugs
VABS-3: Vineland Adaptive Behavior Scale - third edition

Edited by T Leung; submitted 03.03.24; peer-reviewed by HA Alsayouf; comments to author 21.07.24; revised version received 15.09.24; accepted 16.10.24; published 30.01.25.

Please cite as:
da Rosa ALST, da Costa MRB, Sorato GB, Manjabosco FDM, de Bem ÉB, Dellazari L, Falcão AB, Cia LDO, Bezerra OS, Borges RB, Rohde LA, Graeff-Martins AS
Clozapine for Treatment-Resistant Disruptive Behaviors in Youths With Autism Spectrum Disorder Aged 10-17 Years: Protocol for an Open-Label Trial
JMIR Res Protoc 2025;14:e58031
URL: https://www.researchprotocols.org/2025/1/e58031
doi:10.2196/58031
PMID:

Protocol

Evaluating the Benefit of Home Support Provider Services for Positive Airway Pressure Therapy in Patients With Obstructive Sleep Apnea: Protocol for an Ambispective International Real-World Study

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Abstract

Background: Adherence and persistence to positive airway pressure (PAP) therapy are key factors for positive health outcomes. Home support providers participate in the home implementation and follow-up of PAP therapy for patients with obstructive sleep apnea (OSA). In Europe, home support provider service levels are country (or area) specific, resulting in differences in content and frequency of patient interactions. However, no robust evaluation of the impact of these differences on clinical and patient outcomes has been performed.

Objective: The AWAIR study aims to evaluate and compare the impact of different home support provider service levels on PAP adherence and persistence in 4 European countries.

Methods: This real-world, ambispective, cohort study—conducted in France, Belgium, Spain, and Portugal—will recruit adults with OSA who started PAP therapy between 2019 and 2023 and were followed by an Air Liquide Healthcare home support provider. Given the large number of eligible participants (around 150,000), the study will use a decentralized and digital approach. A patient video will present the study objectives and the participation process. A secure electronic solution will be used to manage patient information and consent, as well as to administer a web-based questionnaire. Retrospective data, collected during routine patient follow-up by home support providers, include the level of service and device data, notably PAP use. Prospective data collected using an electronic patient-reported outcome tool include health status, OSA-related factors, patient-reported outcomes including quality of life and symptoms, OSA and PAP literacy, patient-reported experience, and satisfaction with PAP therapy

and service. Hierarchical models, adjusted for preidentified confounding factors, will be used to assess the net effect of home support provider services on PAP adherence and persistence while minimizing real-world study biases and considering the influence of country-level contextual factors. We hypothesize that higher levels of home support provider services will be positively associated with adherence and persistence to PAP therapy.

Results: As of December 2024, the study has received approval in France, Portugal, and 2 regions of Spain. The study began enrollment in France in October 2024. Results are expected in the second quarter of 2025.

Conclusions: The AWAIR study has a unique design, leveraging an unprecedented number of eligible participants, decentralized technologies, and a real-world comparative methodology across multiple countries. This approach will highlight intercountry differences in terms of patient characteristics, PAP adherence, and persistence, as well as patient-reported outcomes, patient-reported experiences, and satisfaction with the home service provider. By assessing the added value of home support provider services, the results will support best practices for patient management and for decision-making by payers and authorities.

International Registered Report Identifier (IRRID): PRR1-10.2196/65840

(JMIR Res Protoc 2025;14:e65840) doi:10.2196/65840

KEYWORDS

obstructive sleep apnea; positive airway pressure; real-world evidence; home support provider; adherence; electronic patient-reported outcome; comparative real-world study

Introduction

Obstructive sleep apnea (OSA) is the most prevalent form of sleep-disordered breathing, affecting nearly 1 billion adults aged 30-69 years worldwide [1]. OSA is characterized by repetitive collapse of the upper airway during sleep, resulting in complete (apnea) or partial (hypopnea) airway obstruction [2]. OSA can cause daytime symptoms that impair quality of life and has been linked with a variety of cardiometabolic diseases, neurocognitive impairment, depression, road traffic accidents, and all-cause mortality [3-12]. Identification and management of OSA are therefore important to reduce those risks.

Positive airway pressure (PAP) therapy remains the gold standard treatment for severe OSA because high-quality evidence and long-term assessment are lacking for noncontinuous PAP therapies [13,14]. PAP therapy has been shown to reduce road traffic accidents, blood pressure, cardiovascular risk, and health care use [15-19]. However, the effectiveness and cost-effectiveness of PAP therapy are linked to sufficient daily device use, with regular and continued long-term usage [16,19-24], which appears challenging in all geographies [25,26].

In most European countries, home support provider companies supply the PAP device and support its use by the patient. However, the type and level of services provided differ markedly between countries. Services can range from mainly logistical support (ie, device delivery in Belgium, Germany, and the Netherlands) to a personalized support plan for patients integrating motivational interviews to enhance adherence (as in some regions of Spain and Portugal) [27-29]. Also, the number of regulated home visits varies from none to several per year (like in France and Portugal). The use of PAP telemonitoring also varies widely, being routine for almost all patients in France throughout the PAP treatment period [30] but not used (or only used in the first months of therapy or in specific situations) in other countries. Criteria for the reimbursement of PAP therapy also differ markedly between European countries and are likely to influence adherence and persistence. For example, while the fees paid to the home support providers in France increase as the number of hours of PAP use increases [30,31], in Belgium and Germany, nonadherence can result in the cessation of patient reimbursement.

The large number of patients treated with PAP therapy and the heterogeneity of home support provider service levels across Europe provide a unique opportunity to evaluate the optimal management approach. This requires an assessment of the added value of the service and of its impact on PAP adherence and persistence; quality of life; patient-reported outcomes (PROs), including quality of life and symptoms, patient-reported experience (PREs), and satisfaction.

Air Liquide Healthcare (ALH) is composed of several home support provider companies operating in more than 40 countries worldwide and 10 European countries. Support to patients with sleep apnea requiring PAP treatment is provided in all these countries. ALH designed the AWAIR (Assessment of the Benefit of the Home Support Provider Service Level Associated With Positive Airway Pressure Treatment in Patients With OSA on Treatment Adherence and Persistence: an International Real-World) study to assess and compare PAP adherence and persistence across 4 different European countries and according to the level of service. The study will consider the main confounding factors for adherence and persistence to PAP therapy and will provide unique information about differences in patient profiles across countries, PROs, OSA and PAP literacy, and experience and satisfaction with PAP therapy and service (PREs).

Methods

Study Design

This international, ambispective, real-world, cohort study is being conducted in 4 European countries (France, Belgium, Spain, and Portugal). It includes a retrospective analysis with the reuse of home support provider data routinely collected for PAP-related services and a prospective evaluation with the

collection of patient data using a web-based patient questionnaire.

Study Objectives

The main objective of the study is to compare PAP adherence and the PAP therapy persistence rate between countries and between different levels of home support provider service.

The study's other objectives are to (1) identify service components that influence PAP adherence and persistence; (2) identify factors associated with PAP adherence and persistence; (3) describe in each country sociodemographic and OSA-related clinical characteristics, home support provider PAP-related service, OSA and PAP literacy of participants (perceived and actionable competence), patient experience and satisfaction with PAP therapy and home support provider support, patient-reported OSA symptoms, and quality of life (determined using the EQ-5D-5L questionnaire [32]); and (4) describe patterns of PAP use.

Participants

Process for Selecting Patients

Eligible participants are adults (aged 18 years and older) who started PAP therapy between January 1, 2019, and December 31, 2023; for whom PAP services were delivered by an ALH affiliate in France, Belgium, Spain, or Portugal; and had a valid email address or smartphone number.

Potential participants were identified by applying these inclusion criteria to the data sourced from each home support provider database. In France and Portugal, all patients who met the above inclusion criteria were informed about the study. In Spain and Belgium, which have regional- or hospital-level regulatory processes, potential participants are only included from representative investigational sites. After providing the information about the study, patients who either consented to participate (Portugal, Spain, and Belgium) or did not "opt-out" (France) are enrolled in the study. These processes are described in more detail in the Ethical Considerations section.

The digital and decentralized nature of the study using e-consent and an electronic patient-reported outcome (ePRO) tool means that patients are not directly recruited by investigators. Instead, a secure electronic solution, Dr Data Consent, is used to provide direct and individual information about the study, obtain consent, and provide access to the web-based questionnaire. This solution is compliant with European and French legislation and regulations on the protection of personal data, as well as ethical guidance about patient's rights management. Its technology is powered by blockchain thus guaranteeing full traceability on e-consents.

Process for Contacting and Recruiting Patients

The list of eligible patients that was extracted from each home support provider database contains patient contact details (ie, email address or smartphone number). This list is uploaded into Dr Data Consent and an algorithm checks the validity of the contact details. Eligible patients with valid contact information receive an email or SMS invitation to connect to this platform for the consent process. The invitation does not include sensitive data.

An explanatory video is provided, within the Dr Data Consent account of each patient, to ensure that potential participants fully understand the study's aims, procedures, and their rights.

Those who provide consent are granted access to the ePRO tool and invited to complete the questionnaire, which should take them an estimated 10 minutes.

Ethical Considerations

The study protocol was developed in collaboration with a scientific committee composed of experts in OSA and methodologists from the 4 countries involved. The regulatory process and patient consent for a study with the reuse of data and a questionnaire were different for the 4 countries.

In France, the study followed the methodology MR-004 of the French Data Protection Authority (Commission Nationale Informatique et Liberté) concerning research that reuses data that have already been collected [33] and was approved by the local ethics committee of Angers University Hospital in November 2023 (2023-159). In Portugal, the study was considered observational and required approval by a central ethics committee; the approval was obtained from the ethics committee of Lisboa in May 2024 (24/24). In Spain, the study was considered observational and required approval by the ethics committee at each participating hospital; approval was obtained from the CEIm Hospital Universitario Ramón y Cajal of Madrid in July 2024 (095/24) and from the CEIm Hospital Universitario Doctor Peset of Valencia in December 2024 (127/24) and is pending for other regions. In Belgium, the study was considered interventional and required approval by a central ethics committee (Commissie voor Medische Ethiek Ziekenhuisnetwerk Antwerpen Institutional Review Board, Ziekenhuis aan de Stroom Middelheim) and by the local ethics committee at each participating hospital. Ethics approvals from the belgian central ethics committee are still pending.

In France, potential participants have the option to decline the reuse of their personal data through an "opt-out" process. Conversely, in Belgium, Portugal, and Spain, an "opt-in" process has been established, requiring explicit consent from participants to join the study.

No compensation is provided to participants.

Outcome Measures

Study outcomes, time points, and data sources are summarized in Table 1. An ePRO tool will be used to administer the patient questionnaire. The ePRO tool was designed to assess various aspects of a patient's status, condition, and experience at 2 time points: the time of ePRO completion and the beginning of PAP therapy. This included sociodemographic characteristics (age, relationship status, employment, education level, and social support), health status (BMI, smoking status, alcohol intake, comorbidities, sleep duration, and use medications to aid sleep), OSA-related factors (when PAP therapy was started, apnea-hypopnea index before starting PAP, and OSA symptoms), PAP therapy experience and satisfaction (tolerability of PAP, attitude to PAP, device noise, and level of motivation

to use PAP), patient experience and satisfaction with home support providers, quality of life (including current health status), and OSA-PAP literacy. The full ePRO questionnaire is provided in Multimedia Appendix 1.

Home support provider service will be assessed using 4 components: frequency of interactions between the home support provider and a patient; content of support (logistical, educational, supportive, or behavioral); personalization of support according to patient profile or needs; and telemonitoring (telemetry, data visualization, and alerts triggering home support provider interventions).

Table 1. Study outcomes.

Category and outcome	Time points	Source
Sociodemographic and OSA[a]-related clinical characteristics		
• Demographics (age and sex) • BMI	At the start of PAP[b] therapy	ALH[c] ERP[d]
• Occupational status and highest education level • Sleep characteristics: bed sharing, sleep duration, and sleep medication • Smoking status and alcohol consumption • BMI	At the time of ePRO[e] completion	ePRO tool
• Comorbidities: diabetes, stroke, myocardial infarction, coronary stenting or heart surgery, heart failure, cardiac arrhythmia, hypertension, GORD[f], COPD[g], asthma, chronic rhinitis, cancer, anxiety or depression, and insomnia	Before starting PAP therapy	ePRO tool
• Apnea-hypopnea index at the time of diagnosis	Before starting PAP therapy	ALH ERP and ePRO tool
PROs[h]		
• Symptoms: snoring, excessive daytime sleepiness, daytime fatigue, lack of energy, waking up feeling tired, poor sleep, falling asleep at the wheel, nocturia, abrupt awakening with choking and gasping, morning headache, irregular breathing during sleep, decreased libido, depression, anxiety, irritability, and memory or concentration difficulties	Before and after starting PAP therapy	ePRO tool
• Quality of life using the EQ-5D-5L [32]	At the time of ePRO completion	ePRO tool
OSA and PAP literacy		
• Perceived and actual competence related to disease literacy and PAP use assessed using 13 variables with binary responses	At the time of ePRO completion	ePRO tool
Experience and satisfaction with PAP therapy		

• Measured using a visual analogue scale for
  • Difficulty tolerating PAP (discomfort related to pressure, and mask)
  • Likelihood of continued use
  • Perceived health benefits
  • Global satisfaction
  • Noise acceptance/impact
  • Motivation to use
	At the time of ePRO completion	ePRO tool

Experience and satisfaction with home support provider		

• Measured using a 5-point Likert scale for
  • Home support provider availability for logistical support
  • Home support provider availability for educational support
  • Satisfaction with home support provider
  • Perceived value of home support provider
	At the time of ePRO completion	ePRO tool

Characteristics of PAP therapy		
• Type of PAP device and mask	At the start of PAP therapy	ALH ERP
• Elevated apnea-hypopnea index • Elevated unintentional leaks	1, 4, 6, and 12 months after starting PAP therapy and annually thereafter	Device data
Home support provider PAP-related service		
• Number and type of interactions (home visit, phone call, and digital interaction) • Number of mask changes • Implementation of telemonitoring	1, 4, 6, and 12 months after starting PAP therapy and annually thereafter	ALH ERP

Category and outcome	Time points	Source
PAP adherence		
• Mean number of hours per day of PAP use • Mean PAP use categorized as: 0-2 hours/day, 2-4 hours/day, 4-6 hours/day, and ≥6 hours/day • Proportion of adherent patients defined as (1) mean PAP use ≥4 hours/day, (2) mean PAP use ≥4 hours/day on ≥70% of days, and (3) mean PAP use ≥4 hours/day on ≥80% of days	1, 4, 6, and 12 months after starting PAP therapy and annually thereafter	Device data
PAP persistence		
• Percentage of days with or without PAP use defined as the ratio between the number of days with PAP usage (starting from 1 minute of use) over the number of days in the follow-up period • Patients without PAP discontinuation (still in therapy), with temporary discontinuation, or with permanent discontinuation • Patients still in therapy and with mean PAP use ≥4 h/day	4, 6, and 12 months after starting PAP therapy and annually thereafter	Device data and ALH ERP

[a]OSA: obstructive sleep apnea.

[b]PAP: positive airway pressure.

[c]ALH: Air Liquide Healthcare.

[d]ERP: Enterprise Resource Planning.

[e]ePRO: electronic patient-reported outcome.

[f]GORD: gastro-esophageal reflux disease.

[g]COPD: chronic obstructive pulmonary disease.

[h]PRO: patient-reported outcome.

Data Sources, Flow, and Management

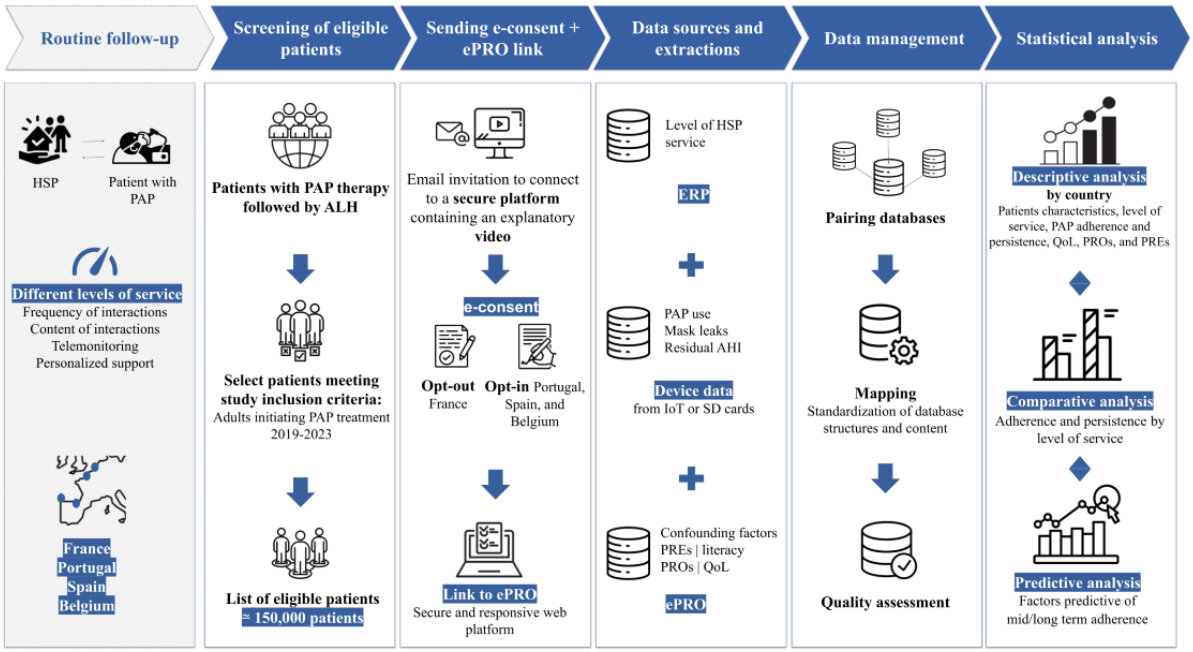
Potential participants will be identified by applying the inclusion criteria to the data sourced from the ALH Enterprise Resource Planning (ERP) systems. Initially, potential participants will receive an email or SMS invitation to connect to a secure platform for the consent process. Those who provide consent will be granted access to the ePRO tool and will be invited to complete the questionnaire, which takes about 10 minutes.

The study database will be created from 3 data sources: the ALH ERP systems that contain data routinely collected for PAP-related services; the database containing information about PAP device use (collected remotely through the Internet of Things or by download from device memory cards during home provider support visits); and the ePRO tool. Database structure and content will be standardized across countries.

Because the ALH ERP and PAP device use databases are primarily designed for administrative, logistical, and patient follow-up purposes, rather than research, all data will undergo thorough review for completeness, accuracy, and reliability before statistical analysis. These reviews will be conducted in accordance with a detailed data management plan, involving multiple experts with complementary areas of expertise. All decisions made during the review process will be fully documented.

All identifiable personal information will be protected and stored in the study database in pseudonymized form so that it cannot be viewed by the study sponsor or any external vendors that are processing the study data. A summary of data sources and data flow is provided in Figure 1.

Figure 1. Diagram of data sources and data flow. AHI: apnea-hypopnea index; ALH: Air Liquide Healthcare; ePRO: electronic patient-reported outcome; ERP: Enterprise Resource Planning; HSP: home support provider; IoT: Internet of Things; PRE: patient-reported experience; QoL: quality of life.



Statistical Methods

Sample Size

This study aims to include all adults starting PAP therapy managed by an ALH home support provider in the participating countries who met the selection criteria during the study time period. This approach minimizes selection bias and sampling errors, ensuring precise and reliable results. Inclusions will be possible at the national level (France) or only at some investigational sites in countries requiring regional or hospital-level regulatory processes. All potential participants will be informed whenever ethics committee approval is obtained from the respective regions or hospitals. It is expected that around 30% of the 150,000 eligible participants will not be enrolled due to the absence of (or incorrect) email, or refusal to participate. Therefore, the number of included patients is expected to be around 100,000. With a sample of this size, the probability of showing a statistically significant difference in adherence between different levels of service if one exists is >99%, even if there were important imbalances between groups.

Statistical Analysis

Statistical analyses will be performed according to a predefined statistical analysis plan (Table 2).

Table 2. Statistical analysis plan details.

Objectives	Main outcomes	Key explanatory variables	Statistical methods
Compare PAP[a] adherence and the PAP therapy persistence rate between different levels of home support provider service	• PAP adherence: (1) mean number of hours/day of PAP use and (2) adherent patients defined as those with mean PAP use ≥4 hours/day • PAP persistence: (1) percentage of days with PAP use, (2) patients still in therapy, and (3) patients still in therapy and adherent	• Fixed effect: Level of service (standard of care, personalized care plan, or high service level) • Random effect: Country	Multilevel model adjusted for selected confounding factors
Identify service components that influence PAP adherence and persistence	• PAP adherence: (1) mean number of hours/day of PAP use and (2) adherent patients defined as those with mean PAP use ≥4 hours/day • PAP persistence: (1) percentage of days with PAP use, (2) patients still in therapy, and (3) patients still in therapy and adherent	• Fixed effect: Frequency of interactions, content of support, personalization of support, and telemonitoring • Random effect: Country	Multilevel model adjusted for selected confounding factors
Identify factors associated with PAP adherence and persistence	• PAP adherence: (1) mean number of hours/day of PAP use and (2) adherent patients defined as those with mean PAP use ≥4 hours/day • PAP persistence: (1) percentage of days with PAP use, (2) patients still in therapy, and (3) patients still in therapy and adherent	• Fixed effect: Frequency of interactions, content of support, personalization of support, telemonitoring, sociodemographic characteristics, OSA[b]-related clinical characteristics, and characteristics of PAP therapy • Random effect: Country	Multilevel model
Descriptive Analysis	• Sociodemographic characteristics • OSA-related clinical characteristics • OSA and PAP literacy • Experience with PAP therapy • Experience with home support provider support • Quality of life • Home support provider PAP-related service	N/A[c]	Usual descriptive statistics: Analysis by country
Describe patterns of PAP use	• Mean PAP use categories over time	N/A	Data visualization such as Sankey diagrams

[a]PAP: positive airway pressure.

[b]OSA: obstructive sleep apnea.

[c]N/A: not applicable.

Patient Datasets

Retrospective data will be available for all included patients (included population). Prospective data from the ePRO tool will be available for the subset of patients who complete the questionnaire (ePRO population).

Multilevel Models

Individuals living in the same country share a common health care system, lifestyle, and climate, and tend to be more similar than individuals from other countries. Therefore, individuals are considered nested within a country. This correlation of observations violates the assumption of independence for standard regression analysis leading to biased standard errors of parameter estimates. Therefore, we will fit multilevel linear or logistic mixed models using the country variable as a random effect to test the association between adherence or persistence and levels of service while accounting for this nested data structure.

Confounding Factors

Potential confounding factors were identified a priori based on a literature review and clinician expertise, and include age, sex, BMI, sleep duration, symptoms before starting PAP therapy, occupational status, highest education level, bed partner, comorbidities, smoking status, alcohol consumption, apnea-hypopnea index at the time of diagnosis, and prescriber specialty. Factors consistently described as being associated with PAP therapy adherence or persistence will be automatically included in statistical models comparing the effect of service on adherence or persistence. Other potential confounding factors will be selected based on their association with adherence or persistence in a univariate analysis. Full details of the confounding variables considered and the supporting sources are provided in Multimedia Appendix 2. Quantitative bias analysis will be performed to evaluate the impact of unmeasured confounders using a metric named the e-value [34]. The e-value can be defined as the strength of association that an unmeasured confounding factor would need to have in order to explain away the observed association.

Data Visualization

Data visualization (eg, with the use of Sankey diagrams) will be used to represent the pattern of changes in mean PAP use categories over time.

Sensitivity Analyses

Sensitivity analyses will be performed after removal of data collected during the COVID-19 lockdown periods, and before and after June 2021 (the time of the Philips Respironics world product recall [35,36].

Ancillary Study

While the association between PAP adherence and costs has been demonstrated in the United States [21,23,37-42], data from Europe remain limited [43,44]. To further determine the benefits of home support providers, an ancillary study, named APAIR (Association Between Positive Airway Pressure Adherence, Morbi-Mortality and Costs Among Patients With Obstructive Sleep Apnea in France: Real World Study Using Claims and Telemonitoring Data), will be conducted in the subset of AWAIR study participants from France. APAIR will investigate the association between PAP adherence and persistence, and key outcomes (mortality, morbidity, and health-related costs). AWAIR study participants from France will be identified in the French Healthcare Claims Database (Système National des Données de Santé), which provides longitudinal patient-level data for approximately 99% of the French population [45]. Data on hospitalizations and sick leave related to the complications of OSA will be retrieved for these individuals. The aim of APAIR is to obtain data relating to new and more relevant thresholds for PAP adherence and the personalization of PAP therapy support (eg, for those with higher health risks or higher health care resource use).

Results

As of December 2024, the AWAIR study has received approval in France, Portugal, and 2 regions of Spain. Patient enrollment started in France in October 2024, with around 90,000 patients informed about the study. Results of the AWAIR study are expected in the second quarter of 2025.

Discussion

Study Rationale

The high and increasing number of patients with OSA treated with PAP therapy drives concerns among health systems regarding the associated health care resource consumption and costs. This has led some countries to implement significant changes in the patient pathway, notably toward more home-centered models [30,46]. Regardless of the care setting, PAP adherence and persistence are essential because they are associated with health benefits [19], whereas poor adherence and PAP therapy terminations have been associated with increased disability, health care resource consumption, and direct or indirect costs [47-49].

Despite a large body of evidence regarding the factors associated with PAP adherence [50] and persistence [25,51], and the reimbursement of PAP-related services in many European Union countries, there is currently a lack of evidence regarding the impact of home support provider services on these outcomes. In addition, although defined by country or local regulations, the level of home support provider service is poorly described. Differences exist in service frequency, content, and communication channels between home support providers and patients, the use of PAP telemonitoring, and the qualifications of home support provider personnel. Some of these components have been shown to impact PAP adherence [29,30,52,53].

Our working hypothesis is that a higher level of home support provider service would be associated with better PAP adherence and persistence. This study will also investigate between-country differences in terms of patient characteristics, OSA-related characteristics, and services, and identify which components of service are most effective at improving adherence and persistence.

We anticipate that this research will provide valuable evidence to inform decision-making by authorities and payers regarding the regular reassessment of services and associated tariffs. It could also support guidelines relating to the follow-up of individuals receiving PAP therapy.

Design Rationale

The comparative, real-world design with between-country comparisons was the most feasible approach for this study. A randomized controlled trial was not viable because home support provider services are implemented for all patients prescribed PAP. The need to include a control group without services in a randomized trial would have markedly reduced ethical approval and acceptance of the study and would have introduced important bias related to behavioral factors for those accepting home support provider management. Furthermore, the controlled conditions of clinical trials do not adequately capture the complexity of factors influencing adherence in real life. Furthermore, there was a need for evaluation of the real-world impact of home support providers on a representative, unselected population. Real-world studies provide information about outcomes with less rigid treatment patterns compared with a controlled trial [54] and bridge the gap between clinical research and everyday practice. We followed the Haute Autorité de Santé methodological recommendation for real-world studies, proposing a design consistent with identified questions, using preexisting high-quality data, integrating PROs and PRE, and ensuring transparency [55].

Strengths

One of the major strengths of this study is its large sample size, which enhances the representativeness of the population and the generalizability of the findings. The retrospective design allows for long-term evaluation of PAP adherence and persistence and ensures that there is no influence on participants' behavior because data were collected prior to their inclusion in the study. In addition, the AWAIR study will describe between-country differences in home provider services and patient characteristics for the first time, and report on patient satisfaction and experience with PAP therapy.

In contrast with conventional clinical trials, the real-world setting ensures that the results will reflect the usual course of care [56]. This is particularly important for evaluating adherence because it minimizes the risk of bias that could arise from study participation. Furthermore, real-world evidence is particularly relevant for meeting health authority post-approval effectiveness requirements [57]. Well-conducted comparative effectiveness research can provide valid results similar to randomized trials for this measure of known confounding factors [56], and can use methods (such as stratification, matching, or regression analyses) to account for or adjust for such factors and yield valid results [58]. In the real-world comparative AWAIR study, adjustment for potential confounders identified through literature review and clinical expertise, combined with the use of hierarchical models accounting for contextual differences related to the international nature of the study, will help the data to provide an accurate assessment of the net effect of home provider services on PAP adherence and persistence while minimizing the potential biases inherent in real-world studies. Additionally, the use of an ePRO tool facilitates the collection of data on confounding factors that would not otherwise be available in the retrospective database analysis, along with PROs, PREs, and health literacy across a large and diverse patient population from various geographic regions [59].

Limitations

Selection bias cannot be entirely ruled out because participants were required to have a valid email address or smartphone number to be eligible for the study. This may lead to underrepresentation of certain subgroups of PAP users, such as older adults. Patients who answer the questionnaire might also differ from those who do not answer it. In addition, this study will only include individuals who use PAP supplied by a home support provider affiliated with ALH and it is possible that the level or content of additional services may differ slightly from other home support providers in the same country. To assess the potential impact of such biases, we will compare the characteristics of our study population with published data on OSA, focusing on age, sex, and disease severity.

Data from the ePRO tool may be subject to recall bias and inaccuracy because participants will complete the web-based questionnaire at variable periods of time since the start of PAP therapy (up to 5 years later for those who started PAP in 2019) and medical data will directly be provided by the patient. Confounding bias other than the key confounding factors considered is another limitation, particularly with respect to medical follow-up (data that will not be collected in this study).

Finally, the period over which this study was conducted included times before and during the COVID-19 pandemic (including lockdowns), and the worldwide recall of a PAP device made by Philips Respironics [36]. Sensitivity analyses will be performed to determine whether these factors had any influence on the overall study findings.

Challenges

The study faced several challenges, including the regulatory classification of an ambispective study and the heterogeneous regulatory processes between countries. In France, the reuse of data for clinical research is facilitated by a simplified procedure that does not exist in other countries. Although the decentralized approach used in this study (ie, e-consent + ePRO tool) has advantages, especially in terms of managing a large number of participants, proposing the study to potential participants remotely can decrease the rate of enrollment. This is why a video-based approach was chosen because using videos to explain the research aims and procedures to potential participants of a clinical trial was preferred by patients over paper-based systems and improved their understanding [60].

Another challenge is the quantity of data to be processed due to the large number of participants and the daily PAP data collected over up to 5 years, requiring robust data management and quality control systems. Moreover, data were collected for routine home support provider services, in different countries with different services and enterprise resource planning systems, with different data collection processes, which adds another layer of complexity to the study. Therefore, those involved in the study need to have a good understanding of the data collection processes, data structures, formats, contents, and constraints of each system to allow standardization of data to constitute a research-ready database.

Opportunities

Clinical trials are critical in the assessment of health products and services. However, managing and executing randomized controlled trials pose significant challenges in terms of inclusion, data collection, follow-up, comparator group, and costs [61]. Specifically in patients with OSA treated with PAP, it was shown that recruitment strategies in randomized trials could result in a lack of representativeness of the participants, because only up to 20% of typical patients with OSA meet the eligibility criteria, limiting the generalizability of the results [62]. The expanding availability of real-world data combined with advancements in operational tools and methodologies presents a significant opportunity to develop alternative study designs that leverage existing data. Furthermore, the European Health Data Space will create a common framework in Europe for the reuse of health data for research [63]. The design of the AWAIR study integrates multiple real-world data sources (including operational databases, device data, and an ePRO tool), the use of comparative real-world methods, and the implementation of e-consent. This innovative approach not only makes the study more robust but also sets a precedent for future research in similar fields, particularly regarding the number of participants who will consent and complete the ePRO tool. The design allows the study to be continuously enriched with data from new countries to measure the effect of other service levels and also to extend patient follow-up to assess longer-term persistence or include other patients in the countries of interest to assess the impact of changes in service levels.

Conclusions

The AWAIR study has a unique design, leveraging an unprecedented number of eligible participants, decentralized technologies, and a real-world comparative methodology across multiple countries. This approach will highlight intercountry differences in terms of patient characteristics, PAP adherence and persistence, PROs, PREs, and satisfaction with home

support provider services. By assessing the added value of home support provider services, the results will support best practices for patient management and decision-making by health authorities and payers.

Acknowledgments

Medical writing assistance for the preparation of the first draft manuscript was provided by Nicola Ryan, an independent medical writer. This study was funded by Air Liquide Santé International, Paris, France.

Authors' Contributions

SA, MS, HT, CF, FB, and SB contributed to the study conception and design. HT and SO were involved in the regulatory process. JT, FG, PP, ICP, and LB provided the scientific validation of the outcomes and the content of the patient questionnaire. SA, HT, SB, HS, and BB designed the ePRO. MS, FB, SA, and CF provided the statistical methodology of the study. SA and MS outlined the first draft of the manuscript. All authors reviewed the manuscript and provided critical revisions of the manuscript. All authors approved the final version of the manuscript.

Conflicts of Interest

HS and BB have no conflicts of interest to declare. ICP, PP, LB, and FG have received consulting fees from Air Liquide Group. SA, JT, MS, HT, SB, and MHG are employees of Air Liquide Group. FB and CF are employees of Horiana, the contract research organization (CRO) of the study. SA, MS, and HT are shareholders at Air Liquide.

Multimedia Appendix 1
Full study questionnaire.
[DOCX File , 1425 KB - resprot_v14i1e65840_app1.docx]

Multimedia Appendix 2
Confounding factors.
[DOCX File , 30 KB - resprot_v14i1e65840_app2.docx]

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Abbreviations

ALH: Air Liquide Healthcare
APAIR: Association Between Positive Airway Pressure Adherence, Morbi-Mortality and Costs Among Patients With Obstructive Sleep Apnea in France: Real World Study Using Claims and Telemonitoring Data
AWAIR: Assessment of the Benefit of the Home Support Provider Service Level Associated With Positive Airway Pressure Treatment in Patients With Obstructive Sleep Apnea on Treatment Adherence and Persistence: an International Real-World Study
ePRO: electronic patient-reported outcome
ERP: Enterprise Resource Planning
HSP: homecare support provider
OSA: obstructive sleep apnea
PAP: positive airway pressure
PRE: patient-reported experience
PRO: patient-reported outcome

Edited by A Schwartz; submitted 29.08.24; peer-reviewed by S Bourguignon; comments to author 17.10.24; revised version received 29.11.24; accepted 02.12.24; published 31.01.25.

Please cite as:
Alami S, Schaller M, Blais S, Taupin H, Hernández González M, Gagnadoux F, Pinto P, Cano-Pumarega I, Bedert L, Braithwaite B, Servy H, Ouary S, Fabre C, Bazin F, Texereau J
Evaluating the Benefit of Home Support Provider Services for Positive Airway Pressure Therapy in Patients With Obstructive Sleep Apnea: Protocol for an Ambispective International Real-World Study
JMIR Res Protoc 2025;14:e65840
URL: https://www.researchprotocols.org/2025/1/e65840
doi:10.2196/65840
PMID:

Protocol

Core Outcome Set Development for Tension-Type Headache Treatment Using Traditional Chinese Medicine: Protocol for a Delphi Consensus Study

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Abstract

Background: Tension-type headache (TTH) is the most common type of headache and the second most common health-related complaint among children and adults. Traditional Chinese medicine (TCM) offers unique therapeutic benefits in treating TTH. However, the lack of standardized evidence—such as inconsistencies in outcome selection and reporting in clinical studies, a lack of consensus on outcomes and measures, high risks of selective reporting bias, and missing data—has limited the development of robust evidence supporting the efficacy of TCM in treating TTH. Therefore, establishing a core outcome set (COS) is crucial for standardizing TCM clinical studies for TTH, thereby enhancing the quality and comparability of research findings.

Objective: This study aims to develop a COS for future clinical studies on the treatment of TTH with TCM.

Methods: The COS will be developed through the following 3 stages. First, systematic reviews and semistructured interviews will be conducted to identify potential essential outcomes, which will be evaluated by the steering committee to finalize a preliminary list of outcomes. Data will be processed using thematic analysis to ensure comprehensive coverage of relevant outcomes. Second, a 2-round Delphi survey will be conducted, inviting stakeholders, including health care experts and patients with tension-type headaches, to determine the importance of each outcome. Statistical analysis will be used to assess the level of consensus and prioritize outcomes based on predefined criteria. Third, a face-to-face consensus meeting will be held to finalize the COS and recommend measurement times for each outcome. Key outcomes will be interpreted based on their clinical relevance and feasibility of measurement, ensuring the COS is comprehensive and applicable in clinical settings.

Results: The protocol has been registered in PROSPERO, with the review commencing on October 1, 2024, and anticipated results by November 15, 2024. The systematic reviews will be finalized, followed by the Delphi survey and consensus conference in late 2024 and early 2025. The COS findings will be reported per COS-STAR (Core Outcome Set–STAndards for Reporting) guidelines, published in an international journal, presented at conferences, and disseminated to participants for clinical application.

Conclusions: This study is necessary as developing a COS for future TCM clinical studies in the treatment of TTH can maximize the value of data from individual trials and provide high-quality research evidence.

Trial Registration: Core Outcome Measures in Effectiveness Trials Initiative 1473; https://tinyurl.com/3ts62s2p

International Registered Report Identifier (IRRID): PRR1-10.2196/63481

(JMIR Res Protoc 2025;14:e63481) doi:10.2196/63481

KEYWORDS

tension-type headache; core outcome set; traditional Chinese medicine; systematic review; Delphi; protocol

Introduction

Background

Tension-type headache (TTH) is a neurological disorder characterized by mild to moderate headaches [1]. It is the most common type of headache and second most common health-related complaint among children and adults [2,3], and negatively affects their ability to participate in various activities in school, sports, social, and home settings, especially when the headache becomes chronic and frequent [4]. Many studies have shown that TTH significantly impacts mood, sleep, and liveliness; anxiety or depression is more common in patients with headaches than in those without headaches [5-7].

Traditional Chinese medicine (TCM), which includes Chinese herbal medicine, acupuncture, and massage, plays an increasingly important role in the treatment of TTH [8-13]. In particular, acupuncture is frequently used to treat TTH [14] and has been approved as a supplementary therapy option for TTH by the European Federation of Neurological Societies [15]. Several randomized controlled trials (RCTs) of TCM for TTH have been conducted in China. Although an individual RCT is valuable, pooling data from numerous RCTs can give more substantial evidence to support therapeutic decision-making [16]. The normalization and homogeneity of research outcomes are crucial when pooling data from multiple studies. However, we found the following problems in the selection and reporting of outcomes in RCTs and systematic reviews on the effects of TCM on TTH.

Many studies only reported the effectiveness rate of composite indicators [17], and certain clinical studies failed to include critical or relevant outcomes, such as headache frequency, severity, duration, impact on quality of life, and analgesic use. As a result, these studies were not suitable for secondary analysis [18], which precludes the incorporation of many results into systematic reviews or meta-analyses. This limitation undermines the ability to provide higher-level evidence for clinical practice, thereby diminishing the research's value and contributing to unnecessary waste. In addition, selective reporting of results may exist in current clinical studies, as researchers are more likely to select statistically significant results, leading to overestimation of outcomes and exaggeration of efficacy [10,13,19]. Outcome measures were poorly defined, with total effectiveness rates inconsistently defined using a variety of concepts [17]. The outcome measures for different studies were heterogeneous, and systematic reviews have shown significant heterogeneity among studies, which is not conducive to intervention comparisons and meta-analysis [10,11,13]. Furthermore, outcomes were developed without considering the opinions of patients and other stakeholders. The International Headache Society Committee proposed an evaluation of outcomes in clinical trials [20]. However, there is still a lack of consensus on the collection and reporting of RCTs of TCM for the treatment of TTH, which limits the comparison and aggregation of data from individual trials and reduces their research value.

Therefore, to address the above problems, it is necessary to develop a core outcome set (COS) for TCM clinical studies (COS-TCM) for TTH. Developing, disseminating, and implementing a COS can address and overcome inconsistencies in outcome selection, measurement, and reporting [21]. Currently, there is no specific COS-TCM for TTH. After searching the Core Outcome Measures in Effectiveness Trials (COMET) database, we identified 1 COS associated with TTH. The International Headache Society Committee proposed an evaluation of TTH outcomes in clinical trials in 1995 (1st edition) [22] and 2010 (2nd edition) [15]. However, the standardized outcome set in COS may be biased toward Western patient populations and lack access to Chinese clinical experts and Chinese patients. There are no COSs available that include outcomes relevant to TCM syndromes. Therefore, developing a COS-TCM for TTH will enhance the quality of evidence from clinical studies of TCM for TTH, promote the translation of clinical research into clinical practice, and provide recommendations for health care decision-making [23,24].

This study was registered in the COMET Initiative (1473) and will be conducted according to the Core Outcome Set-STAndards for Development [25] and Construction of Core Outcome Set of TCM Clinical Trials guidelines [26]. This study protocol referred to the Core Outcome Set-Standardized Protocol Items [27], which are shown in Multimedia Appendix 1.

Scope and Aim

Aim

This study aims to develop a COS for future clinical studies on TCM for the treatment of TTH, in order to improve the use of evidence synthesis by standardizing outcome reporting and guaranteeing that all studies contribute valuable data.

Scope

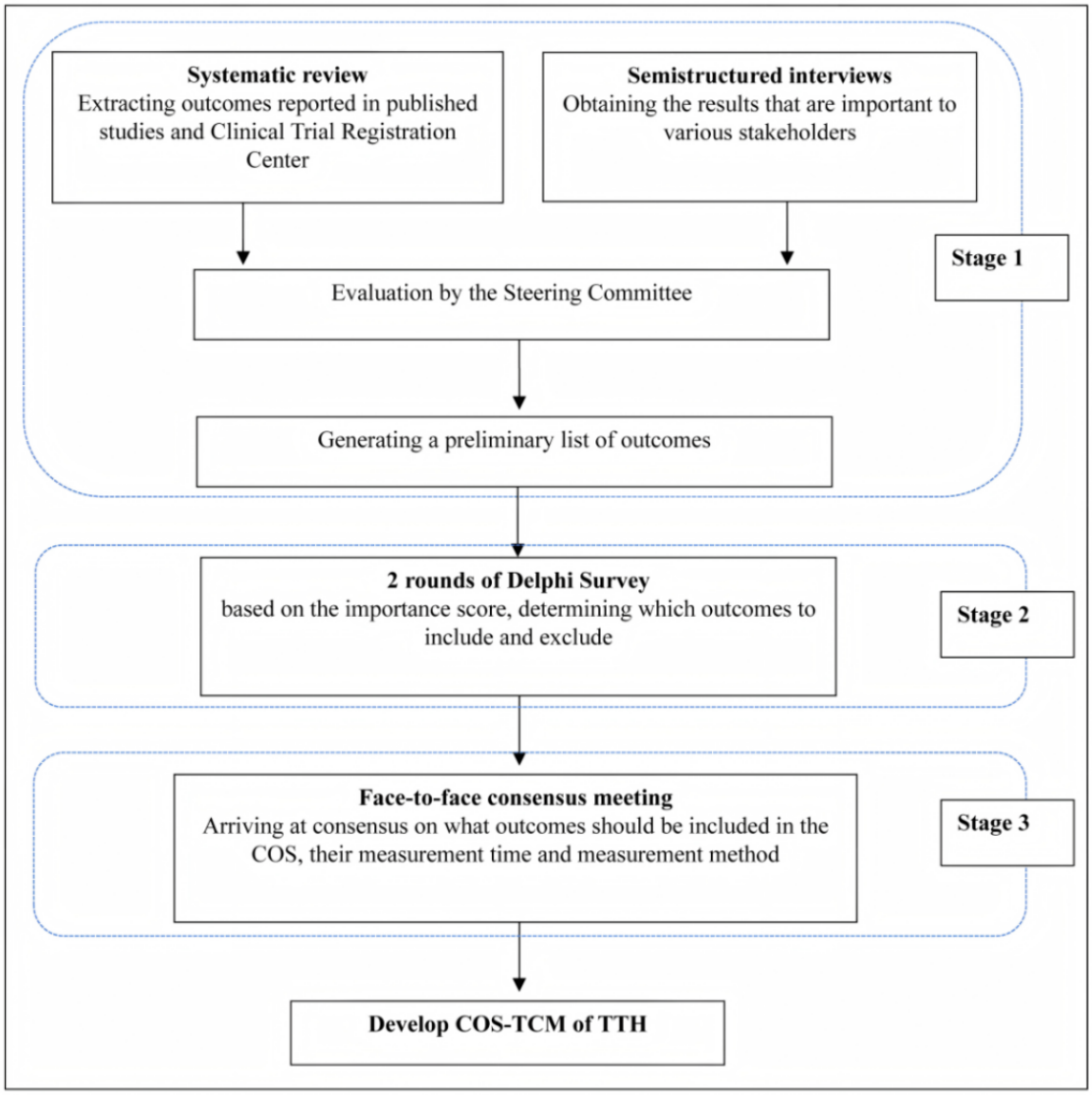
The scope of the COS-TCM encompasses several key areas. It focuses on the health condition of TTH and targets a population of patients with TTH who are aged 18 years and older. The types of interventions included are various TCM therapies, such as herbal medicine decoction, Chinese patent medicine, acupuncture, moxibustion, cupping, massage, Tai Ji, Baduanjin, Qigong, and other nondrug treatments. This scope applies to any type of clinical study.

Methods

Design

The study design is structured in 3 stages, providing a comprehensive framework for developing the COS-TCM. Initially, semistructured interviews and a systematic review will be conducted to identify potential essential outcomes. This will culminate in a preliminary list of outcomes, evaluated and finalized by the steering committee. The second stage involves selecting various stakeholders to participate in a 2-round Delphi survey, aiming to gather diverse opinions on the COS-TCM. Finally, a consensus meeting with key stakeholders will be convened to finalize the COS-TCM. Figure 1 illustrates the flowchart of the study process.

Figure 1. The flowchart of the study core outcome set (COS). TCM: traditional Chinese medicine; TTH: tension-type headache.



Steering Group

The steering group will consist of 5 individuals from various scientific fields, including 2 TCM clinical neurology experts, 2 Western medicine clinical neurology experts, and a methodologist. The group will examine and approve the study protocol, determine the preliminary checklist of the reporting outcome set, and take part in a consensus conference to advance the construction of the COS.

Working Group

The working group will consist of 20 members, including clinicians, methodologists, professors, and graduate students from Xiyuan Hospital, China Academy of Chinese Medical Sciences. The group will be responsible for conducting routine research tasks and related meetings, contacting experts, and seeking advice from the steering committee when disagreements need to be resolved.

Involvement of Stakeholders

Various stakeholders, including health professionals and patients, will be included in the COS development process. Health professionals will include TCM and Western medicine practitioners who specialize in cerebrovascular disease, methodologists who specialize in evidence-based medicine, and researchers. Core journal editors will select from journals focusing on neurological diseases, such as the *Chinese Journal of Neurology*, *Chinese Archives of Traditional Chinese*

Medicine, *Journal of Neurology and Neurorehabilitation*, *Chinese Journal of Evidence-Based Medicine*, and *Global Traditional Chinese Medicine*. Other relevant experts include clinical trial personnel, industry representatives, and policy makers. The study will invite patients with TTH to participate.

Patient and Public Involvement

Considering that patients' opinions are significant for the formulation of the COS, this study will involve semistructured interviews, 2 rounds of Delphi survey, and consensus meetings.

Stage 1: Identification of Potentially Significant Outcomes

Step 1: Systematic Review

According to the guidelines of the COMET Initiative [21], a systematic evaluation will be performed to screen the spectrum of critical potential outcomes. Previous COS-TCM studies will be used for systematic review as the research starting point [28-30]. This study will include all clinical studies (regardless of research type) that report TTH outcomes.

Search Strategy

PubMed, the Cochrane Library, Embase, Web of Science, SinoMed, Chinese National Knowledge Infrastructure, Chinese Citation Database, China Science Periodical Database, Chinese Clinical Trial Registry, and Clinicaltrials.gov will be systematically searched from inception to January 31, 2024. The search strategy for English databases is shown in Multimedia Appendix 2. The languages will be restricted to English and Chinese.

Inclusion Criteria

The inclusion criteria for the study encompass several key aspects. First, the study must be a clinical investigation, which can include randomized controlled studies, case-control studies, cohort trials, or case series. Participants should be patients diagnosed with TTH who are 18 years or older. The diagnosis must be made using any internationally recognized classification, such as those outlined in the International Classification of Headache Disorders, including the first edition (1988), the second edition (2004), and the third edition (2013) by the Headache Classification Committee of the International Headache Society. The intervention under consideration should involve TCM therapies for those included in the treatment group. In addition, if a study primarily investigates secondary TTH as a consequence of conditions such as mental disorders, infections, or endocrine diseases, a thorough review of the full text will be conducted to determine the presence of headache-related outcome measures. Studies that report such outcomes will be eligible for inclusion.

Exclusion Criteria

The exclusion criteria encompass several specific aspects. Clinical trials that investigate the outcomes of comorbidities related to TTH, such as nausea caused by TTH, are excluded. In addition, studies primarily focused on assessing pharmacodynamics or pharmacokinetics are not considered. A study involving fewer than 10 cases is also excluded.

Data Extraction

A data extraction table was designed and will be used to extract basic study information, including author information, year of publication, country, Western medicine diagnostic standards, type of TTH, TCM syndrome names and diagnostic criteria, interventional measures, study type, conclusions, outcomes and their definitions, time points, and method of outcome measurement. A total of 2 trained reviewers will be responsible for independent study screening and data extraction. Disagreements will be resolved by consulting with a third researcher. If any data is missing, the reviewers will contact the authors of the research by email or telephone to obtain the missing data.

Step 2: Semistructured Interview

A systematic review has been conducted to summarize the outcomes of existing clinical studies. However, this mainly represents the researchers' perspectives. According to the current guideline recommendations of the Core Outcome Set-STAndards for Development [25] and the COMET handbook (version 1.0) ADDIN [31], the opinions of clinicians and patients on the treatment of TTH with TCM can be obtained through semistructured interviews.

Participants

In this study, we will use heterogeneous and purposive sampling methods to recruit participants. Purposive sampling is widely used in qualitative and mixed-methods research because it enables researchers to select samples based on specific study objectives and criteria. This approach allows for the selection of more representative samples within a limited timeframe, thus conserving significant time and effort and reducing costs. Specifically, we will recruit patients diagnosed with TTH from the Xiyuan Hospital of the China Academy of Chinese Medical Sciences, as well as clinical doctors from 15 tertiary hospitals nationwide, to ensure the diversity and representativeness of the sample. The criteria for patient selection include age, gender, type of disease, duration of illness, and type of treatment, aiming to capture a broad range of patient experiences and treatment outcomes. For clinical doctors, the selection will focus on geographical diversity and professional background to obtain a wide spectrum of clinical perspectives. We plan to recruit 30 clinical doctors and 30 patients. Although no standardized method exists for determining the sample size for semistructured interviews, previous studies suggest that data saturation typically occurs when the sample size reaches 30 [24,30,32]. By adhering to these criteria and methods, we ensure that the selected sample adequately reflects the diversity and complexity of the research topic, thereby enhancing the quality and reliability of the study findings. Detailed inclusion and exclusion criteria for clinical doctors and patients in the semistructured interviews are provided in Table 1.

Table 1. Inclusion and exclusion criteria for clinicians and patients in semistructured interviews.

Category	Inclusion criteria	Exclusion criteria
Clinicians	• Senior titles in neurology or TCM[a], with more than 5 years of work experience. • At least a bachelor's degree. • Engage in headache treatment.	• None.
Patients	• Diagnosed with TTH[b], no limitations on status. • Aged 18 years and older. • Receiving TCM treatment. • Sign informed consent forms. • Capable of reading, understanding, and speaking Chinese or English.	• Severe diseases such as heart failure, cerebral infarction, cerebral hemorrhage, and tumors.

[a]TCM: traditional Chinese medicine.

[b]TTH: tension-type headache.

Data Collection

Considering previous studies and the characteristics of TTH, we designed a semistructured interview. The development of the interview questions involved a thorough review of existing literature and consultation with experts in the field to ensure content validity. The interview will be conducted by professional researchers in a specific consultation room or office, with face-to-face interactions with participants conducted as often as possible. All interviews will be recorded to facilitate comprehensive data analysis. Before the interview, participants will be informed of the study's purpose and content, and they will be required to sign an informed consent form.

For patients, the semistructured interview will explore several key areas. Participants will be asked about the duration of their headache experience or how long they have been diagnosed with TTH. They will describe their main symptoms and the treatment they are currently receiving. In addition, they will be queried about their satisfaction with the current treatment and any recommendations they have for its improvement. Further questions will address the areas they would most like to improve and the outcomes they hope to enhance after treatment.

For clinicians, the interview will focus on their professional experience and treatment approaches for TTHs. Clinicians will discuss how long they have worked in their field and their methods for treating tension-type headaches. They will be asked about the outcomes they believe the therapies will enhance for patients. Furthermore, they will identify which outcomes they prioritize in the treatment of TTHs, listing at least 5 indicators they are concerned with.

To evaluate the validity of the interview questions, we conducted a pilot test with a small group of participants and clinicians not involved in the main study. Feedback from this pilot test was used to refine the questions, ensuring clarity and relevance. In addition, an expert panel reviewed the questions to confirm that they accurately capture the dimensions of interest related to TTH.

Data Analysis

A total of 2 researchers will independently conduct the data analysis. Disagreements will be resolved through discussions or with the assistance of a third researcher. After sorting out the recorded text, the data will be analyzed using the frame analysis method, including familiarity, identifying thematic frames, indexing, charting, mapping, and interpretation to obtain essential outcomes for patients and clinicians [33].

Step 3: Merging and Collating Outcomes

After completing the systematic review and semistructured interviews, the results from these 2 components will be merged. Guided by the COS-TCM standard, 2 researchers will independently collect the outcomes, resolving any disagreements through consultation or with the input of a third researcher. The data collation process begins with importing the extracted indicators into a Microsoft Excel table for sorting. Outcomes are assigned and matched to the corresponding study numbers to facilitate tracing. Following this, the outcomes undergo preliminary sorting, during which duplicates are removed. All study numbers and amounts indicating the results and frequency of application for each outcome are recorded.

Subsequently, the original outcome measures are standardized. For example, the names of outcomes are standardized, and composite results are reduced to a single result without altering the original meaning of the index. Finally, the names and frequencies of all outcomes are counted. The outcome domains are then determined, with the collected outcomes further classified into 7 domains according to the COMET manual [31] and COS-TCM [26] standards: TCM syndromes, symptoms and signs, physical and chemical testing, quality of life, long-term prognosis, economic evaluation, and safety events.

Step 4: Generating a Preliminary List of Outcomes

A preliminary list of outcomes will be finalized after evaluation by the steering committee. If the number of results collected in the indicator pool is small (≤100), all the outcomes will be included in the outcome list. If the number exceeds 100, the steering committee will conduct an internal vote on the indicator pool. If 90% of the members do not agree to include an item in the original list, it will be removed. Outcomes added by the steering committee will also be included to form the initial outcome list.

Stage 2: Delphi Survey

Involvement of Stakeholders

Stakeholders, including health care experts and patients with TTH, will be invited to participate. Health care experts include

TCM and integrated Chinese and Western medicine practitioners who are engaged in the field of cerebrovascular disease, Western medicine clinicians in the field of cerebrovascular disease, methodologists in the field of evidence-based medicine, researchers, core journal editors, and other relevant experts.

As the project team's leading unit, the China Academy of Chinese Medical Sciences formed the Encephalopathy Project Team of the TCM Evidence-based Medicine Center with 15 hospitals from 15 provinces. Qualified health care experts from these 15 hospitals will be recruited to participate in the Delphi survey. Patients will be recruited from the Encephalopathy Department of Xiyuan Hospital. The inclusion and exclusion criteria for the health care experts and patients are listed in Table 2.

Table 2. Inclusion and exclusion criteria for health professionals and patients in the Delphi survey.

Category	Inclusion criteria	Exclusion criteria
Health professionals	• More than 1 year of work experience. • Bachelor's degree or above. • Experience working in tertiary hospitals. • Published at least one clinical trial on cerebrovascular disease.	• None.
Patients	• Diagnosed with TTH[a], no limitations on status. • Aged 18 years and older. • Receiving TCM[b] treatment. • Sign an informed consent form. • Capable of reading, understanding, and speaking Chinese or English.	• Patients with severe diseases such as heart failure, cerebral infarction, cerebral hemorrhage, and tumors will be excluded based on medical history, physical examinations, and auxiliary tests.

[a]TTH: tension-type headache.

[b]TCM: traditional Chinese medicine.

Sampling Strategy

Since there is no reliable method for estimating the required sample size, the sample size will be determined according to the needs and conditions of the study [34]. Based on the sample size of previous studies and the implementation specification for the Delphi survey in the COS-TCM [26,35,36], we aim to involve 100 stakeholders, including 30 TCM and integrated Chinese and Western medicine clinicians, 15 Western medicine clinicians, 45 patients, 5 researchers, and 10 methodologists. In total, 2 rounds of the Delphi survey will be conducted.

Round 1 of the Delphi Survey

Developing a Questionnaire for Round 1 of the Delphi Survey

A questionnaire for round 1 of the Delphi survey will be formulated based on a preliminary list of outcomes obtained from systematic reviews, semistructured interviews, and evaluation by the steering committee. The questionnaire will consist of 4 parts, including the description of the purpose of the study, personal information of the respondent, evaluation of the importance of outcome indicators, and open questions. Participants will need to provide arguments for the inclusion or exclusion of each outcome in a COS. These arguments can then be summarized and used to develop proposals for voting on the inclusion or exclusion of each outcome in the second round. The open questions will be mainly supplementary to the questions considered necessary by the participants but not included in the questionnaire. To improve the intelligibility of the questionnaire, different terms will be designed for different stakeholder groups. For example, for Western medicine experts, the interpretation of TCM terms can be translated into the Western medicine language in which they are proficient. A general explanation will be added for patients. Stakeholders will be involved in the design of the questionnaire in advance. Delphi survey items commonly use a 9-point critical or relevant outcome to score the importance of outcomes [26,31]. Scores of 1-3 indicate that the outcome is nonessential," 4-6 indicate that the outcome is "important but not vital," whereas 7-9 indicate that the outcome is "necessary for inclusion." If participants are unable to assess the importance of some outcomes, they will be able to select "uncertain."

Process of Round 1 of the Delphi Survey

The first round of the Delphi survey is expected to be completed within 3 weeks. We will email the electronic version of the questionnaire to health care experts. They will be required to complete the questionnaire within 3 weeks and will be reminded by text messages 1 week and 48 hours before the end of the survey. The working group will assess the number of participants at the end of the second week. If the response rate to the Delphi survey (number of respondents/number of invited participants) is less than 70%, the survey will be extended for another 2 weeks. To increase the awareness rate, the questionnaire will be distributed on workdays. We will recruit eligible patients from the Department of Encephalopathy at Xiyuan Hospital. The consulting doctor will be responsible for introducing the content of the questionnaire to the patient and obtaining their consent and signature on the informed consent form. Team members will then hand out questionnaires to patients for immediate completion. We will try our best to answer the patients' questions.

Data Analysis for Delphi Round 1

The working group will gather all submitted questionnaires and calculate the response rate, average score, score distribution among health professionals and patients, and the number of participants from various stakeholder groups for each outcome item. To ensure that the outcomes of Delphi round 1 are fully shown and can be rescored, all outcomes will be retained in subsequent rounds [31,35,36]. Newly added items can be

included in Delphi round 2 if the steering committee deems them to be different from the results of Delphi round 1.

Round 2 of the Delphi Survey

Process of Round 2 of the Delphi Survey

Participants who completed the first round of the Delphi survey will be invited to participate in the second round. Each participant will be shown their first-round results, the score distribution of other stakeholders, and a summary of arguments. Based on this feedback, participants will be requested to regrade and score the additional questions in the second round. If the score for an outcome changes significantly between rounds, for example, from "not important" (1-3 points) to "critical" (7-9 points), the rationale for the change will be asked to be mentioned. Participants will also be able to provide suggestions for each survey item.

The Delphi round 2 questionnaires will be distributed like that of round 1 and will be expected to be completed within 3 weeks. For health care professionals, we will provide an electronic version of the questionnaire. A week and 48 hours before the end of the survey, we will send text messages to participants who have not completed the questionnaire. We will recruit eligible patients from the Department of Encephalopathy of Xiyuan Hospital and send the questionnaires to them after obtaining their consent.

Data Analysis for Round 2 of the Delphi Survey

After completing the questionnaire, the working group will calculate the response rate, average score, and score distribution for each item. After analyzing all the data, the average scores for the 2 rounds will be compared, and the reasons for score changes will be analyzed to evaluate whether there was attrition. Considering the results of the second round, in combination with the consensus definition, the outcomes will be categorized as "consensus in," "consensus out," and "no consensus" (Table 3) [31].

Table 3. Definitions of a consensus.

Classification of consensus	Description	Exclusion criteria
Consensus in	Consensus that the outcome should be included in the COS[a].	≥70% of participants score the outcome as 7-9, and <15% score it as 1–3 in both stakeholder groups.
Consensus out	Consensus that the outcome should not be included in the COS.	≤50% of participants score the outcome as 7-9 in both stakeholder groups.
No consensus	Uncertainty about the importance of the outcome.	Anything else.

[a]COS: core outcome set.

Stage 3: Consensus Meeting

Stakeholder Selection

After the 2 rounds of the Delphi survey, we will conduct a consensus meeting. To ensure the quality of the meeting and enhance the credibility of the results, we will invite representatives of various interest groups who have completed all Delphi surveys, steering committee members, and other representative senior experts from various stakeholder groups, regardless of their participation in the previous research process. At the same time, senior clinical experts in the field of TCM, especially academicians, TCM masters, nationally famous TCM practitioners, and leaders of academic groups, will be invited. Patients who participated in both rounds of the Delphi survey will be invited to the consensus conference. The inclusion and exclusion criteria for health professionals who will participate in the consensus meetings are listed in Textbox 1.

The first and the second must be qualified, while the third and the fourth can be qualified by any one of them.

Textbox 1. The inclusion and exclusion criteria for health care professionals who will participate in the consensus meeting.

Inclusion criteria:

- Master's degree or above, with more than 10 years of work experience.
- Clinicians with experience working at tertiary hospitals and at least in the position of associate chief physician.
- Participated in or hosted clinical research projects related to headache.
- Familiarity with evidence-based medicine and methodological research.

Exclusion criteria:

- None.

Sampling Strategy

According to the current guideline recommendations of COS-TCM standards [26], we will invite 25 stakeholders from all over the country, including 9 TCM experts, 5 Western medicine experts, 3 researchers, 5 methodologists, and 3 patients, to participate in the consensus meeting.

Consensus Meeting Process

The consensus meeting to determine the final COS will be face to face, preferably in Beijing. In exceptional cases, a network video conference will be held. The meeting will last for 2 days.

We will report on our previous work, including the preliminary list of outcomes generated using a systematic review and semistructured interviews and the results of the 2 rounds of Delphi. We will focus on reporting the outcomes of the second round, with outcomes categorized as "consensus in" from all stakeholder groups being prioritized for inclusion in the COS, and outcomes categorized as "consensus out" being excluded. The outcomes categorized as "no consensus" will be discussed at the meeting, and all participants will rate their importance using a 9-point Likert scale. The final COS will be developed according to the consensus definitions [5]. If some outcomes are still considered "no consensus" after 2 rounds of grading, the steering group will determine their inclusion in the final COS.

After formulating the final COS, the measurement method for the outcome index will be determined. The questionnaire will be designed based on the results of the system evaluation. Participants will discuss and vote on the measurement time and methods of the outcome indicators. For the measurement time and method of each outcome indicator, we will select the indicator with the highest percentage recommended in the consensus meeting.

Ethical Considerations

This study received approval from the Ethics Committee of Xiyuan Hospital, China Academy of Chinese Medical Sciences (approval number 2021XLA003-1). We followed the committee's ethical guidelines rigorously to ensure compliance and safeguard participant rights. All participants provided informed consent after receiving comprehensive information about the study, and they were assured that their involvement was voluntary, with the option to withdraw at any time without repercussions. We are dedicated to maintaining participant privacy and confidentiality; all data were anonymized and securely stored, accessible only to the research team. The findings will be presented in a way that does not reveal individual identities. There are no conflicts of interest in this study, and while participants did not receive financial compensation, we extend our heartfelt thanks for their contributions. Data for the systematic review were sourced from publicly available literature, in line with ethical standards for data sharing. The outcomes from the Delphi survey and consensus meeting will contribute to the development of the COS-TCM and will be reported without identifying individual participants.

Results

The protocol for this study has been registered in PROSPERO. The literature search has been completed, and the analysis of the systematic review results is currently under review. The findings will be published once the review process is finalized. A total of 19,033 articles were retrieved from 8 databases. After merging Chinese and English records and removing duplicates, 8074 duplicate articles were identified. Through title and abstract screening, 8844 articles were excluded for irrelevance, and 45 articles were excluded for being in languages other than Chinese or English. Further full-text review led to the exclusion of 672 articles for irrelevance, 67 articles due to inaccessible full texts, and 5 articles due to single-author, noncore publications. This process resulted in 1335 articles related to TCM.

Among these, there were 52 guidelines and clinical pathways, 102 systematic reviews and meta-analyses, 590 RCTs (including 177 on acupuncture, 293 on Chinese herbal medicine, and 120 on other therapies), 66 nonrandomized controlled trials, 1 cohort study, 4 case-control studies, 27 protocol registrations, 113 case series, 28 case reports, 21 cross-sectional studies, 226 review articles, 91 expert opinions, and 14 animal experiments. After the abstract screening, 650 articles were excluded, and 24 articles were excluded after a full-text review due to a lack of reported outcomes. Finally, 626 articles were included for further analysis. The PRISMA-P (Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols) checklist is provided in Multimedia Appendix 3 of the initial draft. The Delphi survey involving stakeholders is scheduled to begin on November 30, 2024, and will be followed by a face-to-face consensus conference on February 1, 2025.

Upon completion of the development of the COS, the study findings will be reported in adherence to the COS-STAR (Core Outcome Set–STAndards for Reporting) statement [37]. This study will be disseminated through publication in an international journal and presentation at national and international conferences focused on TTH to promote the adoption of the Clinical Outcome Scale. The COS findings will be distributed to all participants by email or courier to support its clinical use.

Discussion

Expected Findings

Given the differences among various headache types, it is essential to specify the headache type of study participants in the clinical research design to ensure study accuracy. TTH represents the most common primary headaches and are characterized by pressing or tightening (nonpulsating) sensations on both sides of the head, are of mild or moderate intensity, and are not exacerbated by activity [38]. The current research on COS for headaches mainly focuses on migraine, such as the guidance on the design of outcome indicators for clinical trials of medications, patient-valued indicators, and identification of meaningful migraine outcome measures [38-40]. Compared with migraine, TTH generally receives less attention but has a substantial impact on individuals and society, compromising the quality of life in terms of work, study, and sleep and causing a social burden that cannot be overlooked [2,41-43]. Currently, only 1 published COS is available for TTH, which was initially published in 1995 [22] and updated in 2010 [20]. The clinical research of TCM on TTH have been increasing over the past 10 years [17]. However, there is no COS for TCM clinical research on the treatment of TTH. TCM has a unique diagnosis and treatment mode, and there are significant differences between the evaluation outcomes of TCM and Western medicine

[44]. Thus, developing a COS for clinical studies on TCM for the treatment of TTH is necessary.

This study was designed according to standard procedures and developed in 3 stages [25,26,31], with each stage conducted under the guidance of the steering group. In designing the COS, special attention is given to several key aspects. In the systematic review, we aim to include the intervention methods of TCM as comprehensively as possible to ensure the thoroughness of literature retrieval. Given the prevalence of nonstandard outcomes in clinical trials of TCM, we will standardize the outcomes obtained from systematic reviews and semistructured interviews. This includes standardizing the names of outcomes, dividing composite outcomes into single outcomes, and classifying outcomes into specific domains to ensure the standardization of COS [37].

Given the limited number of clinical RCTs for TCM treatment of TTHs, we have included observational studies to enrich the core outcome set, increase the diversity of outcomes, and enhance the robustness of our core outcome set. This approach ensures a more comprehensive evaluation of the effectiveness and safety of TCM treatments. To address the differences between these 2 types of studies, we plan to establish different core outcome sets for experimental (RCT) and observational studies. For example, in RCTs, we may focus on factors such as treatment duration and cost, whereas in observational studies, we may emphasize long-term outcomes and the impact on quality of life.

In this study, we included various TCM treatment methods to evaluate their comprehensive impact on tension-type headaches. This diversity helps capture the broad efficacy and patient responses to different treatment methods. However, it also introduces complexity in interpreting the results. We believe this approach is beneficial. First, the inclusion of treatment diversity allows us to assess the overall impact of TCM treatments on tension-type headaches. This method enables us to observe potential synergistic effects and individual differences among different treatment methods, providing more comprehensive guidance for clinical practice. Second, to address the variability of treatment methods, we used standardized outcome measurement tools in the study design. These tools ensure the comparability of results between different treatment methods. In addition, we used stratified analysis and subgroup analysis to handle data heterogeneity, ensuring the robustness of the results. It must be acknowledged that including various TCM treatment methods may introduce a certain degree of heterogeneity, which could affect the interpretation of results. Therefore, we used mixed-effects models in the analysis to adjust for potential differences between different treatment methods.

The study will also comprehensively cover different stakeholders in the Delphi survey and consensus meetings. This includes TCM and Western medicine practitioners, methodologists, researchers, core journal editors, and other relevant experts, as well as patients with TTH, to ensure the representativeness and authority of the COS. In designing the questionnaire for the Delphi survey, we will focus on improving its intelligibility. For instance, TCM terminology will be translated into the language of Western medicine for specialists, while patients will receive a general explanation. The questionnaire distribution will be tailored to the characteristics of stakeholders: healthcare experts will receive a combination of email and electronic questionnaires for efficiency and better data statistics, while patients will complete the questionnaire face to face with a doctor to enhance compliance and understanding. These measures are intended to ensure a higher response rate.

Conclusion

There is a lack of COS for TCM treatment of TTH; therefore, developing one is essential. This study will solve problems posed by nonstandard outcome indicators and limited measurement time, maximize the value of individual trial data, and provide high-quality research evidence for treating TTH with TCM.

Acknowledgments

We thank the patient advisers for contributing to the research. This research was supported by the project “Development and Research of Chaiqiong Qiwei Granules, a Class 1.1 Innovative Traditional Chinese Medicine for the Treatment of Tension-Type Headache” (XYZX0303-12), the Fundamental Research Funds for the Central public welfare research institutes (ZZ13-024-3), the Scientific and Technological Innovation Project of China Academy of Chinese Medical Sciences (CI2021B006), Capital’s Funds for Health Improvement and Research (No. 2020-2-4173), the National TCM Leading Personnel Support Program (NATCM Personnel and Education Department (2018; 12), the Innovation Team and Talents Cultivation Program of National Administration of Traditional Chinese Medicine (ZYYCXTD-C-202007), and the China Academy of Chinese Medical Sciences Innovation Fund (CI2021A01301 and CI2021A00911).

Authors' Contributions

GF, YC, Liang X, JW, and YZ conceived the study. CG, JW, and YZ provided insight into the tension-type headache patient experience. GF, YC, XF, XG, and WC contributed to the systematic review, and Teng J, Tang J, and Liao X provided supervision for all aspects of the manuscript. GF, YC, Liang X, JW, and YZ wrote the protocol and manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
The COS-STAP (Core Outcome Set-STAndardised Protocol Items) Statement.
[DOCX File , 20 KB - resprot_v14i1e63481_app1.docx]

Multimedia Appendix 2
The search strategy of English databases.
[DOCX File , 20 KB - resprot_v14i1e63481_app2.docx]

Multimedia Appendix 3
PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) checklist.
[DOCX File , 29 KB - resprot_v14i1e63481_app3.docx]

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Abbreviations

COMET: Core Outcome Measures in Effectiveness Trials
COS: core outcome set
COS-STAR: Core Outcome Set–STAndards for Reporting
COS-TCM: core outcome set for TCM clinical studies
PRISMA-P: Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols
RCT: randomized controlled trial
TCM: traditional Chinese medicine
TTH: tension-type headache

Edited by A Schwartz; submitted 21.06.24; peer-reviewed by MP Roman, CM Marto; comments to author 08.08.24; revised version received 02.09.24; accepted 11.12.24; published 05.02.25.

Please cite as:
Fu G, Chen Y, Liang X, Guo C, Fan X, Gong X, Chen W, Teng J, Tang J, Liao X, Wei J, Zhang Y
Core Outcome Set Development for Tension-Type Headache Treatment Using Traditional Chinese Medicine: Protocol for a Delphi Consensus Study
JMIR Res Protoc 2025;14:e63481
URL: https://www.researchprotocols.org/2025/1/e63481
doi:10.2196/63481
PMID:

Protocol

Histopathological Comparison and Expression Analysis of COL1A1, COL3A1, and ELN in the Proximal and Distal Ventral Dartos of Patients With Hypospadias: Protocol for Prospective Case-Control Study

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Abstract

Background: The exact cause of penile curvature in hypospadias remains unknown. Resection of the dartos fascia has been observed to straighten the penis, indicating the involvement of the dartos fascia in the superficial chordee. However, the characteristics of dartos tissue in the distal territory of the ventral penile shaft may differ from those in the proximal aspect of the penile shaft.

Objective: This study aims to investigate the distinct histopathological profiles and expression of COL1A1 (collagen type 1), COL3A1 (collagen type 3), and ELN (elastin) in proximal and distal ventral dartos of patients with hypospadias compared to those without hypospadias.

Methods: This prospective case-control study compares the ventral dartos tissue of patients with hypospadias at different locations with that of patients without hypospadias. Dartos samples will be taken during surgery, with age matching. Histopathology examination uses hematoxylin and eosin and Masson's trichrome stain. The mRNA expression of *COL1A1*, *COL3A1*, and *ELN* will be quantified using a 2-step reverse transcription–polymerase chain reaction analysis.

Results: Previous studies have documented different characteristics of dartos tissue between patients with hypospadias and those without hypospadias. Some studies even suggest resection of the dartos tissue during hypospadias repair. However, this is the first study to compare the characteristics of ventral dartos tissue in patients with hypospadias based on its location along the penile shaft, suggesting potential differences between the distal and proximal locations. We have obtained ethical approval to conduct a prospective case-control study aimed at elucidating these differences in dartos tissue characteristics. The findings of the study are anticipated to be available by 2025.

Conclusions: Differences in the characteristics of dartos fascia based on its location may require tailored surgical strategies. If the properties of distal dartos tissue closely mirror those of typical dartos tissue, the possibility of avoiding its excision during hypospadias surgery could be considered.

International Registered Report Identifier (IRRID): DERR1-10.2196/70075

(JMIR Res Protoc 2025;14:e70075) doi:10.2196/70075

KEYWORDS

chordee; superficial chordee; COL1A1; COL3A1; dartos tissue; dartos fascia; ELN; elastin; histopathological

Introduction

Hypospadias is a common congenital malformation characterized by the displacement of the urethral meatus on the ventral side of the penis, incomplete ventral prepuce development, and penile curvature known as chordee [1-3]. Hypospadias represents the most prevalent form of penile deformity, with data indicating its occurrence in 1 out of every 125-300 male births [4-6]. The severity of this anomaly varies, with meatus locations ranging from the glans to the scrotum [3].

Hypospadias is typically categorized as either distal or proximal, depending on the location of the meatus [7]. Approximately 70% of cases are classified as distal hypospadias, typically considered as less severe [3,8]. However, certain variants of distal hypospadias may present with severe chordee, necessitating more intricate reconstruction procedures [9]. Chordee, one of the triads of hypospadias, can be further classified as either superficial or deep [6,10]. Superficial chordee involves the superficial fascia, whereas deep chordee affects deeper structures such as the deep fascia, urethral plate, corpus spongiosum, and tunica albuginea, and may involve a disproportion of corpora [10].

The exact cause of the chordee remains unknown. However, resection of the dartos fascia during hypospadias procedures has been observed to straighten the penis, indicating the involvement of the dartos fascia in the superficial chordee [11]. Changes in the structure of collagen (predominantly collagen type 1), reticulin (collagen type 3), and elastin components within the dartos fascia could influence its elasticity and mobility in cases of hypospadias [12]. Previous research has indicated that dartos fascia in hypospadias tends to be thicker and less elastic [13,14]. Dartos fascia also exhibited lower concentrations of collagen types 1, 2, and 3 compared to the normal control group [15].

Studies exploring the association between dartos fascia and chordee remain limited, primarily consisting of qualitative studies [16]. Some studies have suggested the resection of dartos fascia during hypospadias reconstruction surgery [15]. However, there is a lack of studies comparing the characteristics of ventral dartos in patients with hypospadias based on their location towards the meatus, classified as proximal and distal dartos. Variations in dartos fascia characteristics according to location may necessitate different surgical approaches. Therefore, this study aims to investigate the distinct histopathological profiles and expression of COL1A1 (collagen type 1), COL3A1 (collagen type 3), and ELN (elastin) in proximal and distal ventral dartos of patients with hypospadias compared to those with a normal penis.

Methods

Study Design

This study is a prospective case-control study comparing ventral dartos in cases of proximal and distal phenotypic variants of patients with hypospadias with dartos of patients without hypospadias. Dartos samples will be collected during hypospadias repair surgery (cases) and circumcision (controls), with the matching of ages between cases and controls and random allocation. The protocol has been developed in accordance with the 2013 SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) checklist for reporting protocol studies [17].

Study Population and Recruitment

Patients will be recruited from our university-affiliated academic tertiary care hospitals in Jakarta, Indonesia. The inclusion criteria for the cases are as follows: (1) male patients with prepuberty from 6 months to 9 years; (2) a confirmed diagnosis of hypospadias, established through physical examination by a pediatric urologist; and (3) undergoing hypospadias repair at our hospitals during the recruitment period. Conversely, the exclusion criteria for cases are specified as follows: (1) a history of previous hypospadias repair, (2) inadequate tissue samples for analysis, and (3) undescended testis.

The inclusion criteria for the control group consist of (1) male patients with prepuberty from 6 months to 9 years, (2) confirmation of a normal penile condition through a physical examination conducted by a urologist, and (3) undergoing circumcision at our hospitals during the recruitment period. Conversely, the exclusion criteria for controls are outlined as follows: (1) a history of previous genital surgery, (2) insufficient tissue samples for analysis, and (3) undescended testis.

Participants meeting the inclusion criteria and not meeting any of the exclusion criteria will be invited to participate in the study as either cases or controls. According to the sample size formula (5% α and 20% β), each group requires approximately 50 patients (rounded up from 43.18). Considering our patient volume, we anticipate completing recruitment within a 9- to 12-month time frame.

Data Collection

The following data will be collected:

- Patient demographics: information such as age and socioeconomic status.

- Clinical variables: detailed medical history, associated comorbidities, family history, and birth weight.
- Phenotypic data being captured: location of the urethral opening, plate objective screening tool, urethral defect ratio, penile curvature assessment, and glans-urethral meatus-shaft hypospadias score.

Location of Urethral Opening

The location of the urethral opening is given in Figure 1 [18].

Figure 1. Location of the urethral opening.

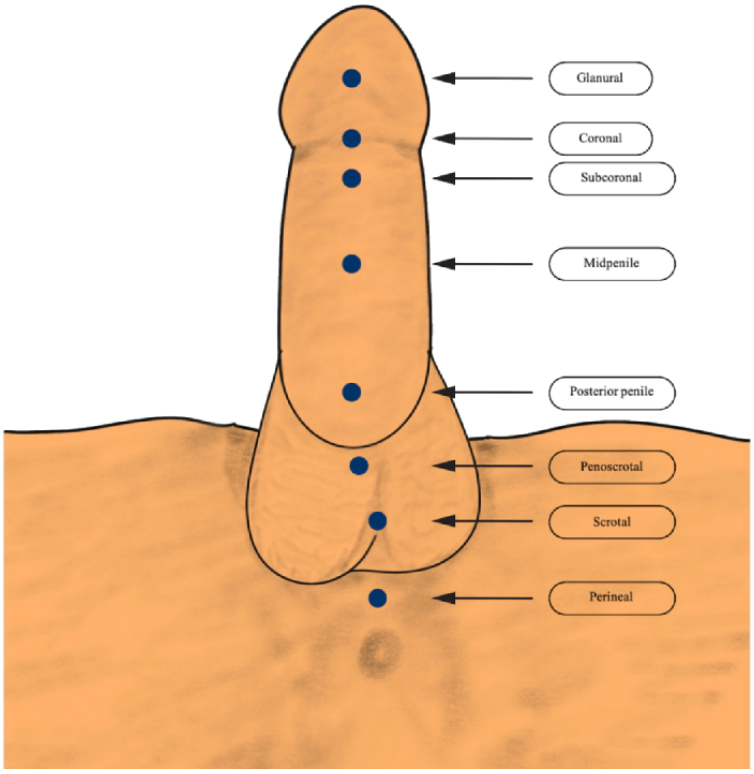
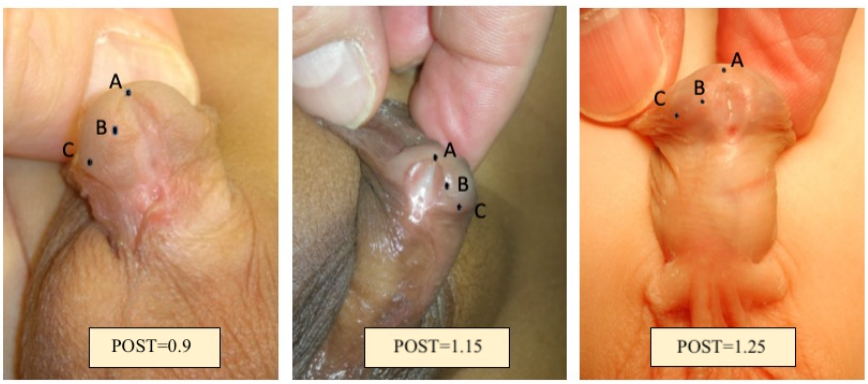


Plate Objective Scoring Tool

Plate objective scoring tool (POST) score is shown in Figure 2 [19,20]. The distal extent of the urethral plate at the midline is identified as point A. The glanular knob, where the mucosal edge of the plate changes direction, is marked as point B, while the glanular-coronal junction is designated as point C. The distance from point A to point B represents the neomeatal length, while the distance from point B to point C indicates the length of the prospective glanular fusion. The POST score has been used to quantify the urethral plate quality in distal hypospadias. This tool's correlation with postrepair complications underscores its relevance in optimizing surgical outcomes [20].

Figure 2. Plate objective scoring tool score calculation (AB/BC). POST: Plate objective scoring tool.

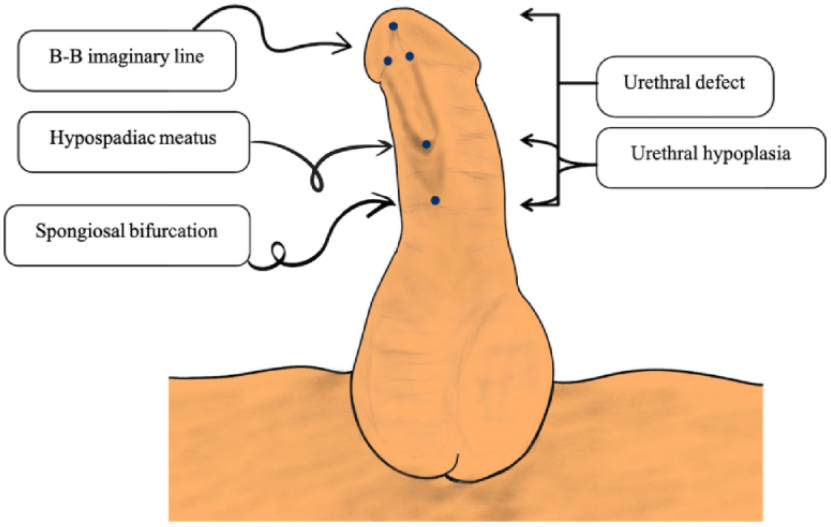


Urethral Defect Ratio

Urethral defect ratio (UDR), which is illustrated in Figure 3, is an objective hypospadias classification system [21]. The stretched penile length is measured along the lateral aspect of the penile shaft, extending from the tip of the glans to the superior border of the pubic bone. Stretching is facilitated using a stay suture in conjunction with a metal ruler. The bifurcation site of the corpus spongiosum penile curvature is evaluated following complete degloving of the penile skin. The distance between the glandular knobs (B–B imaginary line) and the bifurcation site of the corpus spongiosum penile curvature is

defined as the urethral defect, and the UDR is calculated by dividing UD by stretched penile length [21].

Figure 3. Urethral defect ratio. B–B: the distance between the glandular knobs.



Penile Curvature Assessment

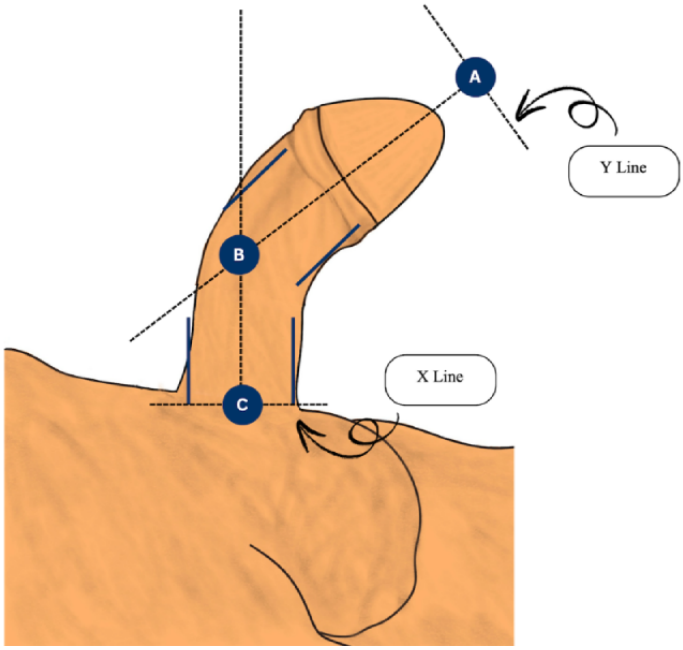
Penile curvature assessment is shown in Figure 4 [22]. To evaluate penile curvature intraoperatively, we have established a standardized protocol using mobile apps. This involves capturing a lateral photograph of the penis from a distance of 25-30 cm, ensuring alignment parallel to the penile shaft, and incorporating an upward oblique angle between 10° and 30° along the same vertical axis. The captured image is subsequently processed using specialized software, such as Angle Meter 360, where 3 critical anatomical landmarks are marked: the penile base, the point of angulation, and the distal midpoint.

In Figure 4, three key reference points are established for measurement: (1) corresponds to the intersection of the midline axis of the distal penile shaft with the Y-line, defined as a perpendicular line originating from the tip of the glans, (2) represents the intersection of the midline axes of the proximal and distal segments of the penile shaft, and (3) signifies the intersection of the midline axis of the proximal penile shaft with the X-line, a perpendicular line drawn at the level of the pubic bone. The degree of penile curvature is calculated by subtracting the measured angle from 180°.

Glans-Urethral Meatus-Shaft Hypospadias Score.

In the glans-urethral meatus-shaft (GMS) scoring system, each of its 3 components is assigned a numerical value ranging from 1 to 4 [23]. The total GMS score can range from a minimum of 3, indicative of very mild hypospadias, to a maximum of 12, representing severe hypospadias. Studies have demonstrated its predictive value for postoperative complications, highlighting its utility in guiding surgical decision-making [24].

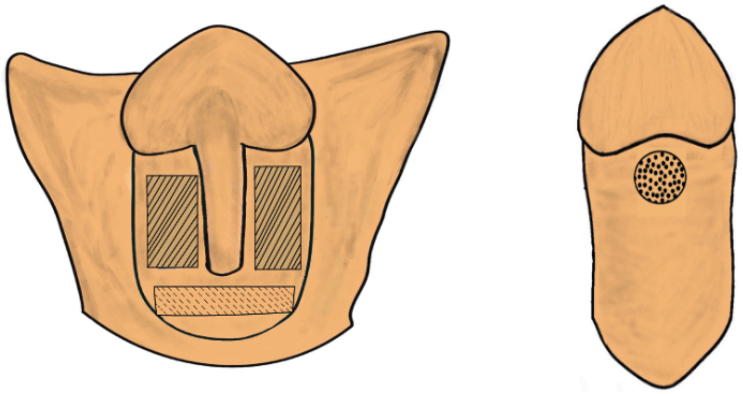
Figure 4. Penile curvature assessment. The distal midpoint (A); the point of angulation (B); and the penile base (C).



Dartos Fascia Sampling

Dartos fascia samples are obtained following penile degloving in the hypospadias group. The dartos tissue is collected from the ventral side at two distinct locations: distal to the urethral meatus (distal to spongiosa bifurcation) and proximal to the urethral meatus (proximal to spongiosa bifurcation). Conversely, in the control group, dartos tissue is acquired from the ventral side coronal area. The illustration of the samples' location is shown in Figure 5. The size of dartos tissue collected at each location ranges from 25 to 100 mm^2. To mitigate collection bias, all samples are obtained by a single surgeon.

Figure 5. Dartos fascia sampling in the hypospadias group (solid line: distal dartos, dashed line: proximal dartos) and control group (circle).



Histopathology Preparation

Dartos samples will be immersed in a 10% buffered formaldehyde solution for fixation. Subsequently, the fixed tissue will undergo dehydration, infiltration, and embedding in liquid paraffin to achieve solidification. The paraffin-embedded blocks will then be sectioned using a microtome at a thickness of 4-5 µm and mounted onto glass slides. Two distinct staining methods, namely hematoxylin and eosin and Masson's trichrome stain, will be used to assess the cross-sectional area and collagen percentage of the dartos tissue. All histopathological assessments and quantifications will be conducted in a blinded manner using the QuPath software.

Reverse Transcription–Polymerase Chain Reaction Analysis

Messenger ribonucleic acid expression levels of collagen genes (*COL1A1* and *COL3A1*) and elastin gene (*ELN*) will be quantified through a two-step reverse transcription–polymerase chain reaction analysis. Dartos tissue samples will be preserved with RNA later, followed by total RNA extraction using an RNA extraction kit. Subsequently, the extracted RNA will undergo reverse transcription to synthesize complementary deoxyribonucleic acid, which will then be amplified via PCR to detect the expression levels of the target genes.

Statistical Analysis

All data will undergo analysis using SPSS (version 24.0; IBM Corp) software. Descriptive statistics will be used, presenting frequency for categorical variables and mean or median for numerical variables. Comparative analysis of collagen percentage and expression of *COL1A1*, *COL3A1*, and *ELN* among proximal hypospadias dartos, distal hypospadias dartos, and normal dartos will be conducted using either 1-Way ANOVA or Kruskal-Wallis test, contingent upon the normality of data distribution. Post hoc analysis may use the Bonferroni test, Games-Howell test, or Mann-Whitney test as deemed appropriate. Subanalysis based on hypospadias classification (distal and proximal) and chordee severity (mild, moderate, or severe) will also be performed. Subanalysis based on the UDR and POST scores will also be performed [17].

Ethical Considerations

The Medical Research Ethics Committee at Universitas Indonesia approved our study protocol in March 2024 (KET-473/UN2.F1/ETIK/PPM.00.02/2024). Participants and/or their guardians will receive comprehensive information both verbally and in writing to ensure informed consent. Upon choosing to participate, they will be requested to sign the informed consent form.

Results

Previous studies have documented different characteristics of dartos tissue between hypospadias and patients without hypospadias [11,13-15]. Some studies even suggest resection of the dartos tissue during hypospadias repair [15]. However, no previous study has systematically compared the distinct characteristics of proximal and distal dartos tissue in patients with hypospadias. We have obtained ethical approval to conduct a prospective case-control study aimed at elucidating these differences in dartos tissue characteristics. The findings of the study are anticipated to be available by 2025.

Discussion

Anticipated Findings

The exact etiology of chordee in hypospadias remains unknown. Nonetheless, inadequate management of chordee during hypospadias repair may escalate the incidence of complications. Moreover, significant chordee can impede sexual function in later adulthood [10]. The aberrant curvature may result in ineffective insemination, painful erections, or hindered vaginal insertion. Therefore, meticulous management of chordee in hypospadias is imperative [18].

Numerous studies have indicated abnormalities in dartos tissue in hypospadias [11,13-15]. Surgical procedures involving penile

degloving and dartos tissue excision have been proposed to alleviate superficial chordee [15,18]. However, our preliminary observations during hypospadias surgery have revealed distinct characteristics between the dartos tissue located proximally and distally to the meatus. Specifically, we have noted that the proximal dartos tissue tends to exhibit greater thickness and reduced elasticity, potentially contributing to superficial chordee. Consequently, we aim to conduct a comparative analysis of the extracellular matrix properties of distal and proximal dartos tissue in this study. Variations in dartos fascia characteristics according to location may necessitate different surgical approaches. Should the characteristics of the distal dartos resemble those of normal dartos tissue, sparing its resection during hypospadias surgery may be feasible. Using the distal dartos as a secondary layer for neourethral coverage could potentially enhance surgical outcomes.

Conclusion

Differences in the characteristics of dartos fascia based on its location may require tailored surgical strategies. If the properties of distal dartos tissue closely mirror those of typical dartos tissue, the possibility of avoiding its excision during hypospadias surgery could be considered.

Acknowledgments

This research is funded by the Directorate of Research and Development, Universitas Indonesia under Hibah PUTI 2024 (grant number 635). Funding for the completion of this study will be pursued through additional noncommercial grant applications.

Data Availability

The datasets generated or analyzed during this study are available from the corresponding author on reasonable request.

Conflicts of Interest

None declared.

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Abbreviations

COL1A1: collagen type 1
COL3A1: collagen type 3
ELN: elastin
GMS: glans-urethral meatus-shaft
POST: plate objective scoring tool
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials
UDR: urethral defect ratio

Edited by A Schwartz; submitted 14.12.24; peer-reviewed by JH Wirmer, J Pitoyo; comments to author 17.01.25; revised version received 18.01.25; accepted 24.01.25; published 18.02.25.

Please cite as:
Raharja PAR, Birowo P, Rachmadi L, Wibowo H, Kekalih A, Duarsa GWK, Abbas T, Wahyudi I
Histopathological Comparison and Expression Analysis of COL1A1, COL3A1, and ELN in the Proximal and Distal Ventral Dartos of Patients With Hypospadias: Protocol for Prospective Case-Control Study
JMIR Res Protoc 2025;14:e70075
URL: https://www.researchprotocols.org/2025/1/e70075
doi:10.2196/70075
PMID:39964742

Protocol

Effectiveness of Composite Ayurveda Regimen in a Black Box Design for the Management of Rheumatoid Arthritis: Protocol of a Single Arm, Community-Based Study

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Abstract

Background: Rheumatoid arthritis (RA) is an autoimmune disease that affects joints and can have extra-articular manifestations. RA usually tends to be progressive and leads to substantial health care burdens, both in terms of disability and economic costs. Despite the various treatment modalities available, there is still an urgent need for safe and effective medicine based on the pattern of disease presentation. The increasing interest in complementary and alternative medicine has created a demand for extensive research in this area.

Objective: This clinical study is designed to evaluate the effectiveness and tolerability of a composite Ayurveda regimen in RA.

Methods: The study is a single-arm (pre-post design), community-based interventional study with a black box design being conducted at 6 study centers. A total of 240 participants aged between 18 and 65 years, diagnosed with RA as per the 2010 American College of Rheumatology and the European League Against Rheumatism criteria are recruited as per the selection criteria. All the participants received Ayush-SG and *Rasnasaptak Kashaya* for 84 days along with customized treatment as per the disease presentation and associated complaints. The outcome measures include the change in disease activity score (DAS)-28 with erythrocyte sedimentation rate, disease-specific biochemical and inflammatory markers, Disability Index score, change in the participant's assessment of pain and frequency of use of conventional analgesics or nonsteroidal anti-inflammatory drugs from baseline. The tolerability of interventions is assessed through the occurrence of adverse events. Categorical variables will be analyzed with McNemar chi-square test, and continuous variables will be assessed using the paired *t* test or Wilcoxon test for pre-post assessment. The level of significance will be 5%.

Results: The recruitment of participants was initiated in December 2023. The participant recruitment was completed in March 2024 and out of 240 participants enrolled, 222 (92.5%) completed the study up to the last follow-up. Data verification, compilation, and analysis are under process. After data analysis, the study's findings will be published in a peer-reviewed journal.

Conclusions: This interventional study that incorporates the black box approach may provide a strong framework for managing RA. This design is a more reliable method for evaluating the effectiveness and tolerability of the composite Ayurveda regimen in RA.

Trial Registration: Clinical Trial Registry-India CTRI/2023/06/054203; https://tinyurl.com/4prvwr6z

International Registered Report Identifier (IRRID): DERR1-10.2196/57918

(JMIR Res Protoc 2025;14:e57918) doi:10.2196/57918

KEYWORDS

rheumatoid arthritis; Amavata; Ayush-SG (coded drug); Rasnasaptak Kashaya

Introduction

Background

Rheumatoid arthritis (RA) is a chronic inflammatory autoimmune disease that can damage joints and affect extra-articular organs. In 2019, 18 million people worldwide were living with RA. Women accounted for 70% of cases, and over half were older than 55 years [1]. The articular manifestation of RA includes symptoms such as musculoskeletal pain, swelling, and stiffness of joints. It is usually symmetric and initially manifests in small joints and progresses to larger joints. Over time, joint inflammation can lead to joint destruction, including loss of cartilage and bone erosion [2]. The symptoms of RA vary in patients; some patients have mild self-limited disease, while many experience joint destruction, severe physical disability, and multiple comorbidities. RA tends to be progressive in nature, involving a worsening of symptoms over time, and often begins for many people during the early or middle years of life, thus causing a heavy burden on society in terms of disability, health, and economic costs. The available evidence for pain management in RA involves the use of disease-modifying antirheumatic drugs and medications such as nonsteroidal anti-inflammatory drugs (NSAIDs) which play an important role in its management but may suppress the immune system and, lead to an increased risk of infections as well other side effects as gastrointestinal disturbances [3,4]. People from all over the world are also developing an interest in traditional herbal practices. It is reported that 60% to 90% of persons with arthritic conditions use complementary and alternative medicines [5-7]. In a study conducted in the United States, it was reported that around 60% of persons with arthritic conditions including RA use complementary and alternative medicines. Of these, 28% reported a history of herbal therapies, and 22% used diet supplements [8].

RA resembles the condition *"Amavata"* (rheumatism due to Ama) described in Ayurveda, where both the *Ama* (undigested or intermediate product of digestion or metabolism that act as a toxin in the body) and *Vata Dosha* (*Dosha* responsible for movement and cognition) become vitiated and located in the *Sandhi* (joints) leading to pain and inflammation in the joints. The causative factors of Amavata are described as *Viruddha Ahaara* (antagonistic food), *Viruddha Vihaara* (antagonistic lifestyle), *Mandagni* (subdued digestive power), a sedentary lifestyle, and exercising immediately after meals. Long-term adherence to these etiological factors causes vitiation of *Vata* along with impaired digestion and metabolism in the body leading to the formation of *Ama*. The gradual accumulation of *Ama* obstructs different *Srotas* (structural or functional channels) in the body and further vitiation of *Tridoshas* (3 regulatory functional factors of the body). The Ama and Vata along with other vitiated Doshas lead to the impairment of *Dhatus* (major structural components of the body) mainly joints causing the *Amavata* [9].

The Ayurvedic classics describe various treatment modalities and therapeutic formulations based on the condition and clinical presentation of the disease. The disease pattern of *Amavata* in a person depends on the extent of *Ama* association, *Dosha* vitiation, and the chronicity of the condition. In cases of *Amavata* with significant *Ama* association, there may be obstructions in the *Srotas*, leading to symptoms like severe pain, swelling, elevated temperature, and redness in the joints. The treatment for this scenario should prioritize digesting *Ama* and clearing the obstructions in the *Srotas* along with alleviation of vitiated *Dosha*. If there is only mild *Ama* association and less *Dosha* imbalance, symptoms may be limited to joint pain, stiffness, and minimal swelling, indicating medications that digest *Ama* and alleviate *Doshas* predominantly *Vata*. In chronic cases, patients may experience symptoms like mild aching stiffness, fatigue, or anemia. The choice of medicines varies according to each pattern of presentation and must be determined by the practitioner following a thorough assessment of the patient's condition. In a standard randomized controlled trial (RCT), it is not feasible to design a customized regimen that tailors medicine selection to specific conditions. In such instances, a specialized trial design should be considered to facilitate the prescription of medicines tailored to the clinical manifestations and disease stage of each individual. To address this issue, it is essential to consider modifying study designs, including exploring alternative approaches such as "black-box" designs [10].

The treatment plan for *Amavata* is focused on the digestion of *Ama* and the alleviation of *Vata*. For digesting the *Ama* and removing obstruction from the *Srotas*, drugs having *Katu* and *Tikta* Rasa (pungent and bitter tastes), *Pachana* (enhancing digestion), and *Dipana* (enhancing metabolic fire) properties have to be administered [11]. Ayush-SG, *Rasnasaptak Kashaya*, and *Guduci* (*Tinospora cordifolia*) have the above-said properties. Ayush-SG is a coded drug developed by the Central Council for Research in Ayurvedic Sciences (CCRAS) for the management of Amavata [12]. *Rasnasaptak Kashaya* is described in the context of *Amavata* treatment in Ayurveda classics [13]. *Brihat Saindhawadi Taila* and *Dashang Lepa* are used for local application to pacify pain and inflammation of the joints [14-16]. Considering the major patterns of disease presentations, a black box design has been planned for this study and the treatment has been tailored according to the accompanying symptoms.

Objectives

The primary objective of the study is to evaluate the effectiveness of a composite Ayurveda regimen on the disease activity score (DAS) in RA.

The secondary objective is to evaluate the effectiveness of the composite Ayurveda regimen on the disease-specific biochemical and inflammatory markers and assess the tolerability of Ayurveda regimen in RA.

Methods

Study Design

This is a single-arm (pre-post design), community-based interventional study with a black-box research design.

Study Setting

The study is conducted through 6 research institutes under CCRAS at New Delhi, Patiala, Guwahati, Gwalior, Vijayawada, and Chennai in identified areas predominantly dwelled by the scheduled caste population near the institute.

Inclusion Criteria

Participants aged between 18 and 65 years, diagnosed with RA as per the 2010 American College of Rheumatology and the European League Against Rheumatism criteria [17], and willing to give written informed consent for participation are enrolled in the study.

Exclusion Criteria

Participants presenting with complications of RA, for example, deformity of joints/bones, pleura-pericardial disease, participants with extra-articular manifestations of RA and gastrointestinal symptoms, those with joint prosthesis or unable to walk without support or confined to a wheelchair, participants with Hemoglobin <8 g/dL, diagnosed with other arthritis like osteoarthritis, gouty arthritis, tuberculous arthritis, psoriatic arthritis, spondyloarthropathy, active fibromyalgia, juvenile chronic arthritis, ulcerative colitis, or other systemic inflammatory conditions and autoimmune diseases, having blood pressure ≥ 160/100 mm Hg, or hemoglobin A_{1c} (HbA_{1c})>8%, on medication with corticosteroids, antidepressants, anticholinergics, etc or Ayush interventions/folk medicine or any other drugs that may influence the outcome of the study are excluded from the study. Participants with diagnosed concurrent neurological, pulmonary, or endocrine disorder, or unstable cardiovascular disease, with concurrent serious hepatic disorder (defined as aspartate aminotransferase or alanine aminotransferase, total bilirubin, alkaline phosphatase > 2 times upper normal limit) or renal disorders (defined as S Creatinine > upper normal limit); participants with alcohol use disorder (CAGE score >2) or any other substance abuse; and pregnant or lactating woman are not enrolled in the study.

Study Procedure

The participants have been screened from the out-patient departments, camps, or door-to-door visits in the identified areas. Before the initiation of the study, the head of the village or local administrative authority and the residents of the area were informed about the study in detail, in their regional language. Participants diagnosed with RA have been enrolled based on the defined inclusion and exclusion criteria.

Laboratory investigations such as complete blood count with an erythrocyte sedimentation rate (ESR), liver function test, renal function test, and C-reactive protein, RA factor (quantitative), serum immunoglobulin G, and serum immunoglobulin M have been conducted at baseline and the end of the treatment (84th day). HbA_{1c} levels are determined at baseline only (Figure 1).

Figure 1. Flow diagram depicting the study schedule for the assessment of the effectiveness of composite Ayurveda regimen for the management of rheumatoid arthritis. ADR: Adverse Drug Reaction; DAS: disease activity score; ESR: erythrocyte sedimentation rate; VAS: visual analog scale.

Intervention

The treatment regime was customized based on the major patterns of disease presentation in each participant. All of them have been given oral medication Ayush-SG one gram in tablet form twice a day with lukewarm water after meals and *Rasnasaptak Kashaya* 20 mL twice a day (80 mL water added in 10 g of course powder and boiled until remains 20 mL) before meals for 12 weeks. Along with this, *Brihat Saindhavadi Taila* has been given for local application in cases with only articular manifestations (joint pain, stiffness, and minimal swelling). Participants with severe pain and swelling (boggy swelling or affusion elicited by fluctuation test), elevated body or joint temperature, and redness of joint, have been administered *Guduchi Ghana vati* (*Sanshamani Vati*) orally in the dose of 500 mg twice a day with lukewarm water after meals and

Dashanga Lepa for local application. *Punarnavadi Mandura* has been given orally in a dose of 500 mg twice a day with lukewarm water after meals in participants with mild aching, stiffness, fatigue, and anemia.

Incidental medication has been given to the participants in case of any associated complaints. For constipation, *Triphala Churna* has been given in a dose of 5 g orally with lukewarm water at night before sleep. For *Mandagni*, *Vaishwanar Churna* has been administered in a 2.5 g dose orally with lukewarm water twice a day just after food. For the participants having insomnia/anxiety, *Ashwagandha Churna*, 3 g has been given orally twice a day. The duration of incidental medication is decided by the investigator as per the requirement.

The medicines were purchased from Ayurveda manufacturing pharmacies that are certified with good manufacturing practices. Ayush-SG was procured from the Central Ayurveda Research Institute's Ayurveda Pharmacy, Jhansi, Uttar Pradesh, India. All other medicines administered in the study were procured from the Indian Medicines Pharmaceutical Corporation Limited (Mohan, Almora, Uttarakhand, India).

Withdrawal Criteria

The participant has been withdrawn from the study if they have not been willing to continue, if there has been a worsening of RA symptoms, or if they have developed any other illness mentioned in the exclusion criteria. The decision to withdraw a participant from the study has been made solely by the Investigator, who has then had to provide a detailed justification and indicate the line of further management if needed.

In the case of any adverse event, serious adverse event, or adverse drug reaction, the Institutional Ethics Committee (IEC) and Data Safety Monitoring Board are to be informed and participants are to be withdrawn from the study.

Compliance

During the intervention period, compliance has been evaluated based on the amount of study medication that is consumed. This has been assessed using a compliance assessment form issued to the participants to fill up.

Concomitant and Rescue Medication

Concomitant therapy has been continued for diabetes mellitus, hypertension, or any other disease, that has not been specifically mentioned in the exclusion criteria**.** The investigators may prescribe any concomitant medications or treatments deemed necessary to provide adequate supportive care during the intervention period**.** The name, indication, dose, unit, frequency, start date, and stop date (if applicable) for all interventions (medicine/procedure/therapy) have been recorded on each participant's case record form (CRF)**.** Administration of any rescue medicines in case of any medical emergency has been documented in the CRF.

Outcome Measures

The primary outcome of the study is the change in the DAS-28 score (with ESR) [18] and it is assessed at baseline and the end of the treatment (84th day). Secondary outcomes include the change in disease-specific biochemical and inflammatory markers (RA factor, C-reactive protein, and ESR) and serum immunoglobulin levels (Immunoglobulin G and Immunoglobulin M), participants' assessment of Pain, Global assessment of disease activity, change in Disability Index score and frequency of use of conventional analgesic/NSAIDs medicines and occurrence of adverse events if any. The change in disease-specific biochemical and inflammatory markers and serum immunoglobulin levels are assessed at baseline and on the 84th day. The participants' assessments for pain and global assessment of disease activity are assessed using the visual analog scale [19] ranging from 0 mm (no pain) to 100 mm (worst possible pain) at baseline, 28th day, 56th day, and 84th day. The change in Disability Index score is assessed using the Indian Health Assessment Questionnaire [20] at baseline, 28th day, 56th day, and 84th day. The frequency of use of conventional analgesic/NSAIDs medicines and occurrence of adverse events are also assessed in a time frame of baseline, 28th day, 56th day, and 84th day (Figure 1).

Sample Size

Due to the low prevalence of RA (around 0.7% to 1%) [21], it is not feasible to recruit the participants based on the scientific line of sample size theory. Therefore, based on feasibility and the availability of resources, a total of 240 participants have been recruited from 6 institutes (40 participants at each center), within the given time frame.

Recruitment

The eligible participants have been screened for inclusion and exclusion criteria from the outreach out-patient departments/ camps/door-to-door visits conducted in the identified area/ village under the selected study sites. The participants have been informed about the study in detail (in their regional language) through banners and IEC materials.

Allocation

Since the study is conducted in a black box study design and the intervention is classified based on major disease patterns, allocation does not apply to this study.

Data Collection Methods

Demographic data, clinical history, details of concomitant medications, the score of 2010 American College of Rheumatology and the European League Against Rheumatism criteria, DAS-28, and other assessment parameters of the participants have been recorded in the CRF. The participants were followed up on the 28th day, the 56th day, and the 84th day**.** During follow-ups, the occurrence of any symptom and the need for any rescue medication have been recorded. The contact number of the investigator along with the address of the CCRAS institute have been provided to the participants at the time of enrollment**.** Participants have been instructed to inform about any adverse event that happens during the study period**.**

Besides a hard copy of CRF, the data have been recorded in e-CRF also. All source documentation supporting entries into the CRFs are maintained and will be kept readily available. To ensure the quality, the data are checked for consistency, omissions, and any apparent discrepancies. The reason for

withdrawal or dropping out of participation is recorded in the CRF.

Data Monitoring

A Data Safety Monitoring Board has been constituted to monitor the clinical study and to ensure the safety of the participants. The inspection of various records of the clinical study (CRFs and other pertinent data) will be done by the CCRAS representatives and regulatory authority to ensure strict adherence to the study protocol and correct documentation of the data. Any problems faced by the research staff at the participating site have been addressed timely. The Clinical Monitoring Committee is responsible for verifying the CRFs at regular intervals throughout the study to verify adherence to the protocol; completeness, accuracy, and consistency of the data; and adherence to local regulations on the conduct of clinical research.

Deviation From the Protocol

Any deviation from the study protocol is implemented in the study only after approval from the IEC.

Ethical Considerations

The study is conducted according to the national ethical guidelines for biomedical and health research involving human participants (2017) by the Indian Council of Medical Research; and Good Clinical Practice guidelines for clinical trials in Ayurveda, Siddha, and Unani Medicine, 2013. Approval from the IEC of all the concerned institutes has been obtained, and the study has been registered with the Clinical Trial Registry-India (CTRI/2023/06/054203 dated June 20, 2023). The participants have been educated by the investigator verbally and using a written patient information sheet in their regional language and have been asked to provide consent in writing regarding their participation in the study. The participants have been made aware that they are free to leave the study if they wish to discontinue without giving a reason, and without my medical care or legal rights being affected. All the information and records of the study participants including their names and identities are kept confidential in password-protected Microsoft Excel sheets. All the study participants are covered by a clinical trial insurance policy which included coverage for any adverse events occurring during the study.

Statistical Analysis

After data collection, verification of its accuracy and limits will be done. The filtered data will be used for additional analysis and interpretation. The Categorical variables will be reported in number (percentage) and analysis of pre-post-trial outcomes will be done by the Mc-Nemar chi-square test. The continuous variables (like scores and lab parameters) will be analyzed by paired *t* test/Wilcoxon test as per the distribution of data in the pre-post trial situation. The assessment parameters assigned in more than 2 follow-ups will be analyzed using the r-ANOVA/Friedman test/ Cochran Q test. The continuous data having normal distribution will be represented as mean (SD) and the data not having normal distribution as median (IQR). The 5% level of significance will be used throughout the analysis. The SPSS (version 26.0; IBM Corp) software will be used to conduct the analysis.

Results

The enrolment of the participants in the study was initiated in December 2023 and the final follow-up was completed in March 2024. Out of 240 participants enrolled, 222 (92.5%) participants have completed the study. Data verification, compilation, and analysis are under process. The findings from the study will be published in peer-reviewed journals after the completion of data analysis.

Discussion

Expected Findings

The selected composite Ayurvedic regimen is anticipated to reduce DASs in study participants with RA. This study was designed using a black box approach, which allows for the selection of medicine according to the pattern of disease presentation and associated symptoms instead of evaluating a specific medicine for a particular diagnosis [10].

Ayurvedic approach to treating a disease depends on the breaking of pathogenesis and alleviation of symptoms. The selection of medicines depends on different stages of pathogenesis that are usually assessed by the presentation of the disease. The available studies for the evaluation of Ayurvedic interventions in rheumatoid mostly used study designs such as single-arm studies, non-RCTs, and RCTs using controls from either Ayurveda or modern conventional drugs [22-25]. In these studies, the intervention was the same for all participants diagnosed with RA and did not consider differences in clinical conditions or the relationships with *Dosha* or *Ama*. Furst et al [26] have used modified RCT as a double-blind, randomized, double-dummy design to evaluate the efficacy of Ayurvedic medicines, both alone and in combination with the standard drug, methotrexate. In this study, 148 distinct Ayurvedic formulations with various dosage forms were used, allowing physicians to prescribe the appropriate combination of drugs based on the specific needs of the patient [26]. In our study, we have designed a single-arm black box design that allows the management of RA in different clinical manifestations on the basis of pathogenesis in terms of the association of *Ama* and *Dosha* along with the chronicity of the disease. For this, a predefined composite Ayurvedic regimen was used that is anticipated to reduce DASs in study participants with RA along with a change in disease-specific biochemical markers. Ayush-SG and *Rasnasaptak Kashaya* were given to all participants, while other medications were customized as per the form of disease presentation.

Ayush-SG contains 3 main ingredients as follows: *Shunthi* (*Zingiber officinale* Roscoe), *Guggulu* (*Commiphora wightii* Bhan), and *Godanti Bhasma* (Incinerated calcium sulfate/ gypsum) [12]. *Shunthi* is known to have anti-inflammatory, analgesic, immunomodulatory, and antioxidant activities [27]. Studies show that guggulipid, the oleo-gum resin of the plant *Commiphora wightii*, demonstrates significant antiarthritic and anti-inflammatory effects by targeting key molecular pathways involved in inflammatory responses [28,29]. *Rasnasaptak Kashaya* contains *Shunthi* along with other herbal ingredients such as *Rasna* (*Pluchea lanceolata* Oliver and Hiem), *Gokshura*

(*Tribulus terrestris* L), *Guduci* (*Tinospora cordifolia* [Willd] Miers), *Punarnava* (*Boerhaavia diffusa* Linn), *Eranda* (*Ricinus communis* Linn), *Devadaru* (*Cedrus deodara* [Roxb] Loud), and *Aragvadha* (*Cassia fistula* Linn). All these drugs possess anti-inflammatory activities and *Gokshura*, *Eranda*, and *Devadaru* have analgesic properties also. *Rasna* and *Guduci* have antiarthritic and *Aragvadha* has antirheumatic properties additionally [30-36]. A previous study on *Vatari Guggulu*, *Rasnasaptak Kashaya*, and *Brihat Saindhavadi Taila* has shown a significant change in DAS-28, disability index (Indian Health Assessment Questionnaire), and quality of life assessment (SF-36) scores when administered for 12 weeks [37].

Guduci Ghanavati contains an aqueous extract of *Tinospora cordifolia*, which possesses antiarthritic, anti-inflammatory, immunomodulatory, and antipyretic properties. The in vivo studies on aqueous extract of *T cordifolia* showed significant anti-inflammatory effects comparable with indomethacin and the mode of action is opined to be similar to that of a nonsteroidal anti-inflammatory agent [36].

Brihat Saindhavadi Taila is described as effective in pacifying pain in Amavata [37]. It is found effective in alleviating pain, swelling, and tenderness when administered locally in combination with other internal medications [14,38]. Most of the ingredients in this formulation possess anti-inflammatory properties [39-44]. *Eranda*, the base oil in the formulation, contains ricinoleic acid that has shown anti-inflammatory properties on peripheral application in an in vivo study in guinea pigs [45].

Dashanga lepa consists of 10 ingredients as follows: *Sirisha* (*Albizzia lebbeck* Benth), *Madhuyashti* (*Glycyrrhiza glabra* Linn), *Tagara* (*Valeriana wallichii* DC), *Raktachandanam* (*Pterocarpus santalinus* Linn), *Ela* (*Elettaria cardamomum* [Linn] Maton), *Jatamansi* (*Nardostachys jatamansi* DC), *Haridra* (*Curcuma longa* Linn), *Daruharidra* (*Berberis aristata* DC), *Kushta* (*Saussurea lappa* CB Clarke), and *Hrivera* (*Pavonia odorata* Willd). Most of the ingredients in this formulation have potent anti-inflammatory properties, and *Tagara* and *Jatamansi* have analgesic action too [46-54]. The anti-inflammatory and analgesic activities of *Dashanga Yoga/lepa* have been demonstrated in an in vivo study conducted on Wistar rats [55].

Anemia is one of the common comorbidities found in RA patients [56]. *Punarnavadi Mandura* contains ingredients such as *Amalaki* (*Phylanthus embelica* Linn), *Danti* (*Baliospermum montanum* Muell – Arg), *Pippali* (*Piper longum* Linn), *Punarnava*, *Kushtha* (*Saussurea lappa* C.B. Clarke) and *Daruharidra* (*Berberis aristata* DC) along with a mineral drug *Mandura bhasma* (incinerated iron oxide). An in vivo study conducted on *Punarnavadi Mandura* has shown significant hematinic activity against mercuric chloride-induced anemia in albino rats [57]. A previous clinical study on the drug also showed significant improvement in serum iron and serum ferritin levels with improvement in the symptoms of anemia such as fatigue, pallor, etc [58].

The pharmacological properties of the ingredients in the formulations and previous studies suggest that the selected composite Ayurveda regimen for the study will be effective in the management of RA. The findings from the study will be disseminated through reputed peer-reviewed journals after the completion of the data analysis. This research represents an initial effort using a black box design, which could lay the groundwork for customized interventions rooted in Ayurvedic concepts of pathogenesis and symptomatology.

Strength and Limitations

This study is planned using a black box design that will help in providing evidence-based data regarding the effect of personalized medications in Ayurveda for the management of RA. However, the study protocol has some limitations also. The study protocol does not include the assessment of inflammatory markers such as anticyclic citrullinated peptide. In this study, 3 distinct categories are considered for the composite Ayurvedic regimen. Future research could be designed to address a wider variety of disease presentations.

Future Scope

This study protocol could be extended to similar conditions that are presented with a wide range of symptoms that require a more individualized approach. Future RCTs may be planned to compare the Ayurveda treatment regimen with conventional standard treatment protocol.

Conclusions

This interventional study that incorporates the black box approach may provide a strong framework for managing RA. This design may be a more reliable method for evaluating the effectiveness and tolerability of the composite Ayurveda regimen in RA.

Acknowledgments

The authors wish to acknowledge the project team at the Central Council for Research in Ayurvedic Sciences (CCRAS) headquarters for their technical support during the drafting of the protocol. CCRAS, under the Ministry of Ayush, Government of India, New Delhi, has funded this study (CCRAS Headquarters, 61-65 Institutional Area, Opp. D Block, Janakpuri, New Delhi 110058). All authors declared that they had insufficient funding to support open access publication of this manuscript, including from affiliated organizations or institutions, funding agencies, or other organizations. JMIR Publications provided article processing fee (APF) support for the publication of this article.

Conflicts of Interest

None declared.

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Abbreviations

CCRAS: Central Council for Research in Ayurvedic Sciences
CRF: case record form
CTRI: Clinical Trial Registry-India
DAS: disease activity score
ESR: erythrocyte sedimentation rate
HbA1c: hemoglobin A1c
IEC: Institutional Ethics Committee
NSAID: nonsteroidal anti-inflammatory drug
RA: rheumatoid arthritis
RCT: randomized controlled trial

Edited by A Schwartz; submitted 01.03.24; peer-reviewed by A Hassan, P Khobarkar, S Dubey, AK Rai; comments to author 04.07.24; revised version received 02.08.24; accepted 19.11.24; published 18.02.25.

Please cite as:
Makhija D, Mata S, Sharma A, Kachare K, Manathottathil A, Jain S, Jameela S, Rao BC, Rana R, Tripathi A, Rana K, Joshi V, Singh A, Srikanth N, Acharya R
Effectiveness of Composite Ayurveda Regimen in a Black Box Design for the Management of Rheumatoid Arthritis: Protocol of a Single Arm, Community-Based Study
JMIR Res Protoc 2025;14:e57918
URL: https://www.researchprotocols.org/2025/1/e57918
doi:10.2196/57918
PMID:

Protocol

Antibiotic Use In Utero and Early Life and Risk of Chronic Childhood Conditions in New Zealand: Protocol for a Data Linkage Retrospective Cohort Study

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Abstract

Background: The incidence of many common chronic childhood conditions has increased globally in the past few decades, which has been suggested to be potentially attributed to antibiotic overuse leading to dysbiosis in the gut microbiome.

Objective: This linkage study will assess the role of antibiotic use in utero and in early life in the development of type 1 diabetes (T1D), attention-deficit/hyperactive disorder (ADHD), and inflammatory bowel disease.

Methods: The study design involves several retrospective cohort studies using linked administrative health and social data from Statistics New Zealand's Integrated Data Infrastructure. It uses data from all children who were born in New Zealand between October 2005 and December 2010 (N=334,204) and their mothers. Children's antibiotic use is identified for 4 time periods (at pregnancy, at ≤1 year, at ≤2 years, and at ≤5 years), and the development of T1D, ADHD, and inflammatory bowel disease is measured from the end of the antibiotic use periods until death, emigration, or the end of the follow-up period (2021), whichever came first. Children who emigrated or died before the end of the antibiotic use period are excluded. Cox proportional hazards regression models are used while adjusting for a range of potential confounders.

Results: As of September 2024, data linkage has been completed, involving the integration of antibiotic exposure and outcome variables for 315,789 children. Preliminary analyses show that both prenatal and early life antibiotic consumption is associated with T1D. Full analyses for all 3 outcomes will be completed by the end of 2025.

Conclusions: This series of linked cohort studies using detailed, complete, and systematically collected antibiotic prescription data will provide critical new knowledge regarding the role of antibiotics in the development of common chronic childhood conditions. Thus, this study has the potential to contribute to the development of primary prevention strategies through, for example, targeted changes in antibiotic use.

International Registered Report Identifier (IRRID): DERR1-10.2196/66184

(JMIR Res Protoc 2025;14:e66184) doi:10.2196/66184

KEYWORDS

early childhood; chronic childhood conditions; antibiotics; data linkage; study protocol; routine data

Introduction

The incidence of many chronic childhood conditions such as type 1 diabetes (T1D), attention-deficit/hyperactive disorder (ADHD), and inflammatory bowel disease (IBD) has increased globally in the last 2 decades [1]. The total global incidence of childhood and adolescent T1D is larger than previously estimated, with nearly 1 in 2 children currently undiagnosed, with most underdiagnoses occurring in low-income countries [2]. Current global incidence estimates range from 128,900 to 149,500 per annum [3,4]. For ADHD, although recent geographical estimates are unavailable, the highest incidence rates are reported in countries with a higher sociodemographic index [5]. The global incidence of IBD is increasing steadily and varies greatly by geographical areas, with the highest annual pediatric incidence of IBD reported to be 23/100,000 person-years in Europe, 15.2/100,000 in North America, and 11.4/100,000 in Asia/the Middle East and Oceania [6].

In New Zealand, the annual incidence of T1D is reported to be 23/100,000, and this is increasing by 4.1% annually [7]. It is estimated that 2%-5% of school-age children in New Zealand are affected by ADHD [8], with a recent study showing that the total ADHD medication dispensing prevalence had almost doubled from 516/100,000 in 2007-2008 to 996/100,000 in 2016-2017, with the highest dispensing prevalence reported for those aged 7-17 years [9]. In the case of IBD, recent New Zealand estimates have shown age-specific incidence rates of 39.5/100,000, which is 1.6-fold greater than what was measured 10 years earlier—this is among the highest in the world [10]. Research indicates significant ethnic differences in T1D and IBD, with European children having higher rates than Māori and Pacific children [7,11]. Furthermore, ADHD prevalence and treatment access vary by socioeconomic status [12].

The etiology of these diseases is not well understood, but environmental factors, genetics, immune-regulatory pathways, and microbial exposures are considered important [13,14]. Early life gut microbiome development is a critical window for immune and neurodevelopment. In early childhood, establishing a healthy microbiome is vital for shaping the immune system and influencing neurodevelopmental outcomes [15]. Microbial colonization begins at birth and evolves with a diverse gut microbiome linked to better health outcomes. Antibiotic use during this period may also be a risk factor that can disrupt the microbiome development by depleting beneficial bacteria, leading to dysbiosis [15,16], which may impair immune training and increase susceptibility to these chronic conditions [17].

Several studies have assessed associations between antibiotic use and the development of these chronic conditions during the prenatal period and early life years [18-20], but results have been inconsistent, with some showing positive associations [20] and others showing no association [21-23]. These inconsistencies may, at least in part, be explained by limitations in study design. For example, antibiotic use is often assessed through recall, which is vulnerable to bias. Moreover, studies often rely on short-term prescription history prior to disease onset, which may result in issues of reverse causality (if antibiotics were prescribed to treat early symptoms of the disease itself) [24,25]. Further, studies have often focused on only one specific class of antibiotics without considering the full spectrum of antibiotics used [25]. Importantly, most research has been conducted in Europe (particularly Scandinavia) and the United States, and it remains unclear whether results can be extrapolated to other parts of the world, including New Zealand, which, compared to other Organisation for Economic Co-operation and Development countries, including Scandinavia [26], is known to have a very high use of antibiotics among children [27].

The series of linked cohort studies for which the methods are described in this protocol paper will assess associations between prenatal and early life antibiotic use and the development of childhood T1D, ADHD, and IBD. These studies using detailed, complete, and systematically collected antibiotic prescription data will provide critical new knowledge regarding the role of antibiotics in the development of these common chronic childhood conditions. Thus, this study has the potential to contribute to the development of primary prevention strategies through, for example, targeted changes in antibiotic use. The central hypothesis of this study is that early life antibiotic use is associated with the development of childhood T1D, ADHD, and IBD.

Methods

Study Design, Setting, and Population

The study design involves several retrospective cohort studies using linked administrative health and social data from Statistics New Zealand's Integrated Data Infrastructure (IDI) [28]. Antibiotic use and T1D, ADHD, and IBD are defined as described below. To date, data for all children born in New Zealand between October 2005 and December 2010 (N=334,204) and their mothers have been extracted from the Department of Internal Affairs birth data in the IDI. Children's antibiotic use has been defined for 4 time periods (at pregnancy, at ≤1 year, at ≤2 years, and at ≤5 years). The development of T1D, ADHD, and IBD (which consists of Crohn disease and ulcerative colitis) has been measured from the end of the antibiotic use periods until death, emigration, or the end of the study in 2021, whichever came first, accumulating approximately 3,000,000 person-years. Children who emigrated overseas or died before the end of the antibiotic use period have been excluded from the analysis, as they cannot be followed up for the occurrence of these chronic childhood conditions. At the end of follow-up, children had reached the age of 11-16 years.

Data Sources

The IDI is a database of deidentified administrative and survey data about people and households in New Zealand [28]. It includes data about health, education, income, social support payments, migration, and other life events, which can be linked at the individual level. The IDI provides a longitudinal record of events and is a growing resource. As of September 2018, the IDI holds over 166 billion pieces of information from more than 14 organizations [28,29]. Table 1 lists the datasets that are being used for this study with a brief description of the data and the variables extracted from these datasets.

Table 1. Data collections available within the integrated data infrastructure for linking cohorts' demographic data with antibiotic use and selected health outcomes [30].

Data collections	Descriptions	Characteristics/variables extracted
Births (from 1840): This data collection was used to define the cohort and identify the mothers of the children.	This collection holds all births in New Zealand, including month and year of birth, sex, ethnicity, first and second parent as recorded on birth registration, and their sex, age, ethnicity, type of relationship, weight at birth, gestation, and their age.	Sex, date of birth, birth weight, ethnicity
Pharmaceutical data (from 2005): This data collection was used to analyze antibiotic prescription.	This collection holds claim and payment information from pharmacists for subsidized medicines, including Pharmaceutical Management Agency (PHARMAC[a]) identifier of primary active chemical ingredient, quantity, number of repeats, and date of dispensing.	Date of prescription dispensing, Anatomical Therapeutic Chemical codes for medicines, including antibiotics and treatments for T1D[b], ADHD[c], and IBD[d]
Maternity (from 2003): This data collection was used to calculate the gestational period and maternal age at birth and to identify the mode of delivery.	The National Maternity Collection provides statistical, demographic, and clinical information about selected publicly funded maternity services up to 9 months before and 3 months after a birth.	Mothers' date of birth, ethnicity, last date of menstruation, mode of delivery, maternal age at delivery
Mortality (from 1998): These data were used to identify the date of death.	This collection holds the underlying cause of death for all deaths registered in New Zealand using the International Classification of Diseases, Tenth Revision, Clinical Modification codes, including all registered fetal deaths and date of death.	Date of death
International travel and migration (from 1997): This data collection was used to identify children who emigrated from New Zealand.	This collection holds arrival and departure records and migration records.	Date of departure
Laboratory claims (from 2003): This data collection was used to obtain laboratory testing information.	This collection holds primary-care test subsidies.	Laboratory test(s) conducted (results of tests are not available), including testing for T1D, ADHD, and IBD
NNPAC[e] (from 2007): This data collection was used to identify any diagnosis procedure for nonadmitted patients.	NNPAC provides national consistent data on nonadmitted patient (outpatient and emergency department) activity.	Diagnosis for various health conditions, including T1D, ADHD, and IBD
Publicly funded hospital discharges (from 1998): This data collection was used to identify the principal and additional reasons for hospitalization and procedure performed during hospital stay.	This collection contains summarized information detailing publicly funded hospital discharges and procedures by New Zealand hospitals using the codes of the International Classification of Diseases, Tenth Revision, Clinical Modification.	Disease/procedure classification, diagnosis for various health conditions, including T1D, ADHD, and IBD.

[a]PHARMAC is a government agency in New Zealand responsible for managing the funding and procurement of pharmaceuticals and medical devices.

[b]T1D: type 1 diabetes.

[c]ADHD: attention-deficit/hyperactivity disorder.

[d]IBD: inflammatory bowel disease.

[e]NNPAC: National Non-Admitted Patient Collection.

Definition of Antibiotic Exposure

Antibiotic exposures in utero and for the first 5 years of life are identified for all cohort members born between October 2005 to December 2010 from pharmaceutical data. Dispensing dates and dose and number of purchases are identified, and each antibiotic prescription is categorized by (1) class, according to the Anatomical Therapeutic Chemical classification J01 "Antibiotics for systemic use" (eg, penicillins, cephalosporins, sulfonamides); (2) spectrum, that is, broad or narrow; and (3) whether antibiotics target Gram-positive or Gram-negative bacteria or both. These categorizations of individual antibiotics are provided in Table 2 [31].

Table 2. Antibiotics by class and spectrum of activity [31].

Class of antibiotics, chemical name of antibiotic used among the cohort	Spectrum of activity (narrow/broad)	Antibiotics targets Gram-positive/Gram-negative bacteria
Cephalosporins and cephamycins		
Cefaclor monohydrate	Moderate	Both
Cefalexin	Moderate	Both
Cefamandole nafate	Broad	Both
Cefazolin	Moderate	Both
Cefoxitin sodium	Moderate	Both
Ceftazidime	Broad	Both
Ceftriaxone	Broad	Both
Cefuroxime axetil	Moderate	Both
Cefuroxime sodium	Moderate	Both
Cephalothin sodium	Broad	Both
Cephradine	Broad	Both
Macrolides		
Azithromycin	Broad	Positive
Clarithromycin	Broad	Positive
Erythromycin	Broad	Positive
Erythromycin (as lactobionate)	Broad	Positive
Erythromycin estolate	Broad	Positive
Erythromycin ethyl succinate	Narrow	Positive
Erythromycin stearate	Narrow	Positive
Roxithromycin	Broad	Positive
Other antibiotics		
Aztreonam	Broad	Negative
Chloramphenicol	Broad	Both
Chloramphenicol sodium succinate	Broad	Both
Ciprofloxacin	Broad	Both
Clindamycin	Broad	Both
Colistin sulfomethate	Broad	Positive
Fleroxacin	Broad	Both
Framycetin sulfate	Broad	Both
Gentamicin sulfate	Broad	Both
Imipenem	Broad	Both
Levofloxacin	Broad	Both
Lincomycin	Broad	Both
Lincomycin hydrochloride	Narrow	Positive
Moxifloxacin	Broad	Both
Neomycin sulfate	Broad	Both
Ofloxacin	Broad	Both
Paromomycin	Broad	Positive
Pyrimethamine	Broad	Both
Sodium fusidate (fusidic acid)	Narrow	Both

Class of antibiotics, chemical name of antibiotic used among the cohort	Spectrum of activity (narrow/broad)	Antibiotics targets Gram-positive/Gram-negative bacteria
Spectinomycin hydrochloride	Moderate	Both
Spiramycin	Broad	Both
Sulfadiazine sodium	Broad	Both
Sulfadiazine	Broad	Both
Tobramycin	Broad	Both
Triacetyloleandomycin	Broad	Positive
Trimethoprim	Broad	Both
Trimethoprim with sulfamethoxazole (cotrimoxazole)	Broad	Both
Vancomycin	Narrow	Positive
Penicillins		
Amoxicillin	Broad	Both
Amoxicillin with clavulanic acid	Broad	Both
Amoxicillin clavulanate	Broad	Both
Benzathine benzylpenicillin	Narrow	Both
Benzylpenicillin sodium (Penicillin G)	Narrow	Both
Dicloxacillin	Narrow	Both
Flucloxacillin	Narrow	Both
Flucloxacillin magnesium	Narrow	Both
Penicillin G benzathine (Benzathine benzylpenicillin)	Narrow	Both
Phenoxymethylpenicillin (Penicillin V)	Narrow	Both
Piperacillin	Broad	Both
Pivampicillin	Broad	Both
Pivmecillinam hydrochloride	Narrow	Both
Procaine penicillin	Narrow	Both
Ticarcillin	Broad	Both
Tetracyclines		
Demeclocycline hydrochloride	Broad	Both
Doxycycline	Broad	Both
Lymecycline	Broad	Both
Minocycline hydrochloride	Broad	Both
Rolitetracycline	Broad	Both
Tetracycline	Broad	Both
Tetracycline hydrochloride	Broad	Both

Definition of Health Outcomes

The selected health outcomes of the study population are determined through linkage with the following data collections: (1) hospital discharges, (2) pharmaceutical data, (3) nonadmitted patient collection, and (4) laboratory claims, for the period starting from birth or end of antibiotic exposure period of each child to the end of 2021. The specific case definitions, including the International Classification of Diseases, Tenth Revision codes corresponding to the health outcomes under consideration, are provided in Table S1 of Multimedia Appendix 1 [32-35]. To ascertain the prevalence of T1D, we used 3 distinct algorithms to identify cases, facilitating a comprehensive comparison of results to ensure consistency. For IBD, the identification of cases, as outlined in Table S1 of Multimedia Appendix 1, will be subject to further validation against several cohorts of patients with IBD obtained from collaborating gastroenterologists. This validation will involve exploring various combinations of medications prescribed for IBD,

including those listed in Table S1 of Multimedia Appendix 1. The analysis aims to provide insights into the diversity of medication regimens associated with IBD cases. Any refinements or enhancements to the algorithms as well as insights gained from the medication combination analysis will be documented and incorporated into the final analysis.

Other Variables

Fixed covariates/confounders that will be considered in the analyses include sex, ethnicity, deprivation index (based on mesh block) [36], birth weight, gestation, mode of delivery, rurality, and maternal age. Time-dependent covariates include hospitalization for infections and other chronic diseases and selected prescription medications (eg, paracetamol, antivirals, antifungals).

Follow-Up of Vital Status and New Zealand Residency

Linkage to border movements and mortality data are used to determine whether cohort members are still alive and are based in New Zealand. Those who have emigrated or died prior to their fifth birthday are excluded from the analyses; the follow-up time for those who died or emigrated after the fifth birthday is censored up to that point, which means that the event of interest or health outcome being investigated may not be observed for some individuals.

Statistical Analysis

To date, the primary focus has been on data preparation that consisted of (1) constructing the cohort through data linkage; (2) identifying the antibiotic exposure variables for all cohort members; (3) identifying other variables, including confounders for all cohort members; and (4) identifying T1D, ADHD, and IBD cases within the cohort using the definitions described in Table S1 of Multimedia Appendix 1. The next stage involves analyses that focus on assessing associations between antibiotic use and the health outcomes described above. For this, we will use Cox proportional hazards regression, with attained age as the analysis time scale. As noted before, children have been followed up until the estimated date of diagnosis, emigration from New Zealand, death, or the end of the study period (December 31, 2021), whichever comes first.

For each health outcome, analyses will be conducted to measure associations with antibiotic use during specific early life periods (pregnancy, ≤1 year, ≤2 years, and ≤5 years, as well as combinations of these periods). Antibiotic use will be based on the number of prescriptions, which will enable the assessment of dose-response associations. In addition to considering all antibiotic classes combined, we will also conduct analyses where antibiotics will be grouped into different classes/categories (Table 2); this will provide insights into which specific groups of antibiotics may be most strongly associated with the 3 outcomes of interest. Analyses will be stratified by mode of delivery to assess whether associations may be different in different subgroups (effect modification) as has been shown for cesarean section births, with larger effect sizes shown for associations between antibiotic use and T1D for caesarean section births [20,37]. In addition to stratified analyses, we will also assess the role of potential confounders such as sex, prioritized ethnicity, deprivation index, and rurality by using multivariable analyses.

Nested case-control analyses will be conducted as an additional way to address potential bias and confounding. Controls will be matched to cases on year and month of birth, sex, ethnicity, and other potential confounding factors such as residence and deprivation. In addition, to address potential medical surveillance bias, matched controls that occur in the same data collections as the cases will be selected. Nested case-control analyses will also enable the evaluation of possible reverse causation (ie, the health outcome of interest resulting in the prescription of antibiotics rather than the other way around) by disregarding antibiotic use in the 6 months before diagnosis of the cases and the equivalent time point of the matched controls. Moreover, control for confounding by maternal factors will be achieved through within-mother analysis of disease-discordant pairs of siblings. Factors remaining constant between pregnancies could, for example, be the mother's attitude toward antibiotic prescriptions as well as the general practitioner's antibiotic prescription practices, which will influence the child's exposure to antibiotics; other types of analyses can typically not adjust for this. Further, confounding by indication, where the reason for prescribing antibiotics may be linked to the development of chronic conditions, will only be addressed once primary care data become available, enhancing the rigor of the study.

Study Power

Based on national and international data, we have assumed that at least half of the children will have been prescribed antibiotics within the first year of life (52% in a Finnish study, 15% for specific antibiotic classes [38]). Based on age-specific statistics of the Virtual Diabetes Register, which is an annually updated national register of all patients with diabetes mellitus from 2010 to 2015, we estimate that 400 cases of T1D can be identified within the cohort [39]. Furthermore, based on hospitalization data, as per the age-specific data, we estimate that at least 200 IBD cases (170 cases of Crohn disease and 30 cases of ulcerative colitis) can be included in the study based on hospitalization data. Finally, for ADHD, and as noted earlier, medication dispensing has doubled from 516 per 100,000 in 2007-2008 to 996 per 100,000 in 2016-2017 in New Zealand [9]. Although a breakdown by age group is not available, we estimate that at least 1000 cases can be identified in the cohort. This is a conservative estimate based on our experience with other IDI projects [34], and it is likely that this number is substantially higher (up to 3% of the study population). Thus, we assume that case sets will have a minimum size of 1000 for ADHD, 400 for T1D, and 200 for IBD. Hazard ratio (HR) estimates that are detectable with 80% power (P<.05, 2-sided) under different population size and exposure prevalence scenarios are summarized in Table 3. Assuming an exposure prevalence of 33%, this study has 80% power to detect an HR of 1.2 for ADHD, 1.4 for T1D, and 1.5 for IBD. Analyses of specific strata of the study population (eg, based on sex or ethnicity) will have sufficient study power to detect similar effect sizes (Table 3). Considering a lower exposure frequency of 10% (eg, for specific antibiotic classes), the study has 80% power to detect an HR of 1.3 for ADHD, 1.5 for T1D, and 1.7 for IBD. Assuming a further

reduction in exposure frequency of 5% (eg, for specific antibiotics), the study has 80% power to detect an HR of 1.5 for ADHD, 1.7 for T1D, and 2.0 for IBD (Table 3).

Table 3. Study power: hazard ratio detectable (power 80%, $P<.05$, 2-sided) under different population size and exposure prevalence scenarios.

Strata	Study population (N)	Scenarios for attention-deficit/hyperactivity disorder					Scenarios for type 1 diabetes					Scenarios for inflammatory bowel disease				
		Cases (n)	Exposure prevalence (hazard ratio)				Cases (n)	Exposure prevalence (hazard ratio)				Cases (n)	Exposure prevalence (hazard ratio)			
			50%	33%	10%	5%		50%	33%	10%	5%		50%	33%	10%	5%
All	300,000	1000	1.2	1.2	1.3	1.5	400	1.3	1.4	1.5	1.7	200	1.5	1.5	1.7	2.0
Sex	150,000	500	1.3	1.3	1.5	1.6	200	1.5	1.5	1.7	2.0	100	1.7	1.7	2.0	2.4
Ethnicity	60,000	200	1.5	1.5	1.7	2.0	80	1.8	1.8	2.2	2.5	40	2.2	2.2	2.7	3.2

Ethics Approval

This study was approved by Human Research Ethics Committee of the University of Otago (reference: HD21/053). Microdata access approval for the project was provided by Statistics New Zealand. To ensure confidentiality, all data are deidentified before access. Access to linked datasets is limited to authorized personnel, and data handling follows ethical guidelines. Sensitive data will be managed securely. Although the data within IDI are fully deidentified, there are several requirements that govern the use of IDI data that this study will adhere to. These are (1) statistical outputs can only be disseminated after outputs have been checked and approved by Statistics New Zealand, (2) the IDI confidentiality rules require the suppression of counts and associated results of analyses on samples smaller than 6, and (3) the random rounding of counts can be up or down to the next multiple of 3.

Results

As of September 2024, we have completed the data linkage, involving the integration of antibiotic exposure data with outcome variables and all relevant covariates for 315,789 individuals. Preliminary analyses show that both prenatal and early life antibiotic consumption is associated with T1D. Full analyses for all 3 outcomes, that is, analyses adjusted for potential confounders, stratified by ethnicity and sex, and further sensitivity analyses will be completed by the end of 2025.

Discussion

Antibiotics are widely used in human populations, particularly children. It is therefore important to assess and quantify potential adverse effects of this exposure at the population level so that they can be balanced against the many benefits of these therapies. We hypothesize that antibiotic use will result in a positive and significant hazard risk for the development of chronic childhood conditions. The unique data infrastructure established through Statistics New Zealand's IDI provides a robust way of assessing such relationships across a large cohort, consisting of the entire New Zealand population who can be followed up for many years. Findings will be of relevance both locally and internationally, particularly in regions with similarly low antimicrobial resistance rates, such as certain European countries [40]. Additionally, in areas with high pediatric antibiotic usage, such as parts of North America and Asia [41], these insights can inform public health strategies aimed at optimizing antibiotic stewardship.

The proposed series of studies, which are large by international standards and based on detailed, complete, and objectively collected antibiotic prescription data, will provide critical new knowledge regarding the role of antibiotics in the development of common chronic childhood conditions. As such, it will provide an important addition to the limited number of studies conducted in humans and has the potential to contribute to the development of feasible avenues for primary prevention, through, for example, targeted changes in antibiotic use in both quantity and type and targeted use of prebiotics or probiotics. Additionally, this study may be expanded to encompass other conditions such as asthma and allergies, which have also been associated with early life antibiotic exposure [42].

The focus of this study is on the effects of antibiotics on the host, but the results are also relevant to the broader issue of antibiotic overuse and its link with increased microbial resistance. New Zealand has comparatively low rates of antimicrobial resistance [43,44]. However, resistance has steadily increased, and experience gained from other countries suggests that this will become more common in New Zealand, raising patient risk and costs for the health system [45]. Antimicrobial resistance is considered one of the biggest man-made public health threats of modern times [43]. Clinicians and public health researchers have advocated that New Zealand needs to urgently institute a range of measures to significantly reduce antimicrobial consumption [46,47]. A systematic review of interventions aimed at reducing antibiotic prescribing for respiratory tract infections across several settings has led to substantial reductions [48], although efforts in New Zealand have not yet resulted in a decrease of antibiotic consumption [45]. This study may provide additional evidence for the need to reduce (unnecessary) antibiotic consumption both in New Zealand and internationally.

Acknowledgments

Funding for this study is provided by the New Zealand Health Research Council (reference ID: 18/509).

Data Availability

The datasets generated and analyzed for this study are not publicly available. Statistics New Zealand's integrated data infrastructure microdata are available for research purposes, and access is granted based on meeting the conditions set by Stats New Zealand through a secure laboratory environment.

Disclaimer

These results are not official statistics. They have been created for research purposes from the integrated data infrastructure, which is carefully managed by Stats New Zealand.

Authors' Contributions

JD, AtM, and MB conceived the original idea for this data linkage study. All authors contributed to the development of the study methodology. SR wrote the first draft of the manuscript, with assistance from JD, AtM, MC, AK, AE and MB. All authors contributed to the writing of the paper and read and approved the final manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Health outcome classification, corresponding International Classification of Diseases Tenth Revision codes, and case definitions.
[DOCX File , 20 KB - resprot_v14i1e66184_app1.docx]

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Abbreviations

ADHD: attention-deficit/hyperactive disorder
HR: hazard ratio
IBD: inflammatory bowel disease
IDI: integrated data infrastructure
T1D: type 1 diabetes

Edited by A Schwartz; submitted 06.09.24; peer-reviewed by M Gasmi , B Fadojutimi; comments to author 12.11.24; revised version received 23.12.24; accepted 21.01.25; published 28.02.25.

Please cite as:
Ram S, Corbin M, 't Mannetje A, Eng A, Kvalsvig A, Baker MG, Douwes J
Antibiotic Use In Utero and Early Life and Risk of Chronic Childhood Conditions in New Zealand: Protocol for a Data Linkage Retrospective Cohort Study
JMIR Res Protoc 2025;14:e66184
URL: https://www.researchprotocols.org/2025/1/e66184
doi:10.2196/66184
PMID:40053783

Protocol

Using a Sober Curious Framework to Explore Barriers and Facilitators to Helping Sexual Minority Women Reduce Alcohol-Related Harms: Protocol for a Descriptive Study

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Abstract

Background: Globally, women consume less alcohol than men, but alcohol consumption among women has declined less in recent years than among men. Drinking rates and alcohol-related harms vary substantially across population groups of women, and sexual minority women (eg, lesbian, bisexual, and queer) are at notably high risk. An emerging body of literature suggests that in addition to minority stress (eg, stigma, discrimination), drinking norms and drinking cultures likely influence sexual minority women's drinking. Almost no research has explored these factors as possible targets of interventions. Sober curiosity is a rapidly growing wellness movement that may be particularly salient for sexual minority women. It encourages individuals to be "curious" about the reasons they choose to drink and alcohol's effects on their life and health.

Objective: The aims of this research are to (1) explore the perspectives of the drinking social worlds of sexual minority women, their awareness of the sober curious movement, perceptions of their own and their peers' drinking and desire to drink less, and perceived barriers and facilitations to changing their drinking behaviors and (2) identify key elements of an alcohol reduction intervention tailored for sexual minority women.

Methods: We conducted a comprehensive review of the literature on alcohol interventions with sexual minority women. The handful of studies we found paid scant attention to drinking cultures, normative beliefs, or other key elements of sober curiosity. To address the study aims, we are conducting 2 descriptive studies with adult (>18 years) sexual minority women using mixed methods. One includes focus group interviews (n=24-36) and a national survey (n=100-120) with sexual minority women in Scotland. The other includes in-depth interviews (n=18-20) with sexual minority women in the United States. Data from the 2 countries and 3 sources will be analyzed using qualitative and quantitative methods to identify patterns and relationships across data to validate or corroborate findings.

Results: Each of the studies received ethics approval in August 2023 and is currently open for recruitment. We anticipate completing data collection in spring 2025. The results of qualitative analyses will be summarized as themes, and results of survey

data analyses will be summarized in tables. Findings will be presented to 2 panels of international experts who will assist in identifying critical elements of an alcohol reduction intervention tailored to the unique needs of sexual minority women.

Conclusions: With the assistance of the expert panels, we will use Acceptability, Practicability, Effectiveness, Affordability, Side-Effects, and Equity criteria to inform the development of a tailored intervention building on tenants of sober curiosity to assist sexual minority women in reducing harmful drinking.

International Registered Report Identifier (IRRID): DERR1-10.2196/63282

(JMIR Res Protoc 2025;14:e63282) doi:10.2196/63282

KEYWORDS

sexual minority women; drinking; sober curiosity; women; sober; minority; alcohol; protocol; barriers; facilitators; disparities

Introduction

Background

Overview

Hazardous alcohol consumption is a pattern of alcohol use that increases the risk of harmful consequences [1]. As a leading risk factor for poor health outcomes worldwide, hazardous drinking is a global public health concern. According to the World Health Organization (WHO) [2], heavy drinking is a causal factor in more than 200 disease and injury conditions; it is also among the top 4 risk factors highlighted in the WHO global strategy for prevention and control of noncommunicable diseases. Efforts to reduce hazardous drinking are a major challenge because in many parts of the developed world, consuming alcohol at risky levels is widely socially acceptable and oftentimes viewed as preferable to abstinence, particularly within social worlds structured around heavy drinking norms [3].

The 2018 WHO Global Status Report on Alcohol and Health [4] suggests that women's drinking has decreased in most countries. However, this is not the case in some Western high-income countries including the United States [5], the United Kingdom [6], and Australia [7]. An increase in women's drinking is among the most prominent trends in alcohol consumption in the United Kingdom in recent history [8]. Further, alcohol consumption patterns and alcohol-related harms are not evenly distributed across population groups of women [9-12]. As described by Bloomfield's [13] "alcohol harm paradox", although different groups of women may drink similar quantities of alcohol, they often experience differential harms based on their level of social disadvantage. It is important to understand the contemporary determinants of health that contribute to hazardous drinking and make it more (or less) difficult for socially marginalized women to reduce alcohol consumption, particularly when alcohol is readily accessible and is used to facilitate or form social connections. In this paper, we review the literature regarding existing alcohol interventions for sexual minority women (eg, lesbian, bisexual, and queer), discuss barriers and facilitators to interventions that support sexual minority women who wish to reduce their alcohol use, and describe 2 studies, one in Scotland and one in the United States, that aim to support the development of an intervention designed to reduce alcohol-related harms among sexual minority women.

Sexual Orientation–Related Disparities in Alcohol Use

Hazardous drinking is among the most prominent health-related disparities when comparisons of heterosexual and sexual minority women are undertaken globally [14-16]. For example, findings from a US national sample found that compared to heterosexual women, sexual minority women were nearly 4 times as likely to engage in heavy episodic drinking [17]. A population-based study conducted in England found that lesbian, gay, and bisexual (LGB) adults (32%) were more likely than heterosexual adults (24%) to drink at harmful levels [18]. This sexual orientation–related disparity is hypothesized to be due to several factors: (1) minority stress related to discrimination and marginalization that impacts mental health and contributes to using alcohol as a coping strategy [14,19-21]; (2) sexual minority women are more likely than heterosexual women to have experienced lifetime trauma, including childhood sexual abuse, childhood physical abuse, adult sexual assault, and intimate partner violence [22-27], that also contributes to alcohol use as a means of coping [28]; (3) the predominantly alcohol-driven nature of the commercial lesbian, gay, bisexual, transgender, queer, and other sexual and gender minority (lesbian, gay, bisexual, transgender, queer or questioning [LGBTQ+]) scene, which facilitates connections and provides a key social environment for many LGBTQ+ individuals and communities [29,30]; and (4) the important role that alcohol plays in identity formation for LGBTQ+ people [14,30,31].

An emerging body of literature suggests that heavy drinking norms also contribute to the heavier drinking patterns of sexual minority women [32]. Drinking is primarily a social activity, often a central part of social occasions in a "social world" where members come together around something they have in common, such as an occupation or an identity [3]. In addition, research suggests that sexual minority women perceive the expectation to drink to be higher in LGBTQ+ spaces than in other contexts [33]. Understanding the drinking norms and drinking behaviors of sexual minority women is essential to informing the development of effective interventions to reduce heavy drinking and alcohol-related harms.

Alcohol Treatment and Sexual Minority Women

In the general population, women are less likely than men to seek help related to their drinking [34-36]. Women who drink heavily report experiencing gendered stigma that negatively impacts their desire or ability to access mainstream alcohol treatment services and their experiences when help is sought. Such stigma may be particularly salient for sexual minority

women who are already stigmatized based on their sexual identity [35,36]. For example, Dimova et al [37] found that sexual minority women (and sexual minority men) who accessed alcohol treatment were rarely asked about their sexual or gender identity, which precluded exploration of how these factors might impact their drinking or desire to reduce drinking. Both lesbian and bisexual women also reported experiencing heterosexist assumptions (eg, that they were partnered with a man) and feeling judged because of their drinking. Moreover, one recent study using data from the 2020 US National Survey of Substance Abuse Treatment Services found that only 2.4% of substance use treatment facilities offered LGBTQ+-tailored programming [38].

Compared to intervention studies aimed at reducing hazardous drinking among women in the general population, those that focus on the experiences of sexual minority women are more recent and more limited [14,39,40]. The small body of literature on interventions designed to reduce drinking among sexual and gender minority populations has focused predominately on sexual minority men [14,41]. A few studies have been conducted on sexual minority women's perceptions and experiences of alcohol treatment in the United States, but nearly all have focused on formal treatment or 12-step programs such as Alcoholics Anonymous (AA) [42-48]. Interventions that might be appropriate for heavy-drinking sexual minority women who are not accessing services or for whom alcohol use is not yet problematic enough to warrant formal treatment—but likely to worsen without early intervention—have not been explored.

Many alcohol treatment programs, especially 12-step programs such as AA, emphasize powerlessness, character defects, and making amends to those harmed by one's drinking—features that may be off-putting for sexual minority women who experience stigma, discrimination, and rejection based on their gender and sexual minority status. While AA is not affiliated with a religious organization, it uses a framework based on religious spirituality. Sexual minority women who do not identify with a particular religion or who have had negative experiences with religious institutions are less likely to access AA [43]. Access to nonreligious and affirming alternatives to AA is important, given research documenting low rates of endorsing religiosity and an absence of a protective effect of religiosity on heavy drinking among sexual minority women relative to heterosexual women [49,50]. Sexual minority women and sexual minority men are more likely than their heterosexual counterparts to express interest in accessible, nonstigmatizing alternatives to AA and traditional treatment approaches [51]. Sober curiosity, described in detail in "Potential Usefulness of an Intervention Based on Sober Curiosity" section, is an identity-affirming approach to alcohol reduction that offers such an alternative.

Existing Evidence Regarding Alcohol Interventions With Sexual Minority Women

In a large global scoping review of studies focused on alcohol and other drug use among sexual minority women, Hughes et al [14] describe the dearth of research related to substance use interventions as "a gaping hole." Although studies of alcohol treatment effectiveness sometimes report findings for sexual minority participants, they rarely report findings specific to sexual minority women. For example, Zajac et al [52] used data from 5 randomized clinical trials to compare the effectiveness of contingency management with financial incentives versus standard intensive outpatient care treatment among 920 LGB and heterosexual participants with a substance use disorder. Differences between LGB and heterosexual participants were compared across 3 substance use outcomes: treatment retention, the longest duration of abstinence, and percent negative substance use screens. Contingency management plus intensive outpatient treatment did not show statistically significant differences for any of the 3 outcomes. However, the LGB group means were higher than those of heterosexual participants for treatment retention and the longest duration of abstinence. Although not strong enough to reach statistical significance, these differences were considered potentially clinically significant. Unfortunately, analyses aggregated LGB participants, which prohibited specific examination of outcomes among sexual minority women.

In another study that combined sexual (and gender) minority participants, Gilmore et al [53] evaluated Positive Change (+*Change*) with 24 undergraduate students from a large university in the Southwestern United States. Of the 24 participants, most (n=17) identified as cisgender heterosexual; 7 identified as sexual minority, gender minority, or both sexual and gender minority. The intervention included content from an integrated alcohol and sexual assault risk reduction program developed for women and a web-based adaptation of a brief motivational interviewing personalized feedback protocol. +*Change* had high usability and acceptability ratings among both cisgender heterosexual and sexual and gender minority participants. Differences based on sexual and gender identity were not examined because of the small sample size.

In the only intervention study undertaken with sexual minority women prior to 2020, Fals-Stewart et al [54] evaluated the efficacy of behavioral couples therapy plus individual therapy compared to individual-based therapy only among lesbian and gay couples, in which at least 1 partner had an alcohol use disorder. Treatment intervention components included developing recovery contracts with partners, teaching partners communication strategies and strategies for reducing triggers and exposure to alcohol, and increasing shared activities. Results indicated that among lesbian couples, those who received the behavioral couples therapy condition reported fewer heavy drinking days at 12-month follow-up compared to those receiving individual therapy only.

Pachankis et al [55] conducted a small (N=60) sexual minority women–adapted cognitive behavioral therapy (CBT) intervention that focused primarily on mental health. This waitlist-controlled trial, Empowering Queer Identities in Psychotherapy, was designed to help sexual minority women understand emotion-driven behavior, reduce emotional avoidance, and learn behavioral skills and other resilience-building strategies. Pachankis et al [55] found that Empowering Queer Identities in Psychotherapy demonstrated preliminary efficacy in reducing sexual minority women's depression, anxiety, emotion dysregulation, and rumination in the intervention compared to the waitlist control group. The

effects of alcohol use were marginally significant, with the immediate intervention group outperforming the waitlist control group. Minority stress responses were not significantly affected by the intervention. In line with previous research, findings suggested that greater attention to sexual minority women's elevated rates of trauma and hazardous drinking is needed to enhance CBT interventions for sexual minority women.

Boyle et al [56] examined the feasibility and efficacy of reducing alcohol-related risks using personalized normative feedback delivered within a digital competition designed to challenge negative stereotypes and norms about sexual minority women's drinking. This study was the first to find that activities aimed at correcting sexual minority women–specific drinking and coping norms via personalized normative feedback reduced alcohol consumption among participants receiving this condition compared to those in the control condition who received information about nonsexual minority–specific topics.

In a study conducted with Australian same-sex attracted women, Bush et al [57] used SMS text messaging to examine the feasibility, acceptability, and efficacy of an alcohol intervention called the Step One program. In total, 97 same-sex attracted women who met the criteria for hazardous drinking by scoring ≥8 on the Alcohol Use Disorders Identification Test were randomly assigned to the Step One condition (n=47; mean age 37 years old)—which included a variety of SMS text messages about the health benefits of reducing alcohol intake—or a control condition of messages containing a link to a website with health information and support services for LGBTQ+ people (n=50; mean age 34 years). Participants in both conditions showed significant reductions in alcohol consumption and improved well-being over 4 weeks. The frequency of help-seeking was low; only 4 intervention group participants and 3 control group participants sought help. In total, 10 participants in the intervention group were interviewed about acceptability. Overall findings indicated that the intervention needed to be revised prior to its implementation.

Except for the study by Bush et al [57], all the intervention studies described earlier were conducted in the United States. Although a variety of approaches were used (eg, personalized normative feedback, couples therapy, and CBT), they were all based on individual behavior change models, which have limited effectiveness for heavier drinkers [58]. Efforts that target individual drinkers typically ignore the fact that most drinking is social, occurring in the company of others, and that how much one drinks is influenced by others (eg, pressure to drink more or less).

In summary, sexual minority women have seldom been the focus of intervention studies. When included as part of LGBTQ+ samples, outcomes are rarely reported separately by gender and sexual identity. Consequently, given this population's social and structural marginalization, it is unknown whether existing treatment options are suitable for sexual minority women. Because the drinking patterns of sexual minority women appear to be in large part motivated by seeking social connection and a sense of belonging, any intervention developed for sexual minority women must address these social and affective needs [59-61]. An intervention that incorporates these elements within sober curiosity, a wellness movement that challenges the centrality of alcohol in social life and questions the notion that alcohol is required on all social occasions [62], offers a potentially scalable approach to alcohol interventions suitable for sexual minority women. Supported by popular and well-known periods of nondrinking such as "Dry January" or "Sober October," sober curiosity is geared toward developing longer-term, sustainable lower-risk drinking practices.

Potential Usefulness of an Intervention Based on Sober Curiosity

There is evidence of substantive social change regarding alcohol consumption, including the exponential rise in the marketing and availability of no or low alcohol (referred to as "NoLo") content wines, beers, and spirits [63,64] and a growing number of sober venues and events, as well as proliferation of web-based support forums that are based on sober curiosity tenets. For example, Grace [65], author of *This Naked Mind* and founder of The Alcohol Experiment, reported on February 22, 2023, that in less than 1 year, more than 80,000 people globally had subscribed to the This Naked Mind web-based alcohol reduction program; notably, most subscribers are women. Similarly, Club Soda in the United Kingdom reportedly has helped "tens of thousands" of people reduce their harmful drinking.

The sober curious movement encourages individuals to question the centrality of drinking alcohol in their daily lives, to make a conscious decision to "be curious" about their reasons for drinking, and to consider if drinking alcoholic beverages is necessary in situations where drinking would typically occur. The growing popularity of sober curiosity provides support for a more positive identity for light or nondrinkers than has been previously available. It offers opportunities for both personal and social change, recognizing that individual alcohol consumption behaviors cannot be separated from their contexts. However, no research has examined how sober curiosity or similar interventions to reduce alcohol consumption are perceived by sexual minority women. An established literature on the links between minority stress and poor health [66-68] provides strong evidence that the contexts in which sexual minority women live and experience life differ in important ways (eg, marginalized identities and shame) from heterosexual women's life experiences, making it critically important that such experiences be considered in any intervention effort to reduce sexual minority women's alcohol consumption.

Drawing on several decades of our own and others' research investigating and seeking to understand sexual minority women's drinking, we believe that a sober curious approach may increase the desire of sexual minority women to reduce alcohol consumption and increase their self-efficacy to resist drinking. Sexual minority women typically participate in alcohol-centric social contexts (social worlds) to connect with other sexual minority people, establish inclusive friendships with like-minded people, and gain social supports that are limited in other contexts [59,60]. These social worlds, although contoured by heavy drinking norms, can be especially helpful during periods of transition or stressful events (eg, coming out, experiencing violence, or relationship dissolution), contexts in

which sexual minority women may be more likely to drink heavily [69].

Sober curious approaches could promote wider availability of alternatives that meet important personal and interpersonal needs but do not involve drinking alcohol. This alternative is promising, given research that has found social norms, particularly perceived peer-drinking norms, are strongly predictive of heavy drinking among sexual minority women [32,70,71]. Sober curiosity focuses on shifting cultural and subcultural heavy-drinking norms (not just individual behavior), and interventions that are shaped around the philosophy of sober curiosity may be an important way to address persistent sexual orientation–related disparities in hazardous drinking among women. Sober curiosity is nonjudgmental; it emphasizes alcohol and its addictive properties rather than the person as the "problem." Research across various domains of sexual minority women's health suggests that approaches that are nonpathologizing and nonstigmatizing, that focus on community norms and social connection, and that emphasize health, wellness, and mindfulness are likely to be most effective for sexual minority women [72]. Yet, no studies have been conducted that use these approaches in conjunction with sober curious principles to address sexual minority women's drinking.

Therefore, we are conducting 2 studies that combined to use a variety of methods to explore the feasibility, potential usefulness, and key elements of a tailored intervention based on sober curiosity for sexual minority women. One of the studies includes focus groups and a national survey with sexual minority women in Scotland; the other includes in-depth interviews with sexual minority women in the United States, followed by a review of findings by 2 international panels of experts. The aims of this research are (1) to explore the perspectives of the drinking social worlds of sexual minority women, their awareness of the sober curious movement, perceptions of their own and their peers' drinking and desire to drink less, and perceived barriers and facilitations to changing their drinking behaviors and (2) to identify key elements of an alcohol reduction intervention tailored for sexual minority women.

Conceptual Framework

The conceptual framework informing our work incorporates "social world" perspectives [58] and tenants of the health equity framework [73]. The social worlds of heavy-drinking sexual minority women are characterized by a connection point that can be thought of as a space where drinking alcohol is perceived to be an important aspect of shared activities or of a shared culture [3]. Research addressing heavy drinking social worlds is nascent; yet, this perspective can provide a unique lens for understanding and addressing harmful drinking in at-risk populations. The health equity framework builds on 3 foundational concepts: equity at the core of health outcomes; multiple, interacting spheres of influence; and historical and life-course perspectives. It illustrates how complex interactions between people and their environments affect health behaviors and outcomes. The importance of each of these concepts for LGBTQ+ people is highlighted in a 2011 landmark report on LGBT health [74].

Why Scotland and the United States?

Scotland

Most sexual and gender minority health research, especially research on alcohol use, has been conducted in North America [14,75-78]. We chose to collect data from sexual minority women in Scotland because the sober curiosity movement appears to be more prominent in the United Kingdom than in other European countries and in most other parts of the world [79,80]. Further, hazardous drinking in the UK general population is more prevalent than in other countries in continental Europe [81], and alcohol-related harm is disproportionately higher in Scotland than in the rest of the United Kingdom [82]. In 2018, as part of a raft of evidence-based strategies to tackle this "alcohol crisis," Scotland became one of the first countries in the world to implement minimum unit pricing with the aim of reducing alcohol-related deaths and decreasing health care use [83,84]. Although relatively little research on alcohol use among sexual and gender minority people has been conducted in Scotland, or in the United Kingdom, limited research has documented higher rates of hazardous alcohol use in sexual and gender minority people in the United Kingdom relative to their heterosexual counterparts [85]. Thus, although no studies have compared rates of sexual and gender minority drinking in Scotland and in the United States, there is reason to believe that sexual minority women in each country are at heightened risk of harmful alcohol use. Our research aims to understand similarities and differences in the cultural contexts of sexual minority women's drinking in the 2 countries and how such differences impact sexual minority women's drinking.

The United States

Because Scotland's population is predominately White (only 4% are Asian, African, Caribbean or Black, mixed, or members of other ethnic groups) [86] and because we wanted to include diverse sexual minority women's perspectives, we chose to also collect data in the United States. We created a sampling frame consisting of diverse sexual minority women in regard to age, sexual and gender identity, race or ethnicity, education, and geographic residence from participants enrolled in an ongoing longitudinal study of risk and protective factors for hazardous drinking among sexual minority women [87].

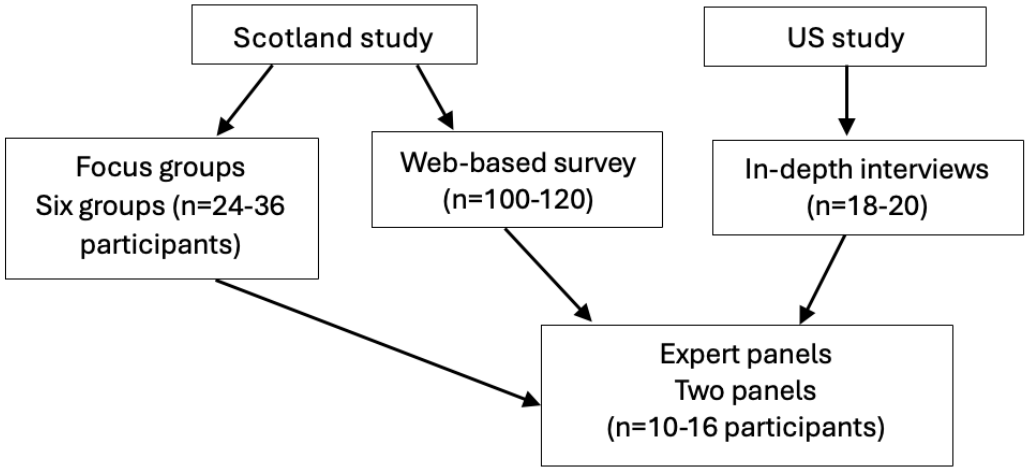
Methods

Study Design

We are currently conducting focus groups and a national web-based survey with sexual minority women in Scotland and in-depth individual interviews with sexual minority women in the United States. This mixed methods or triangulated approach, using both qualitative (focus group and individual interviews) and quantitative (web-based survey) methods conducted in 2 countries, was intentionally chosen to maximize understanding of similarities and differences in cultural contexts and influences on sexual minority women's drinking. Triangulation is commonly used in both qualitative and quantitative research and is especially helpful in understanding complex human behavior. Triangulating methods and data can enhance the

validity and credibility of findings, mitigate potential biases, and give more confidence in the findings [88]. Figure 1 summarizes the qualitative and quantitative components of the studies and includes the planned number of participants in each component of the studies.

Figure 1. Overview of research components.



Focus Groups

The Scotland study will include 5 to 6 focus groups, each with a purposive volunteer sample of 4 to 6 adult sexual minority women. Focus group interviews are conducted in person or via Zoom (Zoom Video Communications) and are led by team members (primarily LB and BM) who are experienced qualitative researchers with expertise in alcohol use among sexual minority women; some team members identify as part of the sexual minority women's community. Focus group discussions are organized around specific topics and include broad areas of inquiry [89] developed by the research team. The focus group interview guide was adapted following the first and second focus group sessions to improve clarity and more effectively address the study aims. Areas of inquiry include (1) perceptions of alcohol use in sexual minority women's "communities" in Scotland; (2) openness to reducing alcohol consumption (are they sober curious?); (3) factors and barriers that impact sexual minority women's decisions and preparedness to reduce consumption (eg, drinking norms and drinking behaviors of peers); (4) attitudes toward, perceived availability of, and experiences with NoLo alcohol beverage alternatives; (5) conditions that would support reducing their own and other sexual minority women's alcohol consumption; (6) messaging and framing about reducing alcohol consumption that sexual minority women would find appealing (or off-putting); and (7) the potential benefits and barriers to a successful sober curious alcohol reduction intervention with sexual minority women. The focus group interview guide is available upon request.

Web-Based Survey

We will complement data collected in focus groups with data collected from a larger convenience sample of Scottish sexual minority women (N=100-120) recruited to participate in a web-based Qualtrics survey. Our team developed the survey using existing literature and a previous study on sober curiosity conducted by Lunnay et al [90] with midlife women in Australia. We pilot-tested the survey with 10 sexual minority women in Scotland and the United States prior to its official launch. The survey includes approximately 80 questions (3-5 questions per page) and takes an average of 15-20 minutes to complete. Like focus groups, the survey includes questions about demographic characteristics, patterns of alcohol use (eg, frequency and quantity), drinking contexts, drinking companions, drinking motivations and perceived drinking norms of peers, as well as help-seeking, familiarity with the sober curious movement, or aspects of it (eg, Dry January, Sober October, and NoLo alcohol beverages), and perceived barriers and facilitators to reducing alcohol consumption. We also include a few open-ended questions to collect qualitative data that will be used to triangulate data from the focus groups (eg, participants' descriptions of barriers and facilitators to reducing drinking).

Scotland Study Recruitment

We are recruiting adult (age 18 years or older) sexual minority women who reside in Scotland and who report moderate (between 7 and 14 units per week) or heavy (>14 units per week) alcohol consumption. Although there is no agreed international definition of low- or moderate-risk drinking [91,92], researchers in the United Kingdom [93] have used 7-14 units per week to indicate "moderate" drinking. Efforts to support effective behavior change must consider local sociocultural contexts and build on existing community assets. In each country, we are working to recruit diverse samples of sexual minority women in terms of age, education, geographic location (eg, rural and urban), and identity (eg, lesbian, bisexual, queer, and nonbinary gender). In addition, because sexual minority women's "communities" are not homogenous, and distinct groups within it are more or less marginalized and have different levels of capacity and resilience than others, we are using recruitment strategies that attract sexual minority women across different sociodemographic statuses. We are posting advertisements in local LGBTQ+ publications, advertising the study via social media and relevant mailing lists, and conducting outreach through partnerships with LGBTQ+ organizations in Scotland (eg, *LGBTQ+ Health & Wellbeing*, *LGBTQ+ Youth-Scotland*, and *The Equality Network*) and LGBTQ+ sports groups. Interested individuals are directed to a web-based screener where

they answer several questions about their age, sexual identity, residence, and current drinking to determine eligibility. Prospective participants are informed that, in appreciation of their time and contributions, they will receive an Amazon gift card worth approximately US $38 for participation in a focus group or US $12.40 for completion of the web-based survey.

US Study

In-Depth Interviews

In a separate but complementary study, we are conducting in-depth interviews with a purposive, diverse sample of approximately 18-20 sexual minority women in the United States. Interviews lasting approximately 60 minutes are conducted via Zoom or phone by 2 researchers (LB and Ellen Riggle) with extensive qualitative training and research experience in sexual minority women's health. Questions explore the same areas of inquiry as the focus groups in Scotland. For example, sexual minority women are asked about their perceptions regarding alcohol use within sexual minority women's social worlds and about their personal experiences with drinking. During interviews, we ask if sexual minority women are aware of the sober curiosity movement, are interested in considering ways to reduce their alcohol consumption (are they sober curious?), factors and barriers that impact their decisions and preparedness to reduce consumption, alternatives to alcoholic beverages and alcohol-based events perceived to be available, attitudes toward and experiences with NoLo beverages, and perceptions of conditions that would support consideration of reducing their own and other sexual minority women's alcohol consumption. The US interview guide is available upon request.

Recruitment for US In-Depth Interviews

We are recruiting adult sexual minority women who participated in a longitudinal study of drinking among sexual minority women led by first author Hughes [14, 94]. This approach permits more efficient and accurate identification of sexual minority women who either drink at moderate or heavy levels (ie, at least 14 drinks per week on average) or reported that they were thinking of cutting down on their alcohol use. The sample will include sexual minority women with diverse demographic characteristics, such as age, race or ethnicity, sexual identity (eg, lesbian, bisexual, and queer), residence (urban or rural), educational level, and relationship status. Interviews last 60-90 minutes, and participants are given a US $50 Amazon gift card in appreciation of their time.

Ethical Considerations

The Scotland study received ethics approval from Glasgow Caledonian University (HSL NCH 22 040), and both the Scotland and the US studies received ethics approval from Columbia University (AAAU7672), the lead institution. The studies were reviewed and deemed to be exempt given that they were judged to pose little or no risk to the research participants. For the Scotland focus groups, informed consent is obtained by the researchers prior to commencing research procedures. An information sheet is provided to individuals who participate in the web-based survey with passive consent implied by virtue of survey completion. For the US study, verbal informed consent is obtained by the project manager prior to scheduling each participant's interview. Following a verbal review of the consent form, questions are asked of each participant to ascertain that they understand what is involved in their participation. Documentation of consent is maintained on a password-protected end-point device. Participants receive a copy of the consent form via email for their records. Scotland focus groups are conducted either in person or on Zoom (to accommodate the participation of sexual minority women who live in rural or other outlying areas). Participants are invited to provide a pseudonym to be used in focus group discussions, and any names or information that could potentially identify a participant are redacted from the transcripts. Each focus group participant is assigned a unique ID number linked to their demographic and contact details, which are saved separately on a password-protected system in a password-protected file. Audio files are destroyed after the transcripts are reviewed and verified. Deidentified transcripts will be available to members of the research team for analyses. Scotland survey participants are also each assigned a unique ID number and are asked to provide an email address in order to receive the link for the study incentive (Amazon gift card). The key that links ID numbers to email addresses is kept on a password-protected system in a password-protected file separate from the dataset with the survey responses. The ID numbers are used to keep track of who has been sent a gift card. Individual interviews in the United States are conducted by phone or Zoom. Audio files are coded with the participant's identification number but without any information that could be used to identify them. The list that links codes to names and addresses is kept on a password-protected end-point device in a password-protected file separate from the audio files. Once interviews are completed, the audio files of the interviews are saved on a secure electronic system (ie, Box). Once the interview transcripts are reviewed and verified, the audio files will be destroyed.

Data Analysis

Given the range of data sources used, it is essential to triangulate data to address the completeness, convergence, and dissonance of key themes. We will analyze data from each of the 3 sources separately.

Data from the focus groups (Scotland) will be analyzed using Krueger's framework analysis [95] for narrative focus group data that considers words, context, internal consistency, frequency of comments, extensiveness of comments, intensity of comments, specificity of responses, and big ideas. This process involves six interconnected steps: (1) data collection; (2) immersion in data; (3) memoing to identify ideas and concepts; (4) indexing descriptive statements; (5) formation of categories, drawing on within- and between-group comparisons; and (6) interpretation. In-depth interview data from the US study will be analyzed using inductive thematic analysis drawing on six phases described by Braun and Clarke [96]: (1) immersion through reading and rereading data and noting initial ideas, (2) generating initial codes, (3) searching for themes, (4) reviewing themes, (5) defining and naming themes, and (6) producing the report, including selection and use of extract examples. Thematic analysis is a method for identifying and organizing patterns of meaning, or themes, across a dataset to make sense of shared

meaning and collective experiences [97]. Analyses of the Scotland and US qualitative data will be guided by a social worlds' perspective, which aligns with constructivist and symbolic interaction theory and "supports identification and investigation of groups below the level of society but above the level of friendship groups, where relatively coherent heavy drinking cultures may operate" [3].

Although data will be analyzed separately, we will be particularly interested in comparing themes from the focus groups and the in-depth interviews to identify similarities and differences in the findings and to identify patterns and relationships across data to validate or corroborate findings. We expect that these comparisons will provide a more comprehensive understanding of factors that serve as facilitators or barriers to sexual minority women who wish to reduce their alcohol intake.

Several strategies will be used to enhance the trustworthiness of the qualitative findings [98]. These include prolonged engagement with the narrative data, researcher triangulation, with multiple researchers each bringing their perspective to analyses, and regular peer debriefing and reflexive meetings via Zoom with research team members (authors of this paper). The team members are part of a research collaboration among Columbia University School of Nursing, Center for Sexual and Gender Minority Health Research and international partners at Glasgow Caledonian University, Research Centre for Health, and Torrens University Australia, Research Centre for Public Health, Equity and Human Flourishing. The research team includes individuals from multiple disciplines (eg, public health, sociology, psychology, nursing, and social work). More than half of the team members identify as being part of either sexual minority or gender minority communities. As a check to ensure findings accurately reflect the experiences and perspectives of the participants, member checking will involve validating the findings with stakeholders involved in the research (eg, members of the research team) and with at least 3 focus group participants and 3 participants from the in-depth interview portion of the study.

Survey data will be analyzed using SPSS (version 29; IBM Corp). Analyses will initially screen for and correct outliers, data entry errors, or other inconsistencies. We will decide whether to use cases with incomplete data (eg, surveys that were only partially completed) based on the number and relevance of key questions that have valid responses. All statistical tests, for example, comparing rural versus urban sexual minority women, will be 2-sided (α=.05). Given the exploratory or descriptive nature of the study, we believe that data from 100 to 120 survey participants will provide sufficient information to inform our research aims. We will explore how findings from closed- and open-ended survey questions map onto key themes from the qualitative studies.

Comparisons of the perceptions and experiences of sexual minority women in Scotland and in the United States will identify thematic commonalities and differences and to formulate hypotheses about how drinking alcohol among sexual minority women relates to social contexts, group identity, and cultural norms. Although we expect to find similarities in the cultural contexts of sexual minority women across these 2 high-income countries, understanding differences and how they shape drinking norms and behaviors will elucidate key elements of a future tailored intervention aimed at helping sexual minority women reduce the risk of harmful drinking.

Results

The study was funded in July 2023, and data collection began in September 2023 after the study received ethics approval from the 2 lead institutions (August 2023). The Scotland study received ethics approval from Glasgow Caledonian University (HSL NCH 22 040) and from Columbia University (AAAU7672). As of December 2024, we completed 4 of the 6 planned focus groups (Scotland) and 18 of the 20 planned in-depth interviews in the United States. Data collection for the web-based survey in Scotland was paused in October 2024 for several months after discovering that about two-thirds of the approximately 150 responses were invalid (exhibited evidence of bot automation, eg, duplicate IP addresses). To address this, we removed the Amazon gift card incentive from recruitment advertisements and submitted the revised protocol to the 2 human participant review committees for ethical approval. As of December 2024, we have 64 valid survey responses. We expect to complete data collection in both Scotland and the United States by June 2025.

Results of qualitative analyses (data from focus groups and individual interviews) will be organized and summarized as themes, and results of survey data analyses summarized in tables. Findings from the studies will be presented to 2 international panels of experts; each panel will include 4-6 experts. Panel participants will consist of researchers with expertise in sexual minority women's use of alcohol, the development of alcohol interventions for women, or sober curiosity approaches. This will serve 2 purposes: peer review (having other researchers or experts review the findings to ensure their validity and to identify potential biases) and identification of key factors to be included in a planned intervention that will incorporate tenants of sober curiosity. We will use Acceptability, Practicability, Effectiveness, Affordability, Side-Effects, and Equity [99] criteria to consider important socioecological and cultural factors that provide an overarching understanding of key elements of an intervention tailored to assist sexual minority women to reduce harmful drinking.

Discussion

Principal Findings

To our knowledge, this project is the first attempt to investigate sexual minority women's openness and readiness to reduce alcohol consumption within a sober curiosity framework and with the view to designing an intervention tailored for sexual minority women. Understanding how sexual minority women might justify or rationalize their alcohol consumption in different contexts and social worlds, their interest in changing their drinking behaviors to reduce their alcohol consumption, and their perceived barriers and facilitators to doing so will provide new insights. We anticipate that findings will provide essential

preliminary data to develop (and subsequently evaluate) an intervention that incorporates tenets of the sober curious movement and is aimed at reducing harmful drinking among sexual minority women, with scalability to other high-income countries with similar drinking-related social norms. Such an intervention will respond to sexual minority women's reported need for social connection and will support alcohol reduction strategies while retaining social support.

Strengths and Limitations

First, the use of mixed methods to collect data, including both qualitative and quantitative methods, and the inclusion of 2 countries are strengths of this research. For example, while the perspectives of sexual minority women about alcohol use and sober curiosity in the web-based survey may be influenced by misunderstandings of the questions, focus group and individual interviews allow for such misunderstandings to be explored and corrected. However, relationships among drinking behaviors and patterns, sexuality, and gender are complex [5,30,60,100], and information to be gleaned from the current research may not capture these complexities. For example, qualitative research from Scotland and Australia highlights the ways in which drinking alcohol facilitates engagement with LGBTQ+ communities, aids in expressing sexuality and identity, and challenges heteronormative perspectives of women's drinking [30,100]. Our focus on sober curiosity and ways that sexual minority women might reduce their alcohol consumption does not consider the performative role that alcohol use, including heavier use, plays in "doing" gender and sexuality and in connecting with the LGBTQ+ community in pleasurable and meaningful ways. Future work should consider the complex meanings and social functions of alcohol in the lives of sexual minority women.

Second, because findings are from nonrepresentative samples of sexual minority women in Scotland and in the United States, they have limited transferability. Both countries are characterized by high income and relatively low levels of stigma (eg, compared to non-Western and low-income countries). There may be important cultural differences that shape alcohol use among sexual minority women who live in countries and cultural contexts where either same-sex sexuality or alcohol use among women is more stigmatized. Further, given limited time and resources, we may not be able to reach as diverse a sample as intended. For example, factors such as poverty and homelessness or disability influence sexual minority women's drinking. More research using mixed methods and larger samples across different cultural contexts is needed to further refine the understanding of factors that influence sexual minority women's drinking and perspectives about sober curiosity.

Third, although trauma is not a focus of the studies, it is well documented that experiences of lifetime trauma, particularly adverse childhood experiences, are more prevalent among sexual minority women [24] and are strongly linked with alcohol use among sexual minority women [14,101]. Thus, our failure to address trauma may limit important insights about key elements of an alcohol reduction intervention for sexual minority women.

Conclusions

The sober curious movement is gaining positive attention and momentum in mainstream society in many parts of the world. Now is an important time to leverage this momentum to address heavy drinking social norms and behaviors within sexual minority women's social worlds. An intervention developed and offered to sexual minority women within this growing movement may provide an acceptable and effective way to support sexual minority women to reduce alcohol-related harms. However, such interventions will likely need to recognize the positive aspects of drinking (eg, facilitating social connections) and the pervasive impact of trauma on sexual minority women's drinking as well as the linkages among connection, coping, and identity, if they are to be optimally effective.

Acknowledgments

The studies were funded by 2 pilot program grants from the Columbia University School of Nursing: the Elaine Larson Global Development Pilot Fund and the Center for Sexual and Gender Minority Health Research Pilot Program. The authors appreciate the time and contributions of the research participants. The authors acknowledge investigator Ellen Riggle (University of Kentucky), coinvestigator on the US study, Amy K McEwan (Glasgow Caledonian University), research assistant on the Scotland study, as well as Sergey Kisselev (Columbia University) for programming the Scotland web-based survey in Qualtrics.

Data Availability

The datasets generated and analyzed as part of this project will be available from the corresponding author on reasonable request after the research team has completed analyses related to the study aims.

Conflicts of Interest

None declared.

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Abbreviations

AA: Alcoholics Anonymous
CBT: cognitive behavioral therapy
LGB: lesbian, gay, and bisexual
LGBTQ+: lesbian, gay, bisexual, transgender, queer or questioning
WHO: World Health Organization

Edited by A Schwartz; submitted 15.06.24; peer-reviewed by J Patterson, E Nicholls; comments to author 25.07.24; revised version received 14.10.24; accepted 21.01.25; published 03.03.25.

Please cite as:
Hughes TL, Bochicchio L, Drabble LA, Lunnay B, Whiteley D, Scheer JR, Meadows B, Ward P, Emslie C
Using a Sober Curious Framework to Explore Barriers and Facilitators to Helping Sexual Minority Women Reduce Alcohol-Related Harms: Protocol for a Descriptive Study
JMIR Res Protoc 2025;14:e63282
URL: https://www.researchprotocols.org/2025/1/e63282
doi:10.2196/63282
PMID:40053757

Protocol

Development and Impact of a Community-Delivered, Multisectoral Lifestyle Management Service for People Living With Type 2 Diabetes (Logan Healthy Living): Protocol for a Pragmatic, Single-Arm Intervention Study

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Abstract

Background: Type 2 diabetes is the fastest-growing chronic condition in Australia, with higher prevalence in disadvantaged groups. Logan Healthy Living by UQ Health Care is a proof-of-concept, interprofessional allied health clinic focused on supporting people with and at risk of type 2 diabetes in Logan, a region in South East Queensland, Australia, with high levels of health inequity. Logan Healthy Living is supported by the Queensland Government through Health and Wellbeing Queensland and a broader multisectoral alliance including primary health care; tertiary hospital and health services; and government, community, and university sectors.

Objective: This paper describes the establishment of Logan Healthy Living and outlines the evaluation protocol for the service's type 2 diabetes lifestyle management program.

Methods: The context and setting of Logan Healthy Living are presented, and the process for establishing the multisectoral partnerships, development and governance of the service, and the facility are described. The lifestyle management program is an 8-week, group-based program that includes 1 hour of education and 1 hour of supervised, individually tailored exercise each week. The theoretical underpinnings and the program are described in detail. The Reach, Effectiveness, Adoption, Implementation, and Maintenance (RE-AIM) framework will guide evaluation of the program and inform key questions regarding the number and characteristics of the clients (reach); diabetes-related distress, health behaviors (physical activity and diet), quality of life, self-management self-efficacy, loneliness, community involvement, anthropometric measures, hemoglobin A_{1c} levels, physical function, and health care use (effectiveness); referral pathways (adoption); fidelity, appropriateness, acceptability, and costs (implementation); and long-term effectiveness (maintenance). Data will be drawn from a purposefully embedded minimum dataset and data registry, with the process for designing and embedding data collection into practice (via surveys, in-person measures, and client management software) described in detail.

Results: Ethics approval has been obtained for the data registry. Logan Healthy Living is a 4-year proof of concept that concludes on December 31, 2024, with findings expected to be reported starting in 2025.

Conclusions: While multisectoral responses are needed for complex community health challenges, the processes for achieving these are rarely documented, and the description of the development of Logan Healthy Living has the potential to inform future partnerships. The findings of the evaluation will provide important new knowledge on the impact of a community-delivered type 2 diabetes program on individuals, the community, and the health system in an area of high health inequity.

International Registered Report Identifier (IRRID): DERR1-10.2196/69477

(JMIR Res Protoc 2025;14:e69477) doi:10.2196/69477

KEYWORDS

type 2 diabetes; lifestyle management; allied health; evaluation; protocol

Introduction

Background

Type 2 diabetes is a chronic condition where the body becomes resistant to the normal effects of insulin and gradually loses the capacity to produce enough insulin in the pancreas [1]. The onset of type 2 diabetes is associated with both nonmodifiable (eg, genetic) and modifiable (eg, health and behavioral) risk factors [1]. Worldwide, in 2020, type 2 diabetes was the ninth leading cause of death, affecting 7% of the population, with prevalence rates only expected to increase [2]. In Australia, type 2 diabetes impacts an estimated 1.2 million people [1], with a further 2 million having prediabetes [2]. It is the fastest-growing chronic condition in Australia [1], with health system expenditure estimated at Aus $3.4 billion (US $2.1 billion) per year [3]. Type 2 diabetes has a significant impact on individuals. Along with the symptoms of the disease itself, many people experience diabetes-related complications (eg, retinopathy, peripheral vascular disease, and ischemic heart disease) and are at increased risk of multimorbidity (eg, cardiometabolic, vascular, and mental health conditions), which collectively impact their quality of life, impair functioning, and increase financial and economic burden [4]. Type 2 diabetes disproportionately affects disadvantaged groups. For example, people of a low socioeconomic status and with low levels of education [5], immigrants, and those from culturally and linguistically diverse backgrounds have increased risk of type 2 diabetes [6]. Furthermore, the intersection of disadvantage is likely to magnify risk and burden of disease [7].

Management of type 2 diabetes is primarily focused on achieving glycemic control through modification of health behaviors (typically physical activity and nutrition) and, where required, medication. Evidence-based management of type 2 diabetes emphasizes person-centered, team-based care with integrated long-term treatment approaches, as well as the involvement of social community support [8,9]. Self-management, where the person with type 2 diabetes works in partnership with their social supports and health professionals to understand, manage, and optimize their health, is the goal. Management of modifiable risk factors is a core component of self-management, with such strategies focused on building positive health behaviors, including physical activity and nutrition, and optimizing psychological well-being [9,10]. Multidisciplinary, group-based approaches to lifestyle modification have consistently been shown to positively impact a range of health and well-being outcomes for people living with type 2 diabetes [11]. To support this in practice, the Australian National Diabetes Strategy (2021-2030) has called for a multisectoral response by government and communities to provide the integrated care required [12].

UQ Health Care (a not-for-profit health care wholly owned enterprise of The University of Queensland) has established Logan Healthy Living as a specialist clinic designed to respond to this need [13]. Purposefully established in South East Queensland in the City of Logan, an area of Queensland with high burden of type 2 diabetes and intersectional disadvantage, Logan Healthy Living was designed with the aim of reducing the burden of disease on individuals, the community, and the health system [13]. The core service of Logan Healthy Living is a group-based lifestyle management program delivered by an interprofessional allied health team focusing on supporting people living with and at risk of type 2 diabetes in Logan. The program has 3 main foci: physical activity, healthy eating, and well-being [14]. Logan Healthy Living is a 4-year proof of concept delivered by a Queensland-first alliance among primary health care; tertiary hospital and health services; and government, community, and university sectors.

A key feature of the establishment of Logan Healthy Living was the integration of an outcome-based funding model—a model that prioritizes value-based care and patient-centered outcomes and leverages multisectoral partnerships. Critical to value-based care models is the collection and use of data to continually evaluate the impact of the service on the participants as well as the health system more broadly [15]. Moreover, leveraging this approach for practice-based evidence generated in “real-world” settings can add to the currently limited evidence on community-based, self-management programs for people living with or at risk of type 2 diabetes [16]. With dimensions at both the individual level and multiple ecological levels, the Reach, Effectiveness, Adoption, Implementation, and Maintenance (RE-AIM) framework [17,18] offers a balanced and pragmatic approach to the evaluation of applied community-delivered programs considering factors such as the characteristics of the participants who take up the program (reach) and participant satisfaction (implementation). The RE-AIM framework has been applied across multiple evaluations, including diabetes health coaching [19], diabetes prevention programs [20], and telephone-delivered type 2 diabetes support [21]. To simultaneously support reporting for the outcome-based funding model and evaluate the real-world

impact of a routinely delivered community program, a comprehensive continuous evaluation protocol informed by the RE-AIM framework was developed.

Objectives

The purpose of this paper is to describe the development of Logan Healthy Living and the protocol for program evaluation of this allied health care service. Specifically, we describe the context and setting of the service, the multisectoral partnership and co-design activities contributing to the service development, governance, and participants and recruitment channels. We then describe the protocol for the evaluation of the service according to the RE-AIM framework.

Methods

This protocol was prepared using the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) checklist [22].

Context and Setting

Logan Healthy Living by UQ Health Care is located in the City of Logan in South East Queensland, Australia. With an estimated population size of 345,098 [23], the City of Logan is identified as one of the most culturally and linguistically diverse and socioeconomically disadvantaged areas in Australia. The proportions of the population speaking a language other than English at home; being born overseas; identifying as Aboriginal or Torres Strait Islander, Māori, or Samoan; being unemployed; and having one or more chronic health conditions are above South East Queensland averages [23]. The region has also experienced rapid population growth and has an aging population [24]. The City of Logan has a strong focus on community services and fostering connection, with a wide range of no- and low-cost community social programs, including Logan City Council Libraries; arts, culture, and heritage initiatives; sport and recreation facilities (including the Active and Healthy program offering >100 weekly free and low-cost health and well-being activities); and parks and community gardens. Logan also has a diverse range of cultural groups and grassroots networks supporting community connection [25].

In Logan, estimates of the prevalence of type 2 diabetes and associated indicators of burden of disease are consistently higher than state-based estimates for Queensland. Almost 20% (18.5%) of people aged ≥75 years living in Logan have type 2 diabetes (12.4% for those aged 55-74 years and 1.7% for those aged 18-54 years) [26], with the third highest rate of insulin-treated type 2 diabetes in Australia (an indicator of advanced or nonresponsive progression of the disease) [24]. Type 2 diabetes accounts for 31% of potentially preventable hospitalizations in Logan, making it the leading cause of potentially preventable hospitalizations [24]. Those living with type 2 diabetes in the area are also disproportionately likely to die from diabetes-related causes, with the average diabetes-specific mortality rate in Logan being 32% higher than that for Queensland in general [24].

Development of Logan Healthy Living

The concept of a multisectoral, allied health–delivered lifestyle management program for people living with type 2 diabetes in Logan emerged from an existing partnership between UQ Health Care and Metro South Health (the region's public health care provider) [27]. In 2014, Metro South Health and UQ Health Care established an innovative, integrated primary-specialist model of care for the medical management of people with complex diabetes, the "Beacon" model [28]. The Beacon model saw complex diabetes management provided within a community practice by a multidisciplinary team consisting of an endocrinologist from Logan Hospital, 2 to 3 general practitioners (GPs) with a special interest in diabetes from UQ Health Care, and a diabetes nurse educator from the Metro South Health community team who provided 1:1 consultation (at times before the GP with a special interest in diabetes to assist in triage). The aim of the Beacon model was to build capacity in primary care for managing complex diabetes through advanced management plans and subsequently diverting people with type 2 diabetes from tertiary care. While the Beacon model demonstrated favorable outcomes in changes in hemoglobin A_{1c} (HbA_{1c}) concentration and the percentage of patients meeting combined clinical targets of HbA_{1c} concentration, blood pressure, and low-density lipoprotein cholesterol [29], key stakeholders acknowledged that the Beacon model alone was not sufficient to address the rising community need. Moreover, it lacked a health behavior change program focused on self-management—a critical component for the management of type 2 diabetes [11].

To address these needs, in approximately 2019, what would eventually be known as "Logan Healthy Living" was envisioned, expanding on the existing partnership between Metro South Health and UQ Health Care and integrating learnings from the Beacon model and UQ Health Care's experience in delivering interprofessional, allied health services at other sites. The first phase of service development was establishing an alliance of partners underpinned by a commitment to prevent chronic disease and keep people well and out of hospital in Logan. UQ Health Care and Metro South Health led the establishment of the alliance, which in turn also included the Brisbane South Primary Health Network, The University of Queensland, and Griffith University. By early 2020, the alliance had established a proof-of-concept model for a comprehensive lifestyle management program delivered by an interprofessional team of allied health professionals and infused with a student allied health workforce.

Concurrently, in 2019, the Queensland Government established the state's first prevention agency, Health and Wellbeing Queensland [30]. The concept of Logan Healthy Living, a service delivering comprehensive lifestyle management programs to support behavior change and self-management, was put to the board of Health and Wellbeing Queensland by UQ Health Care and Metro South Health on behalf of the alliance. The proposal was strongly aligned with the vision and strategic plan of the newly formed Health and Wellbeing Queensland, which included developing and trialing new models of care for the prevention and management of chronic disease.

Here, the intention was to reduce pressure on the tertiary health care system, address health inequities, and build multisectoral partnerships that drive system-level change for improved health and well-being outcomes. In 2021, Health and Wellbeing Queensland joined the alliance, with UQ Health Care and Health and Wellbeing Queensland entering into a 4-year agreement (2021-2024) to support the delivery of a tailored lifestyle management program. UQ Health Care secured additional revenue agreements and financial contributors to deliver on the commitment to reduce financial barriers for participants. The UQ Health Care and Health and Wellbeing Queensland service-level agreement outlined a comprehensive suite of deliverables and biannual key performance indicators. These key performance indicators were designed to evaluate the program according to the RE-AIM indicators across the 3 priorities identified previously (reduce the burden of disease on individuals, the community, and the health system). Examples of the agreed upon key performance indicators are summarized in Table 1.

Table 1. Examples of key performance indicators for Logan Healthy Living.

Evaluation domain	Key performance indicator
Reach	• Participant's type 2 diabetes status (at risk, newly diagnosed, complex, or chronic) • Participant's demographic characteristics • Participant retention • Participant attrition
Effectiveness	• Participant's knowledge, health literacy, and intention to change • Participant's healthy behavior action (health behavior change and anthropometric measures) • Health system impact
Adoption	• Referral pathways
Implementation	• Participant satisfaction • Staff satisfaction • Participant safety (adverse events) • Student training
Maintenance	• Participant sustained healthy behavior • Sustainable funding

The development and design of the service was community led and iteratively co-designed with key stakeholders, including consumers. Activities included participant journey mapping to inform program and resource development, consultation with student placement providers, and learning needs assessments for local GPs. A key event for consumer and stakeholder engagement was a half-day "design-jam" led by UQ Ventures and held on campus at Griffith University in Meadowbrook, where approximately 60 end users, delivery providers, academics, clinicians, community leaders, and representatives of other key stakeholders (eg, Metro South Health, Brisbane South Primary Health Network, and the Aboriginal and Torres Strait Islander Community Health Service) came together to progress their combined vision and implementation plan for the service. Subsequent planning days have also been hosted, which have similarly included Logan Healthy Living staff, key stakeholders, and consumers.

Simultaneously, the plan for routine collection of reporting and evaluation data was co-designed by key stakeholders, including researchers from The University of Queensland; the Logan Healthy Living Clinical and Operations Manager, administration team, and clinicians; and relevant content experts. Key to successfully collecting the range and breadth of data required was the intent to embed data collection into routine service delivery. Led by a researcher employed by the Health and Wellbeing Centre for Research Innovation (a research center jointly funded by The University of Queensland and Health and Wellbeing Queensland; SG), along with a senior academic experienced in evaluation (GH) and a data analyst (EW), a pragmatic data collection and consent process was co-designed and embedded into daily operations. Data are collected through both practice management software (Gensolve) and clinical trial software (REDCap [Research Electronic Data Capture]; Vanderbilt University) and facilitated day to day by the Logan Healthy Living clinical team, with technical and content support on an as-needed basis from The University of Queensland. Implementation of the data collection process was supported by on-site training sessions and a comprehensive manual developed by the data analyst. The Clinic and Operations Managers have been essential in establishing and building a culture for collaboration and prioritization of data collection.

Facilities

Logan Healthy Living went live for operations in July 2021. The service initially operated from Griffith University Logan Healthcare Centre, where it was intentionally colocated with the Beacon Clinic and Metro South Health Chronic Disease Diabetes Service (which included diabetes educators, nurse practitioners, and a podiatry service). In February 2023, Logan Healthy Living moved into its permanent, purpose-built location in a dedicated health and medical clinic, Meadowbrook Medical Centre, colocated with the UQ Health Care Meadowbrook GP clinic and the Logan Hospital endocrinology outpatient services (Logan Endocrine and Diabetes Service). The Meadowbrook Medical Centre is centrally located in the City of Logan and

positioned within the community's transport and retail hub, Logan Hospital, and the Logan Healthy Kids Club and Good Start programs operated by Children's Health Queensland. The site is also set to become part of a larger health precinct, with a planned staged expansion of Logan Hospital and an additional 2 private hospitals.

Logan Healthy Living occupies 400 m^2 at Meadowbrook Medical Centre and includes a gym floor, 5 curtained consultation spaces, 2 individual consultation rooms, 2 large private rooms (used for staff or student rooms or for group education sessions), and an integrated open space dedicated to delivering group education. The open gym includes a range of exercise equipment, including cardiovascular training equipment (treadmill and stationary bicycle), parallel bars, steps and stairs, and resistance and balance training equipment. UQ Health Care invested in state-of-the-art resistance training machines by HUR Australia [31] that use air resistance and SmartTouch software for automatically programming and tracking load and equipment position (eg, seat heights), with participants tapping on and off the equipment with a personalized radio-frequency identification wristband. HUR Australia equipment was selected to reduce the barriers and improve safety with resistance training for older adults and new exercisers; the HUR Australia equipment is fully automated and applies smooth and consistent resistance across the range of motion.

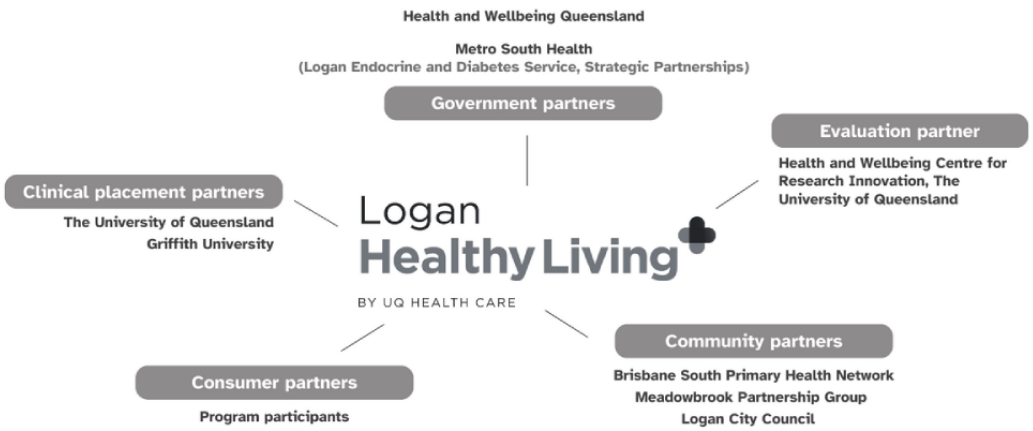
The clinic is staffed by a range of allied health professionals, including physiotherapy, exercise physiology, dietetics, diabetes education, and health psychology professionals. With its student-infused model, the service also provides clinical education and placements for students from Griffith University and The University of Queensland. These include clinical placements for physiotherapy, exercise physiology, dietetics, and psychology students (ranging from 4 to 20 weeks in length) and project placements in a wide range of health disciplines such as nutrition and dietetics, pharmacy, social work, and health service management. Students from a range of disciplines work together to provide an interprofessional model of care. Beyond providing health care services, Logan Healthy Living is also further embedding itself into the community by contributing to the development and career selection of a locally based workforce, with the aim to promote workforce sustainability in the region. Examples of these activities include facility tours with question-and-answer sessions and opportunities for work experience with the Logan Healthy Living team for local high school students with interest in health careers.

Governance

Logan Healthy Living is governed by a multisectoral steering committee that is cochaired by UQ Health Care and Health and Wellbeing Queensland. Beyond UQ Health Care and Health and Wellbeing Queensland, the steering committee includes representatives from The University of Queensland, Griffith University, Metro South Health, Logan Hospital, Brisbane South Primary Health Network, and Logan Healthy Living participants. Members of the steering committee are responsible for providing program leadership and direction (eg, understand strategic implications and outcomes and accept responsibility for program strategy and overall benefit realization) and governance (eg, risk identification and mitigation, stakeholder management, and monitoring of progress) and maximizing program benefits (eg, monitor program outputs and monitor implementation and evaluation). Additional stakeholders are also consulted by the steering committee, such as broader consumer groups, the Aboriginal and Torres Strait Islander Community Health Service, Children's Health Queensland, and Diabetes Australia.

Logan Healthy Living is connected to the broader community governance of the Logan region through the Meadowbrook Partnership Group. Established in 2018, the group comprises representatives from key organizations who are positioned to influence integration and impact in Logan. Membership includes Brisbane South Primary Health Network; Logan City Council; Metro South Health; Economic Development Queensland; Loganlea State High School; The University of Queensland; Griffith University; and the Department of State Development, Infrastructure, Local Government, and Planning. Collectively, the membership represents state, federal, primary care, education, and local government stakeholders. All members have strong community relationships and understanding of local issues. Logan Healthy Living (clinical and operations manager) and UQ Health Care (chief executive officer) are members of the Meadowbrook Partnership Group. Figure 1 shows the network of key stakeholders involved in the development and delivery of Logan Healthy Living.

Figure 1. Logan Healthy Living key stakeholder network.



Program Cost, Participants, Referral Pathways, and Intake Process

Logan Healthy Living delivers services at no cost to participants. Where possible, reimbursement for the lifestyle management program is sought through Medicare, Australia's universal health insurance scheme that provides free or subsidized health care (Medicare Benefits Schedule) and selected medication (Pharmaceutical Benefits Scheme, including diabetes medications) for Australian and New Zealand citizens, permanent residents, and some temporary residents. Specifically, Logan Healthy Living seeks reimbursement through the Medicare Benefits Schedule (group allied health service for type 2 diabetes), which funds 1 intake assessment (Aus $74.80 [US $46.99]) and 8 group sessions (Aus $18.65 [US $11.72] per session per person) per calendar year [32]. To claim Medicare benefits, the group sessions must include between 2 and 12 people; last at least 60 minutes; and be delivered by a credentialed diabetes educator, accredited exercise physiologists, or accredited practicing dietitian [32]. While the lifestyle management program is the primary service, participants are also able to access 1:1 consultations with health professionals on an as-needed basis.

To be eligible for the Logan Healthy Living lifestyle management program, participants must have a diagnosis of type 2 diabetes and be aged ≥16 years. While the program is intended for people living in the Logan region, no one is excluded from the service based on their geographical address. Participants may be excluded if it is identified by the clinical team that a group program may not be a feasible method of service delivery (ie, a participant requiring 1:1 education support). At Logan Healthy Living, services are currently delivered in English, and there is no access to free interpreter services (eg, through state or national government programs). However, clinical services have been delivered to participants who do not speak English when supported by a carer or support person.

Participants are primarily referred to the program by GPs using a referral form for group allied health services under Medicare for patients with type 2 diabetes. Participants are also able to self-refer through an expression of interest form on the service's website. Word of mouth and marketing activities support self-referrals, such as the service's website and newsletter, referrals from specialists (eg, the Logan Endocrine and Diabetes Service), and local advertising (eg, booths at local shopping centers, open days, and notice boards). Self-referrals may also be driven more broadly through the activities and promotion of the service by members of the alliance (eg, Metro South Health, Health and Wellbeing Queensland, Brisbane South Primary Health Network, UQ Health Care, Griffith University, and The University of Queensland). Where participants self-refer and do not have a GP referral, they are encouraged to obtain one so that the service can be reimbursed through Medicare; however, in cases in which there are barriers, this does not preclude admission into the lifestyle management program. For example, participants may experience financial barriers to primary care. While visits to GPs are subsidized by Medicare in Australia for some people, visits often attract a gap payment; services that provide no-gap primary care (bulk bill only) are limited; and some participants may not be eligible to enroll in Medicare and, therefore, ineligible for subsidized consultations. Participants can re-enroll in the program once per calendar year.

Upon presenting to Logan Healthy Living, participants are booked for an intake assessment, which is arranged over 2 appointments (appointments 1.1 and 1.2). The first appointment (1.1) is focused on medical history screening (using referral information where possible) and physical assessments. If it is identified at this first appointment that more information is required to safely prescribe exercise, the team may place the participant's referral on hold until medical authorization to exercise is provided by the referring GP or (if self-referred) the participant's usual GP. The second appointment (1.2) is focused on identifying barriers to participation in the lifestyle management program, goal setting, and an introduction to the exercise program. In between the 2 appointments, participants complete web-based, self-report surveys and are invited to indicate whether they agree or disagree to providing written informed consent for their data to be included in a research data registry (further details on ethics are described in the evaluation protocol in the Ethical Considerations section). Screening for completion of surveys and consent forms is conducted by the reception team, with face-to-face support for completion provided by the clinicians at the second appointment if required. After completion of the intake assessment, participants are allocated to the next available group according to their support needs and whether they are most suited for a "recently" diagnosed or "chronic" group allocation based on time since diagnosis.

Logan Healthy Living Lifestyle Management Program

Overview

The lifestyle management program is the primary service delivered by Logan Healthy Living. The program was developed and is delivered in line with the American Diabetes Association Standards of Care in Diabetes [33], which outline recommendations for a range of factors related to the management of people with type 2 diabetes. In particular, the Logan Healthy Living lifestyle management program follows the key recommendations for diabetes self-management education and support, medical nutrition therapy, routine physical activity, health behavior counseling, and psychosocial care. The program incorporates a range of behavior change strategies (as described in the Behavior Change Technique Taxonomy by Michie et al [34]), including goals and planning (eg, goal setting and action planning), feedback and monitoring (eg, biofeedback), social support (eg, unspecified, emotional, and practical), shaping knowledge (eg, instruction on how to perform the behavior), comparison of behavior (eg, demonstration of the behavior), repetition and substitution (eg, graded tasks), comparison and outcomes (eg, credible source), identity (eg, framing and reframing), and self-belief (eg, verbal persuasion about capability) [34].

Program Structure

The lifestyle management program is delivered face-to-face in groups over 8 weeks using an interprofessional model of care. Each week includes one 2-hour session that comprises a

60-minute education workshop and a 60-minute supervised exercise ("movement") session. Each group has a maximum of 10 participants and is assigned an education workshop and an exercise lead (either health psychologist and exercise physiologist or diabetes educator and physiotherapist, respectively) who supports and provides services to the group throughout the 8 weeks. "Recharge" sessions are offered at 1, 3, 6, 9, and 12 months following completion of the 8-week program to provide an opportunity for participants to reconnect with their health care team, review their goals, and participate in a follow-up assessment before being discharged at 12 months. The 1-month recharge is conducted face-to-face, with the remaining sessions conducted via telephone. The education workshops and supervised movement sessions are conducted on-site at Logan Healthy Living, with movement sessions conducted in the fully equipped, on-site gym.

Program Content

A week-by-week overview of the topics, key concepts, and resources provided in the education workshops is detailed in Table 2. The education workshops were designed to be patient centered and focus on diabetes self-management education with the clinical support needed to facilitate the knowledge, decision-making, and skill mastery necessary for diabetes self-care. Education workshop topics are integrated with social prescribing, where opportunities for community engagement related to that week's content are signposted to support longer-term behavior change and address the broader social determinants of health. In addition to being signposted to local programs, participants are signposted to Health and Wellbeing Queensland's suite of prevention programs, including 10,000 Steps and Deadly Choices [30]. The supervised movement session comprises an individually prescribed exercise program targeting combinations of cardiovascular fitness, strength, or flexibility depending on participant presentations. All participants are provided with the opportunity to have an individually prescribed home exercise program or access to Physitrack [35], an app that supports home exercise prescription and monitoring.

Table 2. Overview of the education workshop topics for the Logan Healthy Living lifestyle management program.

Week	Description	Key concepts	Handouts
1	Welcome and orientation	• Acknowledgment of Country[a] • Overview of the allied health team • Overview of program structure • Instructions and rationale for pre-exercise checks • Group introductions • Group activity: "What health behaviors impact my diabetes?"	• Pre-exercise checklist • Lifestyle management program journey plan • Opportunities for community engagement
2	Diabetes education	• What is type 2 diabetes • The role of insulin, insulin sensitivity, and insulin resistance • Key management strategies • Blood glucose testing, HbA_{1c}[b], understanding one's "normal," hypo- and hyperglycemia, and management strategies • Effects and complications of type 2 diabetes • Understanding the annual cycle of care • Identifying other support (family, friends, and community) • Introduction to self-management • Important services to connect with	• What is type 2 diabetes • Key management strategies • Instructions for blood glucose testing • Team of support and recommended review time frames • Services to find out more about type 2 diabetes—National Diabetes Services Scheme, DESMOND[c] Australia, Diabetes Connect by Diabetes Australia, and Logan Healthy Living Facebook page
3	Nutrition part 1	• Carbohydrates and how different types affect blood sugar • Healthy eating guidelines • Understanding what a diet looks like living with type 2 diabetes (5 main food groups) • Hydration • Healthy eating for diabetes • Meal timing and consistency	• A guide to a nourishing lifestyle—a breakdown of the 5 main food groups • How to build a healthy plate • Recommended meal timing • Tips for staying hydrated • Local services providing nutrition support
4	Nutrition part 2	• Understanding food labels • How food labels can help with diabetes management • Grocery shopping efficiently (saving money) • Modifying favorite meals to make them healthier	• Tips for reading food labels • Tips for enjoying home cooking and putting nutrition advice into practice • Local services providing food banks
5	Movement medicine	• The importance of enjoying movement • what is physical activity and exercise • What are the benefits of exercise • The importance of exercise for type 2 diabetes • Physical activity guidelines • Safely exercising with type 2 diabetes • Group activity: "Where can you find the motivation and inspiration to exercise?"	• Benefits of exercise • Pre-exercise checklist • Types of movement (aerobic, balance, flexibility, and resistance training) • Making exercise work for oneself • Exercise and blood glucose levels • Local services providing opportunities for movement
6	Stress management	• Understanding stress and what happens to the body when one is stressed • Understanding how stress impacts type 2 diabetes • The importance of social support • Group activity: managing stress—stress bucket analogy and brainstorming ways to manage stress	• What is stress • Identifying stressors • Sources of support • Local services providing well-being activities

Week	Description	Key concepts	Handouts
7	Healthy habits	• Understanding how to set goals effectively • Review of goals and progress • Planning for life after the program • Creating and sustaining healthy habits • Planning for future success and overcoming barriers • Group activity: building healthy habits (understanding prompts, habits, and rewards) • Group activity: identifying barriers and "helpers"	• Tips for changing behavior and the habit cycle • Ideas for goal setting related to type 2 diabetes • "Planning for the future" activity—identifying what success looks like, what support systems are needed, and what has worked so far and planning for healthy habits • Information on local organizations offering a range of services (eg, community centers and libraries) • "Active and Healthy" booklet by the City of Logan (free and low-cost activities in the area)
8	Wrap up—review and future planning	• Review of educational workshops • Review of action plans (movement, community connection, nutrition, support networks, and rewards and motivations) • Group activity: bingo (revision of each topic)	• Summary of key takeaways from each topic • How to stay connected with Logan Healthy Living (recharge session schedule, gym memberships, meet-ups, Facebook group, blogs, and allied health consultations)

[a]An Acknowledgment of Country is delivered at the beginning of each week.

[b]HbA_{1c}: hemoglobin A_{1c}.

[c]DESMOND: Diabetes Education and Self-Management for Ongoing and Newly Diagnosed.

Evaluation Protocol for the Logan Healthy Living Lifestyle Management Program

Guided by the RE-AIM framework, the evaluation protocol was developed in partnership with the Health and Wellbeing Centre for Research Innovation at The University of Queensland and the other members of the steering committee and was designed to inform the service-level agreement and key questions regarding the uptake, effectiveness, costs, and sustainability of the program.

Study Design

The evaluation is a single-arm intervention design where participants are evaluated at intake to the service (before the program); at the end of the supervised program (8 weeks); and at approximately 1, 3, 6, 9, and 12 months after the end of the supervised program. For participants who do not re-enroll in the program, annual follow-ups are conducted at 2, 3, and 4 years.

Measures

Overview

A summary of measures that are being collected from participants to describe contextual information, program effectiveness, and acceptability is provided in Table 3, with further details and outcomes from other data sources described in the following sections. All self-report surveys are administered using REDCap, service-level data are extracted from practice management software, and physical measures are administered by clinicians on-site.

Table 3. Outline of participant self-report measures and timing of assessments[a].

Measures	Structured program		Extended follow-ups				
	Intake	8 weeks	1 month	3 months	6 months	9 months	12 months
Contextual information							
Sociodemographic	✓						
Smoking and smoking changes[b]	✓	✓					✓
Digital health use	✓	✓					✓
Community involvement	✓	✓		✓	✓	✓	✓
Program effectiveness							
Diabetes-related distress	✓	✓		✓			✓
Health behaviors (physical activity, sitting, and nutrition)	✓	✓		✓	✓	✓	✓
Quality of life	✓	✓		✓	✓	✓	✓
Self-management self-efficacy	✓	✓		✓			✓
Loneliness	✓	✓		✓			✓
Anthropometry	✓	✓		✓	✓	✓	✓
Physical function	✓	✓					
HbA_{1c}[c] level	✓		✓				
Self-reported health care use	✓						✓
Acceptability							
Satisfaction		✓					

[a]All self-reported 12-month assessments (except smoking) are repeated annually at the 2-, 3-, and 4-year follow-ups.

[b]Smoking status is assessed at intake, and change in smoking status is assessed at 8 weeks and 12 months.

[c]HbA_{1c}: hemoglobin A_{1c}.

Reach Outcomes

Program Uptake

Program uptake will be described by reporting the number of participants who enroll in and commence the lifestyle management program compared to those considered ineligible. These outcomes will be tracked using appointment data from the practice management software, Gensolve. Withdrawals from the program and reasons for withdrawal will be tracked by clinicians using REDCap.

Sociodemographic and Other Contextual Characteristics

Demographic data are collected at intake on time since diagnosis of type 2 diabetes, age, sex assigned at birth, gender, postcode, First Nations status, country of birth, language spoken at home, highest level of education, occupation, and employment status. Other contextual information is collected at intake and tracked throughout the program. Smoking status is assessed at intake, and smoking changes are collected at the 8-week and 12-month follow-ups. Use of digital health technologies (eg, apps, wearables, and telehealth) is collected at intake, 8 weeks, 12 months, and then annually. Community involvement is collected at each of the assessments except for the 1-month follow-up by asking participants to report whether they take part in the following activities outside the home: social-based groups, exercise-based groups, combined social and exercise groups, and art and craft–based activities.

Effectiveness Outcomes

Diabetes-Related Distress

The primary effectiveness outcome for the evaluation is diabetes-related distress. Diabetes-related distress will be assessed using the Problem Areas in Diabetes scale [36]. The Problem Areas in Diabetes scale is a self-report, validated questionnaire that comprises 20 items assessing diabetes-related problems, with participants asked to indicate whether each item is “not a problem,” “a small problem,” “a moderate problem,” or “a somewhat serious problem.” Scores of ≥40 to 40 are considered “severe distress”; distress on specific items is considered when the total is not ≥40 but the score on one or more items is ≥3. Participants have “no evidence of distress” when both previous definitions are not met.

Health Behaviors

Physical activity will be assessed using the Active Australia Survey, a validated self-report measure [37]. The Active Australia Survey is designed to measure participation in leisure-time physical activity. It offers a short and reliable set of questions that can be easily administered via self-report or interview. Sitting time will be measured using an adapted version of the AusDiab multicontext sitting questionnaire, which

asks participants to recall weekday and weekend day sitting time over the previous 7 days [38].

Nutrition-related behaviors will be assessed using 14 self-report items sourced from the 13-item Diet Quality Tool by O'Reilly and McCann [39] and 4 items from the evaluation of the Get Healthy Service [40], with redundant items removed. The Diet Quality Tool [39] has been validated in an Australian clinical population and reflects overall dietary quality relative to national recommendations. The New South Wales Get Healthy Service items, derived from population surveys—daily servings of fruit and vegetables as per the National Nutrition Survey [41], as well as daily servings of sweetened drinks per day and takeaway meals per week from the New South Wales Population Health Survey [42]—are useful stand-alone items for comparing results to those of other interventions such as the Get Healthy Service.

Alcohol consumption will be assessed using the brief 3-item version of the Alcohol Use Disorders Identification Test. The Alcohol Use Disorders Identification Test provides both a continuous score that correlates with alcohol consumption and adverse drinking consequences and a valid screening tool for detecting alcohol use disorders and risky drinking with validity in numerous populations, including primary care samples [43].

Quality of Life

Quality of life will be assessed via self-report using the EQ-5D-5L. The EQ-5D-5L is a widely used and validated tool to measure health-related quality of life [44]. The questionnaire comprises 5 dimensions—mobility, self-care, usual activities, pain or discomfort, and anxiety or depression—and participants are asked to report their level of difficulty with each dimension: *no problems*, *slight problems*, *moderate problems*, *severe problems*, and *extreme problems*. It also asks participants to self-rate their health on a numerical scale from 0 to 100.

Self-Management Self-Efficacy

Self-management self-efficacy will be measured via self-report using the Patient Motivation Questionnaire [45]. The Patient Motivation Questionnaire comprises 10 statements related to patients' understanding and confidence in the self-management of their condition. The score is calculated as a total out of 10, with 8 items required to be completed.

Loneliness

Loneliness will be assessed via self-report using a valid and reliable scale that asks 4 questions to capture different aspects of loneliness [46]. The first 3 questions are from the University of California, Los Angeles, 3-item loneliness scale. Scores from the 3 items are used to determine whether the participants are lonely (scores of 6-9) or not lonely (scores of 3-5). The final question is a direct question on how often the respondent feels lonely.

Anthropometric Measures

A combination of directly measured and self-report methods will be used to assess weight (kg) and waist circumference (cm). Directly measured weight will be assessed during the 1.1 intake appointment, the 8-week group appointment, and any subsequent face-to-face recharge appointments (not including the 1-month follow-up). Where participants do not attend face-to-face follow-up appointments for direct measures, they will be asked to self-report their weight and waist circumference. Instructional videos will be provided on how participants can best self-administer these measures. The combination of self-report and direct measures is standard practice at the clinic to allow for flexibility in collecting the data in a timely way with respect to the measurement time points while also allowing participants to have measures directly taken if they are at the clinic at the time of their follow-up.

HbA_{1c} Measures

HbA_{1c} level will be collected using a combination of approaches. For all participants, data will be collected by state pathology laboratories, with the tests conducted closest to intake and the 1-month follow-up after the supervised program (ie, approximately 3 months after baseline) being requested from relevant data custodians. A subsample of participants will have their HbA_{1c} levels collected via finger prick at intake and at the 1-month follow-up, with the point-of-care protocol introduced in January 2024 due to availability of resources.

Physical Function Measures

The 2-minute step test [47], time to complete 5 sit-to-stand exercises [48], and grip strength [49] will be assessed at intake and at 8 weeks to evaluate physical function.

Health Care Use

Health care use will be assessed using a self-report measure of use of GP, hospital, and emergency services at baseline and the 12-month follow-up based on questions adapted from those used in the Household, Income, and Labour Dynamics in Australia Survey [50,51]. In addition, Queensland Health records will be used to quantify emergency department presentations, hospital admissions, bed days, and potentially preventable hospital admissions related to type 2 diabetes (according to the Queensland Health key performance indicator attribute sheets for diabetes-related potentially preventable hospital admissions).

Adoption Outcomes

Adoption will be described by estimating the number of referrals and their referral sources.

Implementation Outcomes

Fidelity

Fidelity will be assessed using adherence to the program, where adherence is the number of sessions attended. These data will be drawn from the practice management software.

Appropriateness

Appropriateness of the program will be assessed by continuing to monitor program adaptations. These will be tracked using a log similar to that in Table 3.

Acceptability

Acceptability will be determined by assessing participant satisfaction. Participant satisfaction will be assessed using a 4-point Likert scale at the end of the supervised group component of the program (8 weeks), where 1=*not at all satisfied*, 2=*somewhat satisfied*, 3=*satisfied*, and 4=*highly satisfied*. Participants will be asked to rate their overall service

satisfaction, satisfaction with the quality of the services, satisfaction with the first appointment being scheduled within a reasonable period, satisfaction with the staff providing the service, and satisfaction with the written information.

Costs

Cost of delivery will be assessed using appointment data collected using the practice management software and overall operating costs.

Maintenance Outcomes

Primarily, participant maintenance will be considered using their longer-term outcomes collected at approximately 12 months after the 8-week structured program. Additional perspective will be provided by the extent of re-enrollment after 12 months (or as early as 9 months if clinically indicated), as well as the long-term outcomes at the 2-, 3-, and 4-year follow-ups among those who do not re-enroll in the program.

Sample Size

The number of participants receiving treatment is not connected to an a priori sample size requirement as it would be in a traditional intervention study. Nonetheless, it is useful to consider how much evaluation data provide an adequate degree of power to detect changes in outcomes. These approximate requirements, based on simple bivariate tests and presented in Table 4, show that even a brief evaluation with few participants should be adequate for some outcomes (such as physical activity), whereas a long-running evaluation with many participants might be required to detect the expected changes in sitting time or potentially clinically meaningful changes in quality of life based on the EQ-5D-5L visual analog scale.

Table 4. Approximate number of evaluated participants required to detect 0- to 8-week changes in effectiveness outcomes with 80% to 90% power and 5% 2-tailed significance.

Measure	Effect size	Assumed values, *r* (SD)	Required number of participants[a]	
			80% power	90% power
Diabetes-related distress				
PAID-20[b] score	MCID[c]=5	0.65 (15)	52	69
Health behaviors				
Active Australia MVPA[d] (minutes per week)	Moderate effect (0.5 SD)	0.4 1)	40	53
Sitting time (minutes per day)	Expected effect=30	0.4 (340)	1212	1622
Fruit consumption (servings per day)	Small effect (0.2 SD)	0.5 (1)	199	265
Vegetable consumption (servings per day)	Small effect (0.2 SD)	0.5 (1)	199	265
Sweet drink consumption (cups per day)	Small effect (0.2 SD)	0.5 (1)	199	265
Takeaway meals (times per week)	Small effect (0.2 SD)	0.5 (1)	199	265
Quality of life				
EQ-5D-5L visual analog scale (0-100)	MCID=6	0.6 (65)	739	989
EQ-5D-5L index score	MCID=0.262	0.75 (0.2)	5	6
EQ-5D-5L visual analog scale (0-100)	Small effect (0.2 SD)	0.6 (1)	159	213
EQ-5D-5L index score	Small effect (0.2 SD)	0.75 (1)	101	134
Self-management self-efficacy				
Patient Motivation Questionnaire score	Small effect (0.2 SD)	0.5 (1)	34	44
Loneliness				
UCLA[e] Loneliness Scale score	Small effect (0.2 SD)	0.75 (1)	101	134
Anthropometry				
Weight (kg)	Very small change=1	0.99 (26)	427	571
Waist circumference (cm)	Expected effect=2	0.97 (17)	36	48
Physical function				
2-minute step test (steps)	MCID=11	0.65 (25)	31	40
Sit-to-stand test (seconds)	MCID=2.3	0.65 (5.5)	34	45
Grip strength (left hand; kg)	Expected effect=1.5 kg	0.9 (11)	87	115
Grip strength (right hand; kg)	Expected effect=1.5 kg	0.9 (11)	87	115
HbA_{1c}[f]				
HbA_{1c} level (%)	MCID=0.5%	0.7 (1)	21	28
Health care use				
Number of general practitioner visits	Small effect (0.2 SD)	0.5 (1)	199	265
Number of emergency department presentations	Small effect (0.2 SD)	0.5 (1)	199	265
Number of hospital visits	Small effect (0.2 SD)	0.5 (1)	199	265

[a]Number of participants with pre- and postevaluation data collected.

[b]PAID-20: Problem Areas in Diabetes.

[c]MCID: minimum clinically important difference.

[d]MVPA: moderate to vigorous physical activity.

[e]UCLA: University of California, Los Angeles.

[f]HbA_{1c}: hemoglobin A_{1c}.

Data Analysis

Reach, adoption, and implementation outcomes will be reported using descriptive statistics. The effectiveness of the lifestyle management program on effectiveness outcomes (all continuous) will be assessed by examining changes over time in linear mixed models accounting for repeated measures. Missing data in these mixed models will be handled through evaluable case analysis, with adjusted models including any characteristics that may differ between those providing data at different time points. The sensitivity of the conclusions to missing data handling will be evaluated using multiple imputation. All relevant time points will be reported, with the primary end point for effectiveness being 8 weeks (except for HbA_{1c} level and GP visits) and the primary end point for maintenance being approximately 12 months. The main evaluation will focus on all participants enrolled in the program, and a further per-protocol evaluation will consider outcomes for adherent participants only. Health care use in the 12 months before and the 12 months following enrolment in Logan Healthy Living will be compared using appropriate paired nonparametric tests (Wilcoxon signed ranks test and McNemar chi-square test). Costs will be estimated where possible. Sensitivity analyses will be conducted to explore whether health care use differs by a range of factors, including demographic and clinical characteristics.

Ethical Considerations

The data registry has ethics approval from the Metro South Health Human Research Ethics Committee (project ID 84062) and has received ratification from The University of Queensland Human Research Ethics Committee (2022/HE001421). At intake, participants are provided with the participant information and consent form for the data registry by the clinical team electronically and invited to opt in by providing written informed consent. Data for the data registry are collected in an identified manner, with data stored in REDCap and The University of Queensland Research Data Manager in password-protected folders. Participants are not provided with any compensation for taking part. Hospital use data will be drawn from centrally held medical records and obtained on request from relevant data custodians.

Iterative Adaptations to the Program

Since the opening of Logan Healthy Living in July 2021, several iterative adaptations have been made to the service delivery model to better meet the needs of the participants and the clinical team. Adaptations have been informed by stakeholder feedback (clinicians, students, and consumers) and biannual key performance indicator reports. Clinician and student reflections and feedback are discussed in regular team meetings, and participant feedback is openly encouraged through all interactions with Logan Healthy Living. Feedback from participants was sought more formally through qualitative focus groups conducted in the first years of operation that aimed to identify barriers to and facilitators of maintaining behavior change following the lifestyle management program [52]. In addition to identifying barriers that resulted in service changes (eg, ongoing access to resources such as Physitrack and the gym), participants reported that there was a sense of belonging and safety within the program, which facilitates an open dialogue for feedback on services. Key changes in response to consumer feedback are communicated to participants using a range of mechanisms, including “You said...we listened...” posters that outline feedback and corresponding changes to service delivery, which are displayed around the facility, and via clinic newsletters and social media posts. A summary of key service delivery model adaptations is provided in Table 5.

Table 5. Summary of key service delivery model modifications.

Year	Feedback or challenge	Modification
2022	Initially conducted as 1 appointment, the intake assessment took approximately 3 hours, and participants reported fatigue.	The intake assessment was split into 2 appointments (1.1 and 1.2).
2023	Participants wanted the opportunity to continue to attend Logan Healthy Living to exercise.	"Open" gym time was scheduled, where participants could independently use exercise equipment once they had finished the lifestyle management program.
2023	Participants had access to Physitrack during the lifestyle management program and for 3 months after, and feedback indicated that they wanted access for longer.	Participants are provided with access to Physitrack for up to 12 months after the lifestyle management program.
2024	Demand for access to the gym was increasing, and access times were unsuitable for a large number of participants.	"Open" gym concept was expanded to a full, low-cost gym membership model with expanded opening times.
2024	Recharge sessions were scheduled as a group, and attendance was poor.	To improve attendance, recharge sessions are individually scheduled and delivered face-to-face at 1 month and via telehealth (telephone) at 3, 6, 9, and 12 months.
2024	Participants expressed a desire to have ways to continue to connect socially with their peers after completion of the lifestyle management program.	A community engagement social group was started. This included a bimonthly scheduled opportunity for participants to engage with each other socially and to inform them of local community engagement activities. This activity is jointly supported by the community development team of Logan City Council.
2024	The time taken to complete the intake assessment (eg, time from referral to commencing the lifestyle management program) was resulting in high attrition and low rates of uptake of the program.	The intake process was streamlined so that appointments were booked concurrently (1.1 and 1.2) to minimize time between referral and commencing the program.
Ongoing	Feedback is continually sought on the program materials and resources from all stakeholders (participants, students, and clinicians).	Program materials and resources are iteratively adapted to respond to feedback and ensure that they are up-to-date (eg, that local services are current and still operating).

Results

The 4-year proof of concept concludes on December 31, 2024, with reporting of the results anticipated in 2025. Results will be reported in conference abstracts and publications and with stakeholders informed through reports (with authorship determined according to scientific authorship guidelines). Findings will be shared with Logan Healthy Living participants using a range of channels, including clinic posters, newsletters, and social media.

Discussion

Overview

This paper describes the development and evaluation protocol for Logan Healthy Living, an interprofessional, community-delivered allied health service for people living with or at risk of type 2 diabetes in Logan, a region in South East Queensland, Australia. Delivered by a multisectoral alliance including primary and tertiary health care, government, and university partners, Logan Healthy Living is a proof-of-concept service that will be comprehensively evaluated using the RE-AIM framework and drawing from data at the level of the participants, service, and health system.

In this project, the evaluation outcomes are continuously monitored and collected in partnership between researchers and clinicians, with data collection embedded into usual practice. This is driven simultaneously by a value-based funding model and the opportunity for evidence-generating practice, with the establishment of agreed upon key service performance indicators being a pivotal influence in the buy-in required to embed this into practice. While the benefit for research is obvious, what has also emerged is the potential of continuous monitoring to inform iterative adaptations to the program, with the ability to respond in real time to optimize the health care service to suit participant and health system needs. Ongoing findings have also been used to inform collaborative strategic planning between partners to drive further development and expansion of the program and services. These "ripple effects," such as establishing new networks, partnerships, and services to meet the needs of these adaptations, will be monitored and reported in detail in an attempt to capture the nontraditional impacts of the program on the community.

While there is a call for multisectoral responses to complex health system challenges [12], including chronic diseases such as type 2 diabetes, responses to these calls are rarely documented in detail, and the learnings from these processes are potentially lost. The detailed description of the alliance, establishment of the service, and protocol for the evaluation have the potential to inform future multisectoral partnerships and the development of community-delivered models of care for type 2 diabetes prevention and management, as well as for chronic diseases more broadly. For example, there were challenges experienced in streamlining referrals and data sharing between government health care providers and Logan Healthy Living. While they were partners within the alliance, formal pathways for these activities were not established, which meant that referrals were

limited to advertising and recommendations from health professionals and participants were required to replicate intake assessments that could have been avoided, thus reducing burden. Future programs can ensure that such details are determined as part of the establishment process. The limitations of the evaluation must also be acknowledged, including the lack of a comparison group; reliance on survey data due to practical considerations, which may introduce self-report bias; and the potential high rates of missing data given that the evaluation is within a service delivery rather than research context.

Conclusions

The implementation and evaluation of a community program within a culturally diverse region of a low socioeconomic status with rising rates of type 2 diabetes provides an opportunity to further understand the interplay of social determinants of health and chronic disease and the impact that a purposefully designed service can have on reducing the burden on the participants, the community, and the health care system. The outcomes of the evaluation will provide valuable insights into the impact of this model of care in practice, with the findings expected to inform potential scale-up through local, state, and national partnerships.

Acknowledgments

The authorship team wish to thank the participants, clinicians, and administrative teams at Logan Healthy Living for their ongoing contributions to the evaluation of the service. They also wish to acknowledge the Logan Healthy Living steering committee, who have governed and guided the service since its establishment. Those who consented to be named include Debbie Cowan, Metro South Health; Dr Rosy Dobrijevic, UQ Health Care Ltd; and Laura Casey, Brisbane South Primary Health Network. Finally, the authorship team would also like to thank the people who were in key positions of leadership during the development of the service who volunteered their time to help the authors understand the early beginnings of Logan Healthy Living. Those who consented to be named include Mika Hayward, Director of Health Partnerships and Major Projects at The University of Queensland. GNH is funded by an Australian National Health and Medical Research Council and Medical Research Future Fund Emerging Leadership Fellowship. SRG, TA, and EAHW are partly funded by the Health and Wellbeing Centre for Research Innovation, which is cofunded by The University of Queensland and Health and Wellbeing Queensland.

Data Availability

Data sharing is not applicable to this paper as no datasets were generated or analyzed during this study.

Conflicts of Interest

DG and WW are employed by UQ Health Care Ltd, who deliver and operate Logan Healthy Living. JC, JM, and RL are employed by Health and Wellbeing Queensland, who provide a financial and governing contribution to Logan Healthy Living. All other authors declare that they have no competing interests.

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Abbreviations

GP: general practitioner
HbA1c: hemoglobin A1c
RE-AIM: Reach, Effectiveness, Adoption, Implementation, and Maintenance
REDCap: Research Electronic Data Capture
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials

Edited by A Schwartz; submitted 01.12.24; peer-reviewed by A Missel; comments to author 16.01.25; revised version received 30.01.25; accepted 31.01.25; published 10.03.25.

Please cite as:
Gomersall SR, Giguere DY, Cotugno J, Munro J, Westbrook WJ, Littlewood R, Cairney J, Winkler EAH, van der Vliet PM, Goode AD, Alsop T, Healy GN
Development and Impact of a Community-Delivered, Multisectoral Lifestyle Management Service for People Living With Type 2 Diabetes (Logan Healthy Living): Protocol for a Pragmatic, Single-Arm Intervention Study
JMIR Res Protoc 2025;14:e69477
URL: https://www.researchprotocols.org/2025/1/e69477
doi:10.2196/69477
PMID:

Protocol

Improving Pre-Exposure Prophylaxis Provision as Part of Routine Gynecologic Care Among Black Cisgender Women (Project PrEP4Her): Protocol for the Implementation of an Intervention

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Abstract

Background: Although HIV pre-exposure prophylaxis (PrEP) has been proven to be an effective prevention tool in decreasing HIV transmission, achieving adequate PrEP uptake has remained a challenge among Black cisgender women living in the Southern United States. Gynecology clinics, which provide primary health care services for many cisgender women, have the potential to be an ideal setting for the integration of PrEP services.

Objective: We designed an intervention, PrEP4Her, which aims to implement PrEP service delivery at gynecology clinics in Alabama, the United States, as part of routine reproductive and sexual health care visits to improve PrEP engagement rates among Black cisgender women.

Methods: Guided by the information gathered on (1) factors impacting PrEP implementation at gynecology clinics, including key barriers and facilitators to PrEP implementation and potential strategies to address the identified barriers (in-depth interviews with the gynecology care team), (2) structural barriers and provider-level barriers to PrEP implementation (cross-sectional study among gynecologists), and (3) implementation strategies on how to integrate PrEP services into routine gynecology care (in-depth interviews and focus groups with Black cisgender women), a multicomponent implementation strategy, tailored for Black cisgender women, was developed to integrate PrEP in routine women's health visits (ie, PrEP4Her). To determine the efficacy of the program, we will measure implementation outcomes, reach (increase in the absolute number of Black cisgender women receiving PrEP prescriptions), effectiveness (increase in the proportion of PrEP prescriptions over time), and adoption (proportion of team members willing to implement PrEP4Her) using the RE-AIM (Reach, Effectiveness, Adoption, Implementation, and Maintenance) framework. In addition, acceptability (the extent to which providers and Black cisgender women feel PrEP4Her to be acceptable—in-depth interviews); Feasibility (appropriateness of PrEP4Her for a larger, full-scale trial—the Feasibility of Intervention Measure scale); and fidelity (the degree to which PrEP4Her program was implemented as designed—electronic survey with patients) will also be assessed.

Results: The qualitative and quantitative data from the gynecology care team and the qualitative data from Black cisgender women were collected from August 9, 2022, to April 19, 2023, and were integrated through joint displays to identify major themes. The combined findings provided a comprehensive understanding of factors that were fundamental in the development and refinement of PrEP4Her implementation. The PrEP4Her was implemented from January 29, 2024, to August 16, 2024. The information gathered is being used to assess PrEP4Her efficacy (based on reach, effectiveness, adoption, acceptability, feasibility, and fidelity).

Conclusions: Upon completion of our research, our interdisciplinary team, which includes experts in infectious diseases, implementation science, community-engaged research, and psychology, will be primed to lead a multisite type III implementation trial for PrEP service delivery at gynecology clinics across the Southern United States.

International Registered Report Identifier (IRRID): DERR1-10.2196/58976

(JMIR Res Protoc 2025;14:e58976) doi:10.2196/58976

KEYWORDS

Black; cis-Gender women; PrEP; pre-exposure prophylaxis; South; HIV; gynecology

Introduction

Black people only constitute 13% of the US population but account for more than half of the new HIV diagnoses [1]. These disparities are more pronounced in the South [2], where the highest acquisition and mortality rates are documented among Black people [3]. In response to these inequities, the US federal agencies are working in a coordinated manner to end the HIV Epidemic with a mandate to focus on populations facing HIV inequities and geographic hot spots, with prioritization to increase utilization of effective biomedical prevention tools like HIV pre-exposure prophylaxis (PrEP), that reduces HIV transmission with consistent use [4-7]. The US state of Alabama has been prioritized for End the HIV Epidemic efforts due to high HIV incidence and prevalence rates. In Alabama, where the rate of HIV diagnoses in 2020 was 14.1 per 100,000 people, most new diagnoses occurred among Black men and women [8]. In addition, in 2021, Alabama had a PrEP-to-Need ratio of 5.55, with the highest unmet need for PrEP occurring among the Black community (PrEP-to-need ratio among Black vs White individuals: 2.94:11.30) [9].

When focusing on cisgender women, who account for approximately one-fifth of new HIV diagnoses in the United States, only 8% of the 227,010 women with a PrEP indication are currently receiving PrEP prescriptions [10-13]. This low PrEP uptake is similar in Alabama, where only 7% of the PrEP clientele comprised of cisgender women in a university-affiliated infectious diseases-led PrEP Clinic [14]. Among cisgender women, Black cisgender women are even more disproportionally impacted by the HIV epidemic, currently accounting for 54% of all new HIV diagnoses among cisgender women, nationally [15]. These disparities are mirrored in Alabama's HIV incidence, where Black cisgender women are 9 times more likely to be diagnosed with HIV compared with White cisgender women [16]. With Black cisgender women in the Southern United States being disproportionately impacted by the HIV epidemic, approaches to increase PrEP uptake among this population present an opportunity to ameliorate these inequities.

Previous studies among Black cisgender women have found PrEP uptake barriers to occur at multiple levels (ie, individual, interpersonal, and Meso levels) [17]. Some individual-level barriers include a lack of awareness of PrEP and concerns around PrEP-related stigma, including fear of being labeled as HIV-positive with PrEP use, limiting PrEP uptake in this population. In addition, some provider-level barriers have also been discovered, such as a lack of knowledge on current PrEP clinical care guidelines, misconceptions related to insurance coverage, and provider bias preventing culturally appropriate PrEP-related discussions [18]. In addition, providers' stereotypic beliefs or prejudices (ie, having higher levels of color-blind racial attitudes) lead to a decreased willingness to counsel and prescribe Black cisgender women PrEP [19]. As such, overcoming current inequities requires innovative strategies to engage Black cisgender women in PrEP service delivery tailored to their preferences.

Of the total HIV diagnoses among Black cisgender women, the majority occur in those of reproductive age [20]. There is strong evidence to support that 70% of women in the United States are seeking routine annual care for reproductive health and nearly half access contraceptive services [21,22]. Safety-net programs created for cisgender women to receive reproductive health care, like family planning clinics, have been evaluated in Southern states as sites for PrEP implementation [23,24]. However, a major barrier to PrEP uptake is low provider knowledge on the delivery of PrEP services. Interventions focused on improving provider knowledge alone have fallen short on seeing huge gains in PrEP uptake among women [25-28]. In Addition, previous studies have shown that even with increased PrEP access in clinical care settings that specialize in women's health care, PrEP uptake has been low and providers have struggled in optimizing these spaces for PrEP service delivery [22-27,29]. Gynecologists have been shown to be ideal PrEP service delivery candidates, as national data supports higher willingness to prescribe PrEP among gynecologists compared with general practitioners [30]. Furthermore, 81% of patients seen by gynecologists are of reproductive age (18-44 years old), which also reflects the age range among cisgender women more likely to acquire HIV [31]. In line with this, our previous work among Black cisgender women in the state of Alabama also revealed they preferred PrEP services to be delivered by gynecologists in a clinical care setting [32].

Informed by compelling preliminary data, we designed an implementation study to determine the requisite steps and strategies for the implementation of PrEP services into routine gynecological care visits at a university-affiliated clinic in Birmingham, Alabama, which provides services to women with low income across the state [33]. Our gynecological pilot site is a large center that sees over 17,000 patients (40% Black cisgender women) annually, with the majority being of reproductive age, who reside in both urban and rural areas of Alabama. This paper outlines the protocol for this multicomponent implementation strategy, which evaluated key individual-level, inner-setting, and process-level determinants for the implementation of PrEP service delivery in gynecology clinic settings. The intervention aimed to develop and refine a

multicomponent implementation strategy (PrEP4Her) that integrated PrEP in a gynecology clinic, which was then piloted to deliver PrEP for Black cisgender women attending routine gynecologic care visits. The PrEP4Her intervention is aimed at improving PrEP engagement among Black cisgender women in order to reduce the HIV disparity among this population.

Methods

Study Setting

The PrEP4Her was implemented at the University of Alabama at Birmingham gynecological Continuity clinic.

Development of the Protocol

To explore perceived barriers and facilitators for integrating PrEP into routine gynecological care, qualitative and quantitative data were collected. In-depth interviews were conducted with gynecologists, practice managers, medical assistants, nurses, and pharmacists at our gynecological clinical site via teleconference. The interviews covered topics, such as factors effecting PrEP implementation at gynecological clinics, key barriers or facilitators to PrEP implementation, potential strategies to address the identified barriers, and any emerging topic areas for subsequent exploration. In addition, existing PrEP coverage services and programs for uninsured Black cisgender women were discussed with medical service providers, case managers, and social workers. After each interview, interviewers documented field notes, including emerging topic areas for subsequent exploration. The qualitative data were analyzed by an expert qualitative researcher using the NVivo (Lumivero) qualitative data management software. First, a preliminary codebook was developed, which included inductive codes, that emerged from the data, and pattern codes, that connected concepts to one another. The lead qualitative analyst along with a team of 2 researchers applied these codes to a subset of interview transcripts and adjusted the code definitions until an adequate interrater reliability was achieved. The finalized codebook was then used to analyze the remaining transcripts, noting major themes. Finally, data matrices were created to visually represent associations between key concepts and patterns in the data.

In addition to interviews, a cross-sectional study was conducted in collaboration with the Alabama Section of the American College of Obstetricians and Gynecologists and the university's Center for Women's Reproductive Health in the Department of Obstetrics and Gynecology to understand barriers to future state-wide implementation that needed to be measured during this pilot study. Surveys were conducted with English-speaking, currently practicing gynecologists or advanced practitioners at gynecological clinics (n=39), to evaluate structural barriers to PrEP as well as any potential provider-level barriers. The surveys documented information on sociodemographic, HIV, and PrEP knowledge [34,35], HIV- and PrEP-related stigma [36,37], and questions ascertaining current routine testing and screening practices. The data from the surveys reported findings on willingness to prescribe PrEP by the independent variables (sociodemographics: race and ethnicity, clinic name, gender, years of practice, clinic resources, characteristics of populations served; knowledge: PrEP and HIV; stigma: PrEP and HIV; and practice: sexual history, sexual transmitted infections testing, and sexual transmitted infections treatment) as well as willingness to prescribe PrEP (primary outcome) and the capability of the clinical-setting for providing PrEP services (secondary outcome).

To explore the desired PrEP educational materials and communication strategies from gynecologic care teams, in-depth interviews, and focus groups were conducted with Black cisgender women. The inclusion criteria for the in-depth interviews and focus groups were the same and included (1) self-reported HIV-negative status, (2) being Black cisgender women, (3) ability to speak in English, and (4) age of 18 to <54 years (the choice of age range is based on the current HIV epidemiology reporting highest HIV incidence among cisgender women aged <54 years). An informed consent was signed by eligible Black cisgender women before the interview and focus group participation. The semistructured interviews covered topics such as sexual health, education needed to increase awareness and knowledge, stigma, and communication with the care team. The qualitative data were analyzed in a similar manner as described above by the expert qualitative data team.

To develop and refine a multicomponent implementation strategy (PrEP4Her) that aimed to integrate PrEP in gynecology clinics, an intervention mapping technique was used [38]. First, key barriers to PrEP implementation among Black cisgender women and providers were reviewed from the data collected with the PrEP4Her community advisory board (CABs, with the full description provided below). Next, using existing knowledge of components identified from studies that implemented PrEP at family planning clinics in the South, an initial list of components was created. Although family planning clinics may have differences from our gynecological setting in terms of the type of care providers and resources, they share a mission for providing reproductive and sexual health services, which may result in overlap with strategies needed for our research population. Using the knowledge gained through the reported findings, the team modified their list of components for PrEP4Her in a way that was more suited toward our gynecological clinics. Table 1 and Textbox 1 outline the preliminary name, definition, and operationalization of components based on current feedback from the PrEP4Her CAB, established by Proctor et al [39-41]. The team then mapped the implementation strategy and linked it to the desired implementation outcomes. This was followed by developing a content-specific implementation strategy. After implementation strategy materials were refined, appropriate operational steps needed to integrate PrEP into the clinical site were reviewed. JS, who has expertise in implementation science and has previously worked with family planning clinics in Southern settings to improve HIV prevention among Black cisgender women, also helped with PrEP4Her implementation.

Table 1. Specification of components of the implementation strategy ("PrEP4Her").

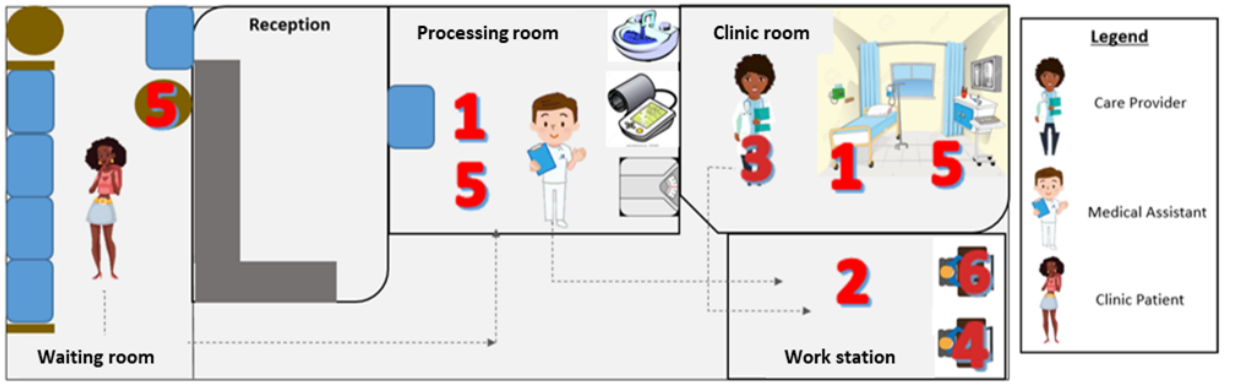
Implementation strategy	Number 1	Number 2	Number 3	Number 4	Number 5	Number 6
Actor	Medical assistant or care provider	Study staff or PrEP[a] expert	PrEP expert	PrEP expert and information technician	PrEP expert and graphic designer	PrEP expert
Action	Charts evidence-based sexual history questionnaire in the medical record	Provides 1.5-hour training on HIV, risk, and PrEP indications and care	Creates easily accessible pocket cards with indications for PrEP	Creates templates in electronic medical records for PrEP visits and order sets	Develops informational content to include in educational materials tailored to Black cisgender women	Develops 30-minute training tutorial on how to communicate with patients about sexual health and PrEP, tailored to Black cisgender women
Target	Patient	Providers or staff	Provider	Provider	Patient	Patient
Temporality	Medical assistant (before every patient encounter with a provider) or provider (beginning of every visit)	1 month before PrEP4Her being implemented at our pilot site	Continuously carried by providers and displayed in shared workspaces	1 month prior to PrEP4Her being implemented with instructions on how to access placed in shared workspaces and sent through email communications	Placed in waiting areas and private examination rooms, accessible during every visit and replenished by study staff members	1 month before PrEP4Her being implemented and presentation accessible in the shared workspace as well as emailed to all providers
Dose	5-minute screener at every visit	1.5-hour training occurring once before 6-month pilot	As needed by providers during clinical care	As needed by providers during charting	Available during the entire 6-month pilot for every clinic	Once before 6-month pilot and then available as needed

[a]PrEP: pre-exposure prophylaxis.

Textbox 1. Pre-exposure prophylaxis 4Her components and outcomes.

- Named pre-exposure prophylaxis 4Her components
- Universal sexual health screening for gynecological patients
- Synchronous training of gynecological care team on HIV, pre-exposure prophylaxis indication, pre-exposure prophylaxis care (for both daily and long-acting injectable regimens), and stigma
- Pre-exposure prophylaxis indication job aids
- Electronic medical record documentation aids, including pre-templated notes and order sets
- Educational materials for Black cisgender women on HIV and pre-exposure prophylaxis
- Asynchronous training on effective communication strategies with patients about sexual health and pre-exposure prophylaxis
- Implementation outcomes affected
- Figure 1. for detailed description of how each implementation strategy maps to implementation outcomes. In short, we will be evaluating the following proximal implementation outcomes: reach, adoption, fidelity, acceptability, and preliminary effectiveness. Distal outcomes will not be evaluated in this study.
- Justification
- Implementation strategy components selected for this study have been selected based on observed, researched, or hypothesized barriers based on a review of the literature. These components may be subject to change based on findings in Aim 1 and feedback from our community advisory board.

Figure 1. Pre-exposure prophylaxis implementation science research logic model. CAB: Community Advisory Board; GYN: gynecology; PrEP: pre-exposure prophylaxis.



PrEP4Her Components		
1. Universal Sexual History – Brief, gender-neutral sexual history screening assessment [42].	**2. Job Aids** – 2-sided pocket cards for white coats/scrubs that will include CDC guidance summary criteria for PrEP among cis-gender women and 5Ps [43,44].	**3. Educational Materials** – Pamphlets, tailored for Black cis-gender women that contain information about HIV and PrEP [45].
4. Synchronous HIV and PrEP Training – ~ 1.5-hour PrEP informational training (adapted from Sales et al. in family planning clinics) made available on UAB CFAR website.	**5. EMR Documentation/Order Aids** – Premade order sets within UABs electronic medical record for initial and 3-month PrEP visits as well as a PrEP note template.	**6. Asynchronous Training on Communication Strategies** – ~ 15 minute training on communicating empowering, "gain-framing" messaging, made available on CFAR website [46].

Conceptual Framework

This multiphase study will be evaluated using the RE-AIM (Reach, Effectiveness, Adoption, Implementation, and Maintenance) conceptual framework and will link our multicomponent implementation strategy to proximal implementation outcomes. Figure 1 depicts the research logic model for the implementation of the PrEP4Her study. The PrEP4Her components box shows the implementation strategies (A to F): A: carrying out the universal sexual health screening for gynecological patients in the medical record; B: providing training on HIV, PrEP indication, PrEP care, and stigma for the gynecological providers; C: creating job aids such as pockets cards to easily identify those with a PrEP indication; D: creating aids for electronic medical record documentation such as creating templates for PrEP-related visits and order sets; E: developing educational material tailored toward Black cisgender women; and F: developing training tutorials on communication methods with patients about sexual health and PrEP, tailored toward Black cisgender women. Moreover, the change of mechanisms box shows how the strategies in the PrEP4Her components box are anticipated to impact the implementation outcomes (the superscripts indicate the implementation strategies that are expected to cause the change). Finally, the proximal implementation outcomes box outlines the expected outcomes that will be assessed as per the RE-AIM framework; the superscripts again indicate the PrEP4Her components that will impact each of the outcomes. The project is expected to improve the conditions deemed as potential barriers to PrEP usage among Black cisgender women, ultimately achieving the desired outcomes of increased PrEP uptake among Black cisgender women. Our study describes the planning and piloting stages of the implementation research logic model, evaluated by the RE-AIM framework, in which we will work with key informants and Black cisgender women to assess the reach, adoption, and preliminary effectiveness of integrating PrEP services within a gynecological clinic in Birmingham, Alabama, with the ultimate goal of increasing uptake of PrEP.

The Role of CABs

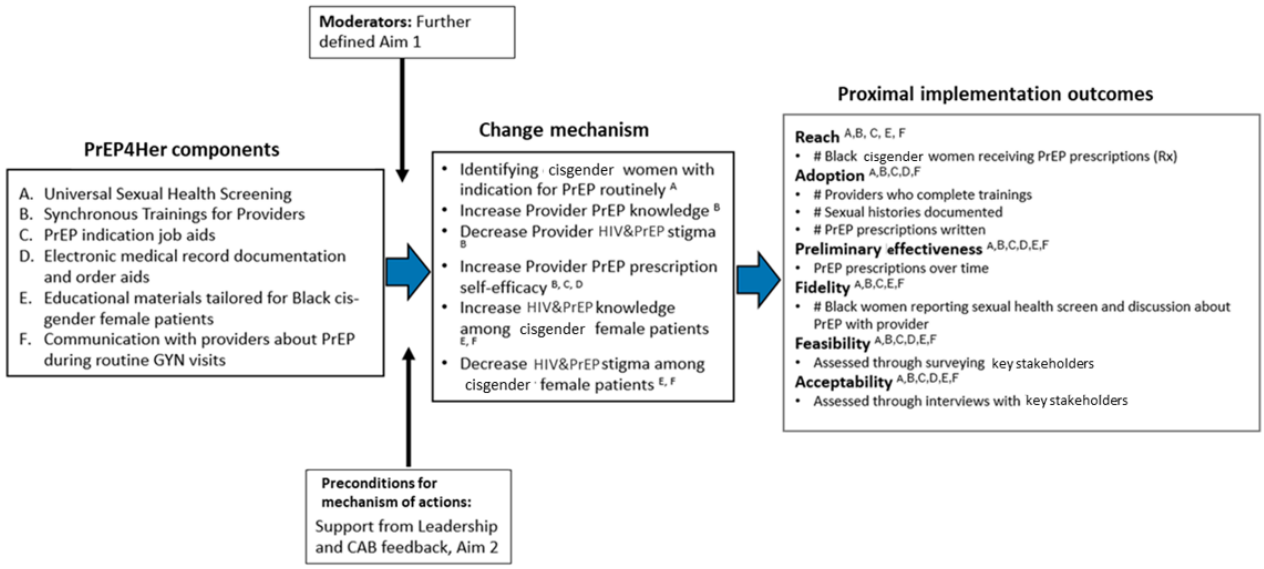
Two CABs, one for Black cisgender women (N=5) and one for gynecology practitioners (N=7), have worked and will continue to work with the study researchers. The CABs are led by a graduate-level researcher, who is also a part of this project. The CABs previously provided help with the interpretation of the qualitative findings and in selecting and refining components of the implementation strategy (PrEP4Her). Currently, the CABs meet monthly and advise on how to disseminate study results. At least 10 meetings were or will be held during the study, with a shared decision-making structure. Detailed notes will be documented to evaluate the meeting processes.

Piloting PrEP4Her to Deliver PrEP for Black Cisgender Women Attending Routine Gynecologic Care Visits

PrEP4Her is a multicomponent implementation strategy, which was evaluated through a 1-arm pilot at a university-affiliated gynecological clinic. We chose a 1-arm trial, as PrEP was not routinely offered at gynecological clinics in Alabama and there were only 3 Black cisgender women on PrEP at the university-affiliated PrEP clinic at the study start, which meant a comparison between other gynecological clinics or between our PrEP clinics would have had limited meaning. Upon completion of PrEP4Her development, gynecological staff members, practice managers, and clinicians received training as well as implementing job and documentation aids within the clinic. In addition, educational materials were placed in all areas where patients are seen within the clinic. Figure 2 outlines the

workflow for PrEP4Her along with the detailed description of each component. Implementation outcomes for PrEP4Her were monitored over a 6-month time frame (Jan-Aug 2024). Of the RE-AIM components, only reach, effectiveness, and adoption will be evaluated as a part of this study. In addition to the 3 components of RE-AIM, we will also evaluate the acceptability, feasibility, and fidelity of the trial.

Figure 2. Pre-exposure prophylaxis 4Her components [42-46]. Image created by LE. CDC: Centers for Disease Control and Prevention; CFAR: Center for AIDS Research; PrEP: pre-exposure prophylaxis; UAB: University of Alabama at Birmingham.



Reach Outcome

Reach in RE-AIM captures the ability to engage the target population in the intervention. In PrEP4Her, this will correspond to the absolute number of Black cisgender women who receive a PrEP prescription. In addition, the proportion of Black cisgender women prescribed PrEP among those who had a PrEP indication, will also be evaluated. PrEP indication will be based on the sexual risk screener (component 1 in Figure 2) documented in the chart during patient visits. For this study, PrEP indication will be defined based on the Centers for Disease Control's guidance summary criteria. According to this guidance, cisgender women not living with HIV meet at least one of the following criteria are considered to have a PrEP indication: (1) HIV-positive sex partner not virally suppressed, (2) bacterial STI in the past 6 months (ie, gonorrhea or syphilis), (3) more than one sex partner, (4) inconsistent condom use, (5) sex for exchange of goods, or (6) being in a high-prevalence network [44]. PrEP prescription data will be obtained from the university's electronic medical records visit data during the pilot period. Although measuring the number of PrEP discussions with Black cisgender women by electronic medical record audit was also considered an important aspect to examine reach, it was deemed to add little value due to the anticipated inconsistencies in documentation by providers in reporting PrEP discussion in their clinic notes. However, we have incorporated this element in our surveys with Black cisgender women, evaluating their experiences with providers in receiving PrEP health counseling.

Effectiveness Outcome

Effectiveness in RE-AIM evaluates the effect of the intervention on the primary outcome as well as effect modification. Effectiveness of PrEP4Her will be determined by the increase in PrEP prescriptions over time. In addition, patient factors associated with PrEP prescription will be evaluated [47]. PrEP prescription data from the electronic medical records will be extracted at baseline, at 3 months, and at 6 months of PrEP4Her implementation, to evaluate effectiveness. Moreover, information on patient demographics (ie, age, race, ethnicity, and insurance status) will also be obtained. Using this data, frequencies for PrEP prescription will be reported overall and for each independent variable at baseline, 3 months, and 6 months.

Adoption Outcome

Adoption in the RE-AIM determines the ability of the setting's staff members to adopt the intervention. This will be determined by measuring the proportion of key informants within the pilot site who were willing to initiate the PrEP4Her implementation strategy. This will be assessed by evaluating the training and sexual history documentation.

Training

A website will be created as a part of this study, to aid in easy access of training materials for providers and staff members. During initial training, the number of providers and staff members who attend the meetings will be documented. In addition, viewing training on the website will be captured through collecting para data (tracking clicks).

Acceptability Outcome

Acceptability is defined as the extent to which key informants felt PrEP4Her was acceptable (ie, providers delivering the intervention and Black cisgender women receiving the intervention). This will be measured by conducting key-informant interviews. The sample will include 15-20 participants, with at least 10 providers, and approximately 10-15

Black cisgender women seen during the 6-month pilot period. Recruitment of providers will be carried out directly from the pilot study, whereas recruitment of Black cisgender women will be done through flyers and direct referrals from clinical staff members. Interview guide questions will be grounded in a theoretical framework of acceptability by Sekhon et al [48]. Interviews will be conducted virtually to allow for flexibility, using a secure system. Interviews will be digitally audio recorded, professionally transcribed, and deidentified. A preliminary codebook will be developed consisting of a priori deductive codes (based on the theoretical framework), inductive codes (emerging from the data), and pattern codes (connecting concepts to one another). The analysis of these data will be carried out in a similar manner as described above by our expert qualitative team.

Feasibility

Feasibility of the intervention will determine if PrEP4Her is appropriate for a larger, full-scale implementation trial. This information will be captured using the validated scale, Feasibility of Intervention Measure [49], through surveys conducted before interviews among key informants. The survey will include straightforward items such as "[PrEP4Her] was appealing to me," "[PrEP4Her] seemed suitable," and "[PrEP4Her] seemed easy to implement," which respondents will rate on a 5-point Likert scale. Descriptive statistics will be calculated to determine feasibility.

Fidelity

Fidelity to the intervention protocol will be assessed as the degree to which the PrEP4Her implementation strategy was implemented as designed [50]. To measure fidelity, all patients seen during the 6-month pilot period will be given a flyer by the staff upon clinic checkout with information to take a brief 5-minute electronic survey. Recruitment will end once 300 surveys have been completed. While this intervention is tailored to Black cisgender women in terms of developed educational materials and provider communication, implementation strategy components are universal to all patients and, therefore, targeted sampling of only Black cisgender women will not be conducted. The brief electronic survey will include the following questions: (1) Did your provider (or other clinical staff members) take a history asking about your sexual activities and health? (2) Did you see educational materials during your visit about HIV prevention and a prevention method called PrEP (3) Did you speak with a provider about PrEP? (4) For those who spoke with a provider about PrEP, would you please describe the conversation and how you felt about communicating with your provider about this prevention strategy? As the survey contains both close-ended and open-ended questions, data will be analyzed both, quantitatively (descriptive statistics) and qualitatively (inductive and pattern coding).

The findings from the pilot will provide the necessary information to refine PrEP4Her for broader dissemination and future multisite implementation studies.

Ethical Considerations

Human Subject Ethics Review Approvals

The following study was approved by the University of Alabama at Birmingham's institutional review board (IRB#300008345) on December 2, 2022.

Informed Consent

An informed consent was collected and documented from all gynecological interview participants. The quantitative data used for this study was covered under the study's institutional review board and was secondary in nature that data was abstracted from available deidentified electronic medical records.

Privacy and Confidentiality

All data were deidentified before being analyzed.

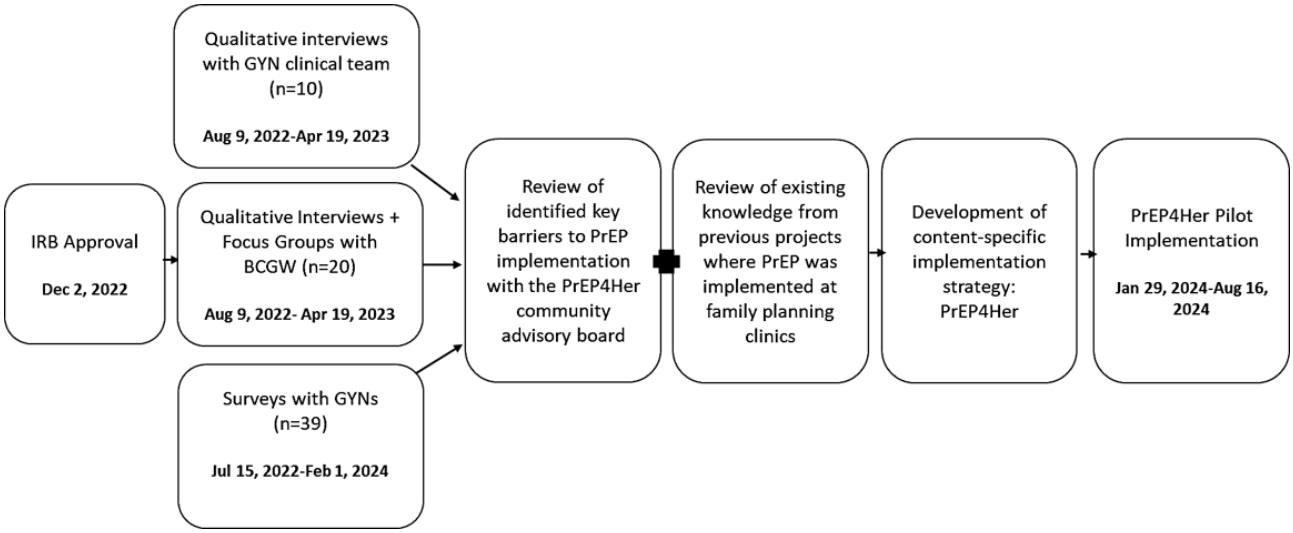
Compensation Details

All CAB members received a US $50 stipend per meeting. Each interviewee and focus group participant was compensated with US $50. Patients who will complete the electronic survey determining Fidelity will receive a compensation of US $20 after completion.

Results

Figure 3 outlines the PrEP4Her study timeline. The in-depth interviews with the gynecological care team were conducted between August 9, 2022, to April 19, 2023. A total of 10 in-depth interviews were conducted (40% were attending or training physicians). In addition, the cross-sectional study used data collected from surveys with gynecologists from July 15, 2022, to February 1, 2024 (n=39; 80% female). Moreover, the in-depth interviews and focus groups with black cisgender women (n=20) were conducted between Aug 9, 2022, to Apr 19, 2023. The qualitative findings from in-depth interviews with the gynecological care team (physicians, nurses, and medical assistants) and in-depth interviews and focus groups with women patients (64% black) highlighted a gap in care delivery for women (manuscript in the process of publication), suggesting additional training of providers may be beneficial. This was added as one of the strategies to improve PrEP uptake under the PrEP4Her implementation.

Figure 3. PrEP4Her study timeline BCGW: Black cisgender women; IRB: institutional review board; GYNs: gynecologists; PrEP: pre-exposure prophylaxis.



The qualitative and quantitative data were integrated through joint displays, bridging results using visual displays to connect major themes [51]. The combined findings provided an in-depth and granular understanding of key factors that were necessary to address in the development and refinement of PrEP4Her, as well as in the development of implementation strategies to support the integration of PrEP services into routine gynecological care. The PrEP4Her pilot was implemented from January 29, 2024, to August 16, 2024. The data gathered during the program are being used toward assessing the program's efficacy by measuring PrEP4Her's reach, effectiveness, adoption, acceptability, feasibility, and fidelity. The findings obtained would help guide the implementation of PrEP4Her at a larger scale.

Discussion

Anticipated Findings

The quantitative and qualitative data gathered to inform the development of PrEP4Her indicated a need to integrate PrEP services into an already existing and stretched gynecology clinic workflow by optimizing medical assistants and apps to aid in sexual history screening and provision of PrEP services. In addition, there was a gap in knowledge around PrEP as an HIV prevention option for cisgender women and the desire among Black cisgender women to have sexual health and PrEP services integrated into routine gynecology care. This information helped guide the PrEP4Her program implementation in the most effective manner.

PrEP is a highly effective method to decrease HIV acquisition among cisgender women. However, its impact to improve HIV outcomes among women has been hindered due to poor understanding of how to effectively identify strategies to improve uptake among cisgender women. Previous studies conducted at family planning clinics, aiming to improve PrEP uptake, found that although many cisgender women were willing to start PrEP, only a few obtained a prescription for PrEP, highlighting a gap between PrEP knowledge delivery and PrEP uptake. While cisgender women are disproportionately impacted by the HIV epidemic, Black cisgender women living in the Southern United States face heightened challenges such as decreased access to health care services and structural racism, which leads to medical mistrust and greater bias when engaging with providers [52]. Keeping these inequities in mind, the study aims to improve PrEP prescription in this population. We designed a novel intervention, PrEP4Her, which will be focused on increasing PrEP uptake as an effective HIV prevention tool among Black cisgender women by improving access and expanding provider options. Given the pilot site's Southern US location and the patient population served, preliminary results from this pilot will provide substantial guidance on the successful refinement and implementation of PrEP4Her in similar clinical-care settings across the South. In addition, sampling of gynecological providers across the Southeast United States allowed for greater generalizability of our implementation strategy to other Southern US states that have similar contexts (eg, access to medical resources, access to transportation, proximity to clinics, socioeconomic status, etc.).

PrEP4Her intervention is a novel approach hypothesized to significantly improve PrEP uptake among Black cisgender women. Completion of this study will result in the development of a culturally tailored strategy to improve uptake of PrEP among Black cisgender women. If PrEP4Her shows feasibility, acceptability, and preliminary efficacy in enhancing PrEP uptake for Black cisgender women, a subsequent R01 application will be prepared to conduct a fully powered implementation trial across multiple gynecology care sites across the South. Even in the absence of preliminary efficacy of the pilot, the knowledge gained around determinants and components to include in the PrEP4Her implementation strategy for integrating PrEP services into gynecological settings will provide novel insights to inform future HIV prevention research among this highly impacted group. The findings obtained from this study will be submitted to peer-reviewed journals for publication and presented at local and national conference meetings. Moreover, to disseminate these findings to the nonacademic community, we are currently in discussion with our patient CAB on the most appropriate method to do so. In addition, we are currently working with our institution's communication team to ensure that the patient

community is made aware of PrEP being offered at the gynecology continuity clinic.

Despite our efforts, our study has a few limitations. It is often challenging to engage clinical care teams to conduct interventions due to workflow demands and time constraints. This may impact the overall efficacy of PrEP4Her due to low adoption and lack of fidelity to PrEP4Her components. To overcome this barrier, investigators will work with leadership in identifying "champions" within the clinic setting to encourage PrEP4Her implementation. Inclusion of a physician practicing in the gynecology continuity clinic as part of our investigative team embeds a committed champion within our pilot site. In addition, recruitment of Black cisgender women will be carried out from our clinical site, to take part in both interviews and quantitative surveys throughout this proposal and this may pose a challenge. To overcome this, we will use well-established research advertising through the university and will also leverage provider referral and referral from our research staff to meet recruitment goals. There is a potential for selection bias, as Black cisgender women who are interested in participating in the study may experience less HIV and PrEP stigma than the general population. To overcome this, efforts will be placed to recruit participants via pamphlets at our clinical site with nonstigmatizing, health-promoting messaging to engage a representative sample. Finally, due to time and budgetary constraints, quantitative evaluation of PrEP adherence with drug level testing via blood or hair for those prescribed, will not be conducted. While this is not currently a primary end point for this study, we will measure PrEP adherence more objectively in a subsequent efficacy trial.

Conclusion

PrEP4Her intervention, by integrating PrEP services into existing gynecology clinic workflow, is aimed at improving PrEP uptake among Black cisgender women, a population disproportionately impacted by the HIV epidemic. Completion of the intervention will be followed by a multisite type III implementation trial for PrEP service delivery at gynecology clinics across the Southern United States.

Acknowledgments

Jessica Sales provided consultation in the development of the intervention.

This study was funded by the National Institute of Mental Health (R34MH128002).

We attest that generative artificial intelligence was not used for the generation of any portion of this manuscript.

Data Availability

The datasets generated during this study or those that will be generated or analyzed in the future will be available from the corresponding author on reasonable request.

Authors' Contributions

LE conceptualized the study and acquired funding for this project. LTM, AW, MCK, DP, HMG, and MJM advised on the project investigation and methodology. BJ performed activities associated with administration. MS wrote the manuscript. All authors provided feedback on the manuscript.

Conflicts of Interest

LE serves as an investigator on a Merck pharmaceuticals research grant.

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Abbreviations

CAB: Community Advisory Board
PrEP: pre-exposure prophylaxis
RE-AIM: Reach, Effectiveness, Adoption, Implementation, and Maintenance

Edited by A Schwartz; submitted 29.03.24; peer-reviewed by Anonymous, S Hill; comments to author 04.07.24; revised version received 07.08.24; accepted 24.01.25; published 14.03.25.

Please cite as:
Sohail M, Matthews L, Williams A, Kempf MC, Phillips D, Goymer H, Johnson, B, Mugavero M, Elopre L
Improving Pre-Exposure Prophylaxis Provision as Part of Routine Gynecologic Care Among Black Cisgender Women (Project PrEP4Her): Protocol for the Implementation of an Intervention
JMIR Res Protoc 2025;14:e58976
URL: https://www.researchprotocols.org/2025/1/e58976
doi:10.2196/58976
PMID:40085134

Protocol

Measuring Mental Health in 2 Brazilian University Centers: Protocol for a Cohort Survey

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Abstract

Background: Global concern for the mental well-being of university students is on the rise. Recent studies estimate that around 30% of students experience mental health disorders, and nearly 80% of these individuals do not receive adequate treatment. Brazil, home to around eight million university students, lacks sufficient research addressing their mental health. To address this gap, we aim to conduct a longitudinal mental health survey at 2 Brazilian universities.

Objective: This paper outlines the research protocol for a web-based mental health survey designed to assess the well-being of Brazilian university students.

Methods: The survey targets undergraduate students (N=8028) from 2 institutions: UniFAJ (Centro Universitário de Jaguariúna) and UniMAX (Centro Universitário Max Planck). Students will be invited to respond to self-reported questionnaires, including theSMILE-U (lifestyle and quality of life), the *DSM-5* (*Diagnostic and Statistical Manual of Mental Disorders* [Fifth Edition]) self-rated level 1 cross-cutting symptom measure, and a brief version of the Adult Self-Report Scale for attention-deficit/hyperactivity disorder. Students who exceed thresholds for conditions such as depression, anxiety, and attention-deficit/hyperactivity disorder will receive additional diagnostic instruments. The survey will be conducted annually, tracking individual and group trajectories and enrolling new cohorts each year. Data will be analyzed using cross-sectional and longitudinal methods, focusing on descriptive, associative, and trajectory analyses.

Results: The first wave of data collection began in February 2024 and is expected to conclude in December 2024. As of October 2024, a total of 2034 of 7455 (27.2 in 100) eligible students had completed the questionnaire. Cross-sectional statistical analysis is planned to commence immediately after data collection and is expected to be completed by June 2025.

Conclusions: This survey uses a scalable, cost-effective design to evaluate mental health conditions among Brazilian university students. The longitudinal framework facilitates the monitoring of mental health trends, supports the development of targeted interventions, and informs policy initiatives in higher education.

Trial Registration: OSF Registries OSF.IO/AM5WS; https://doi.org/10.17605/OSF.IO/AM5WS
International Registered Report Identifier (IRRID): DERR1-10.2196/63636

(JMIR Res Protoc 2025;14:e63636) doi:10.2196/63636

KEYWORDS

study design; university students; mental health screening; longitudinal survey; college students

Introduction

The mental health of university students is a widely recognized global concern. The transition to university life marks a crucial developmental phase characterized by individuation, the establishment of new social connections, and increased autonomy and responsibility [1]. This period aligns with continued, rapid brain development at a time when university students are exposed to multiple risk factors known to affect mental health, including psychosocial stressors, recreational drug use, alcohol binging, and disruptions in sleep patterns [2]. Mental health disorders typically present before or during young adulthood, often going unrecognized for years, resulting in significant delays in receiving treatment. Failing to adequately address mental health issues in a timely fashion can lead to the progression of more complex outcomes, such as school dropout, addiction, and self-harm. Indeed, the international prevalence estimates of mental health disorders reveal higher rates among college students compared to the general population. For example, a multicenter study involving 13,984 students from 8 countries, led by the World Health Organization (WHO), demonstrated that one-third met the clinical criteria for a psychiatric disorder in the previous year [3]. The most frequently reported were depressive disorders (18.5%) and anxiety disorders (16.7%-18.6%), followed by alcohol (6.8%) and other substance use disorders (3%). Moreover, approximately 22.6% of university students reported experiencing suicidal thoughts. Tragically, suicide stands as the second leading cause of death within this population [4].

The presence of psychiatric disorders is linked to numerous detrimental consequences both in the short and long term. In the short term, individuals may experience a decline in their quality of life, poorer academic performance, increased absenteeism, and a higher likelihood of course dropout [5-7]. In the long term, individuals endure lower quality of life, higher unemployment rates, and socioeconomic impairment [8,9].

Though the alarming data presented above were derived from studies conducted in countries with diverse income levels, to date, there is a disproportionately limited body of evidence addressing the mental health issues of young adults attending universities in low- and middle-income countries. The few studies that have been conducted in Brazil have tended to focus on medical students, also unveiling concerns about rates of mental distress in this population [10] with approximately 37% of them undergoing psychiatric treatment. In a study by Campos et al [11], the most prevalent diagnoses were depression (39.1%) and anxiety disorders or phobias (33.2%) and 4.5% declare previous suicide attempts. Severe mental health disorders such as psychotic disorders (3.7%) and bipolar disorder (1.9%) were less common [11].

In Brazil, there are approximately eight million students enrolled in 2714 higher education institutions [12]. Extrapolating from international prevalence estimates, over two million Brazilian university students may be struggling with mental health issues.

UniFAJ (Centro Universitário de Jaguariúna) and UniMAX (Centro Universitário Max Planck) are private university centers located in the medium-sized cities of Jaguariúna and Indaiatuba in the southeast of Brazil. Together, they serve approximately 8000 students enrolled in undergraduate programs spanning technical fields (eg, administration, accounting, architecture, law, or engineering) and health sciences (eg, medicine, nursing, psychology, biomedicine, or veterinary medicine). These institutions are representative of the broader Brazilian university population, as more than 75% of Brazilian students are enrolled in private universities.

To address the gaps in national and international literature, we propose to measure the mental health of all undergraduate students of UniFAJ and UniMAX. The survey will assess the prevalence of psychopathological symptoms and identify associated factors. The survey will also address another largely unexplored facet of mental health issues, namely the longitudinal course of mental health and quality of life. To achieve these goals, we designed a web-based mental health survey suitable for Brazilian students. This paper aims to describe the protocol and methods for conducting a web-based mental health cohort study in 2 private Brazilian universities. We hypothesize that, consistent with international studies, we will find high rates of common mental disorders, such as anxiety and depression. Furthermore, we expect to identify distinct patterns of mental health disorders unique to the low- and middle-income context of Brazil. By following students over time, we hypothesize that mental health disorders will correlate with poorer academic performance and quality of life, consistent with findings in the international literature.

Methods

Overall Design

This study will use validated self-report questionnaires delivered through an electronic web-based survey. The protocol will be repeated annually starting in 2024, allowing for the evaluation of mental health trajectories over time and the inclusion of new cohorts of incoming students to assess potential trends specific to these groups. This study of the university population is an arm of a large mental health project carried out by the National CISM (Center for Research and Innovation in Mental Health) [13]. CISM aims to study and expand, over the next 10 years, knowledge about mental health conditions in the State of São Paulo, the biggest one in Brazil.

Participants and Recruitment

All undergraduate students enrolled at UniFAJ and UniMAX will be invited to participate annually. Invitations will be sent via email, providing a brief explanation of this study's objectives and encouraging participation through the electronic survey link.

We have devised several strategies aimed at maximizing participation. First, we will conduct wide media campaigns in the university to promote awareness concerning mental health and discuss the importance of this study. Second, professors of all disciplines will be encouraged to remind students to engage in the survey. Third, nonresponders and survey noncompleters will receive at least 3 invitation reminders via email, followed by 3 reminders via text message (WhatsApp; Meta Platforms). Importantly, students will be informed that the time spent on the survey will count as an equivalent complementary academic activity. All these steps will be executed anonymously to ensure students' privacy.

Upon receiving the invitation, students are required to read and sign an informed consent form (ICF). The consent form will clearly state that the participation is voluntary and that declining will not affect their academic standing or relationship with the university. Additionally, students who opt out will not receive further invitations.

The exclusion criteria are being younger than 18 years of age and limitations in accessing or responding to the survey (ie, no access to electronic devices or internet connection or being illiterate). These exclusions are expected to be negligible within this study population.

Instruments

We selected empirically validated psychometric self-report questionnaires, all of which have been translated and validated for Brazilian Portuguese and can be administered electronically. A key challenge in designing this survey was balancing the need for a comprehensive assessment of the targeted phenotypes with the potential impact of a lengthy survey on participant engagement. To address this, we adopted a 2-step strategy aimed at minimizing survey duration while maintaining comprehensiveness (Figure 1). In the first step, in addition to collecting sociodemographic and overall lifestyle or quality of life information in Short Inventory Lifestyle Evaluation [14], we will screen for an array of mental health conditions using the *DSM-5* (*Diagnostic and Statistical Manual of Mental Disorders* [Fifth Edition]) cross-sectional adult symptoms scale level 1 [15] and a short version of the Adult Self Report Scale for attention-deficit/hyperactivity disorder [16] (Table 1). In the second step, participants scoring above predefined thresholds in any domain will be invited to complete domain-specific psychometric scales. These scales assess conditions such as depression, mania, generalized anxiety, sleeping disorders, borderline personality disorder, obsessive-compulsive disorder, attention-deficit/hyperactivity disorder, substance use (Multimedia Appendix 1). After completing the relevant scales, participants will have the option to answer a questionnaire on personality traits (the Big Five Inventory [17]). The total time required to complete the survey will vary depending on the domains assessed, ranging from approximately 20 to 40 minutes. This streamlined approach ensures a balance between thorough mental health assessment and participant engagement by limiting survey fatigue.

Figure 1. Initial data collection scheme: The figure illustrates the initial data collection scheme, and the scales applied according to the screening presented. ASSIST 2.0: Alcohol, Smoking and Substance Involvement Screening Test; ASRS-18: Adult Self Report Scale; BFI: Big Five Inventory; BPDS: Borderline Personality Disorder Scale; GAD-7: Generalized Anxiety Disorder Scale-7; HCL-32: Hypomania Checklist scale; OCI-R: Obsession and Compulsion Inventory; PHQ-9: Depression Patient Health Questionnaire-9; PSQI: Pittsburgh Sleep Questionnaire; QSD: Sociodemographic Questionnaire; SMILE-C: University Short Multidimensional Inventory Lifestyle Evaluation.

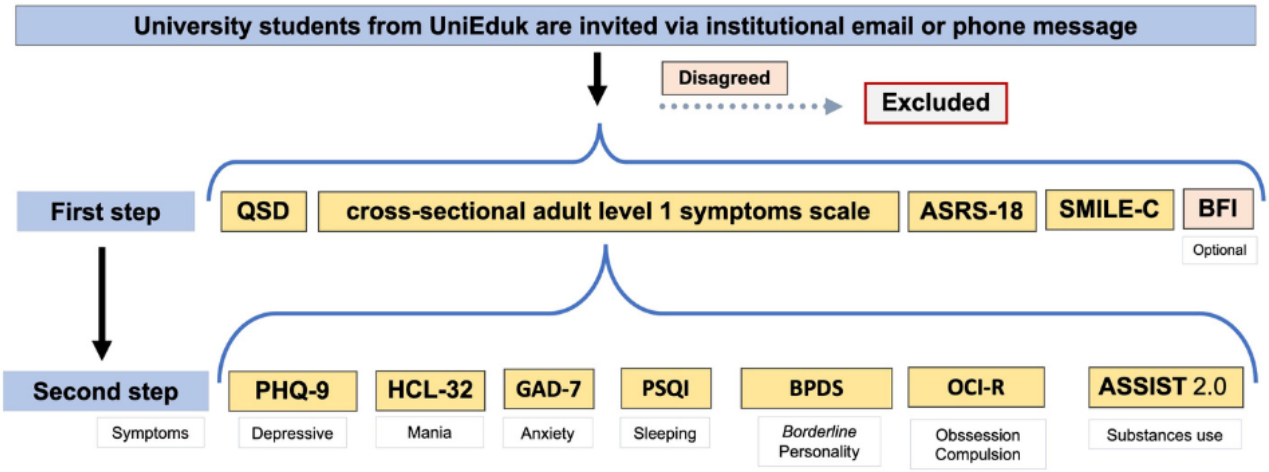


Table 1. Instruments used in step 1.

Instruments	Description
Sociodemographic Questionnaire (QSD)	The questionnaire was developed specifically for this study, including age, sexual identity and orientation, income, academic course, professional and career expectations, religiosity, use of social networks, and medical, psychiatric, or psychotherapeutic history.
The University Short Multidimensional Inventory Lifestyle Evaluation (SMILE-C)	Multidimensional assessment of lifestyle in 7 domains (diet, substance use, physical activity, stress management, social relationship, sleep, and screen time), along with an overall lifestyle score. The instrument comprises 24 questions that evaluate the frequency of behaviors considered healthy, with a response scale ranging from 0 to 4, where a higher score corresponds to a healthier lifestyle.
Adult Self Report Scale (ASRS-18)	Assesses symptoms of attention-deficit/hyperactivity disorder (ADHD) in adults, over the past 6 months, via 18 items divided into 2 domains: A (inattention) and B (hyperactivity-impulsivity). Responses for domain A vary as follows: 0=never, 1=rarely, 2=sometimes, 3=often, and 4=very often. As a screening measure, all participants will complete only the short version of this scale, which consists of 4 items (4, 5, 6, and 9) from part A and 2 items (1 and 5) from part B (hyperactivity). Those who score above 4 points on the short version will receive the complete version. Individuals are considered to have a possible diagnosis if they present at least 6 symptoms in at least 1 of the domains, or in both.
Cross-sectional adult level 1 symptoms scale (CSA) level 1 symptoms scale	Comprises 23 screening items that assess the frequency and intensity of symptoms across 13 domains of relevant symptomatology to frequent or severe psychiatric diagnoses. These domains include: sadness, irritability, mania, anxiety, somatic symptoms, suicidal ideation, psychosis, sleep disturbance, memory, repetitive thoughts and behaviors, dissociation, personality functioning, and substance use. Each item is rated on a 5-point scale (0=not at all; 1=very mild or rarely; 2=mild or several days; 3=moderate or more than half the days, and 4=severe or nearly every day).
Big Five Inventory (BFI)	The “Big Five” is an established model that analyzes 5 dimensions of personality: extroversion (tendency toward assertiveness and sociability), agreeableness (tendency toward reliability and altruism), conscientiousness (tendency to be careful and diligent), neuroticism (tendency toward negative emotions and sadness), and openness (tendency toward creativity and imagination). Likert-type scale with 44 items, where responses range from 1 (totally disagree), 2 (disagree a little), 3 (neither agree nor disagree), 4 (agree a little), to 5 (totally agree).

Data Collection Instruments

Data collection will be performed using REDCap (Research Electronic Data Capture; Vanderbilt University), a secure digital platform designed for data management and research studies. REDCap facilitates the deployment of standardized digital instruments while ensuring participant anonymity [18]. The platform provides a convenient “survey queue” for participants to access the survey questionnaires and a “to-do list” so they can keep track of their progress. This allows for the tracking of initial participation, completeness status, and longitudinal data collection for all participants. The REDCap feature best suited to address automation of the communication process and is, furthermore, better at data collection is the automated invitations. The participants receive an individual link, and we can choose how many reminders will be sent as well as their periodization.

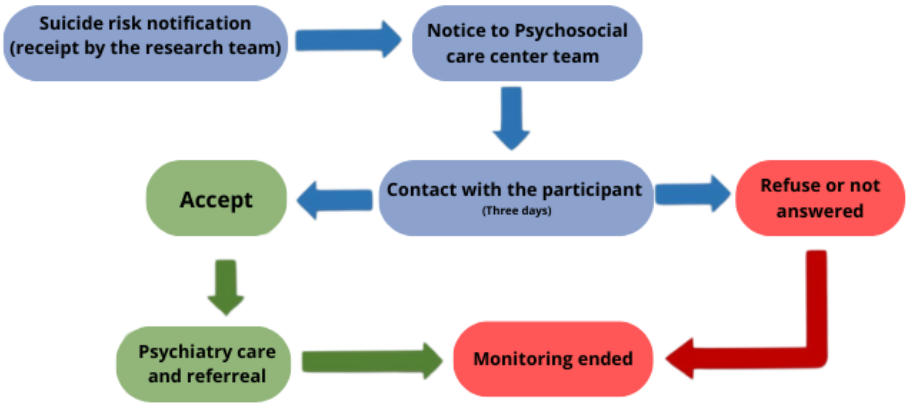
Survey Distribution Tools

We will upload student data straight from a file containing the emails of all enrolled students (provided by the university’s administration sector), in order to generate a unique individual ID link for each student. This will allow us to track the participants’ survey engagement or completion rate.

Reports and Alerts

The reports and alerts feature in REDCap will be used to monitor specific events and outcomes, particularly for suicide risk management (Figure 2). Suicide risk monitoring will rely on responses to the cross-sectional adult level 1 symptoms and PHQ-9 (Patient Health Questionnaire-9 depression) scales. The platform is programmed to generate immediate email alerts to this study’s team if participants affirmatively respond to either of 2 questions directly addressing suicidal ideation and suicide plans. This study’s team then immediately notifies a relevant health care team associated with our research group. Upon receiving this notification, the health care team will contact the participant to offer them appropriate psychiatric care. If the participant does not answer the first contact, the health care team will call again every day for 3 days. If the research participant accepts the offered care, they will be evaluated by psychiatry professionals and given necessary referrals. If they do not agree, this study’s team will register this nonagreement, and monitoring by the research team will end.

Figure 2. Suicide risk monitoring: The figure illustrates the monitoring protocol for participants identified as high risk of suicide.



Statistical Analyses

Given the annual assessments and longitudinal tracking of students throughout their university journey, we will use statistical methods suitable for both cross-sectional and longitudinal analyses. To enhance the representativeness of the sample, poststratification weights will be applied based on demographic data (eg, sex or age major) of the entire target sample provided by the university. All tests will be performed with a significance level of P=.05.

Descriptive Analysis

We will perform descriptive analyses to characterize this study's population. Summary statistics such as means, SDs, and medians will be computed for continuous variables (eg, age and quality of life) and frequencies and proportions for categorical variables (eg, gender or sexual orientation). Psychometric scales will be categorized into binary outcomes (absence or presence) based on established cutoff values.

Simple Cross-Sectional Analyses

We will explore associations between sociodemographic characteristics, quality of life scores, personality traits, and the prevalence of psychopathological symptoms using parametric and nonparametric statistical tests (eg, chi-square tests for categorical variables, *t* tests [2-tailed], or Mann-Whitney *U* tests for continuous variables). For significant associations, odds ratios will be calculated to identify predictors of psychopathological symptoms. Linear or logistic regressions will be used to adjust for potential confounders, depending on the distribution of the outcome variable. Leveraging this study's design and large sample size, we will use data to infer potential changes in mental health indicators throughout the students' academic programs. This will involve comparing data from students at different stages of their academic journey (eg, first-year vs final-year students). To achieve this, generalized estimation equations will be used, with the independent variable year as a proxy for time. Models will control for confounding factors such as gender, age, and socioeconomic status.

Longitudinal Analyses or Cohort Analyses

By tracking students longitudinally throughout their university journey, we aim to identify variations in mental health outcomes and analyze the evolution of symptomatology over time. Generalized estimation equations will be used, including time as an independent variable to model these changes and examine patterns at both individual and group levels.

Ethical Considerations

This study adheres to the Code of Ethics of the World Medical Association (Declaration of Helsinki). This protocol was reviewed and approved by the Ethical Board Committee of the UniFAJ and UniMAX University Center (decision 6.153.870, 2023). This study follows the ethical principles outlined in Resolution 466/2012 of the National Health Council [19], which sets the guidelines and regulatory standards for research involving human beings in Brazil and complies with Law 14,874 which specifically governs human research ethics in the country. This study is registered in the Brazilian national system used to manage and oversee research involving human participants (Plataforma Brasil, under CAAE: 67251922.4.0000.0191), ensuring adherence to national regulations for research registration and monitoring.

Participation in this study is entirely voluntary. They will receive comprehensive information about the research objectives, methodology, and their rights. To ensure informed consent, this study uses a digital ICF via the REDCap e-consent platform. The ICF is presented in a clear and accessible format, explaining the purpose of the research and the voluntary nature of participation, and guarantees confidentiality and anonymity. Participants will be instructed to read the ICF and confirm their consent by responding to a specific question: "Have you understood the guidelines, and do you agree to participate freely, knowledgeably and spontaneously in this research?" If they agree, they are asked to enter their full name so that it can be attached to their acceptance to take part in this study. Additionally, the participant's electronic signature will be collected, and a copy of the ICF will be provided via email. The participant will then be directed to a link to the digital survey. If they do not agree, the participant will receive a thank you note and the contact will be closed.

Participation in this study will be voluntary, with participants' time and autonomy respected at all stages of the research. Participants may withdraw from this study at any time without any negative consequences or impact on their academic standing. This study involves completing a digital survey, ensuring a noninvasive and risk-free process. Study data will be deidentified to protect participants' privacy and for data

protection risks. No monetary compensation will be provided to the participants.

Results

The first wave of data collection for this cohort began in February 2024 and is scheduled to conclude in December 2024. As of October 2024, a total of 2034 of 7455 (27.27%) eligible students had completed the questionnaire. Cross-sectional statistical analysis is planned to commence immediately after data collection and is expected to be completed by June 2025.

Discussion

Principal Findings

The psychological well-being of young adult college students is gaining significant attention, as it is one of the major determinants of their overall academic success, personal development, and prospects. A healthy lifestyle, access to mental health services, and the cultural relevance of mental health interventions are some of the themes that the university students consider relevant [20]. Meanwhile, the existing literature endures a dearth of evidence concerning the mental health of university students in low- and middle-income countries. We have presented the protocol of our cohort study, outlining the design of a web-based survey suited for Brazilian university students, aimed to improve our knowledge about the mental health of this population, mitigating an important literature gap.

In this way, we can address the hypotheses of this research. The prevalence of common mental disorders in the world is, as shown, high. A replication study for other universities in the country allows us to learn about the prevalence of these disorders and the risk factors in Brazil. The prior work of the WHO evaluated sociodemographic correlates of mental disorders among first-year university students. They also used web-based self-report questionnaires about *DSM-IV* (*Diagnostic and Statistical Manual of Mental Disorders* [Fourth Edition]) mental disorders: major depression, mania or hypomania, generalized anxiety disorder, panic disorder, alcohol use disorder, and substance use disorder. Their results show high rates, one-third of the students screened positive for 1 common mental disorder [3]. We had some similarities and differences with the study by Auerbach et al [3]. Our protocol is also a web-based self-report questionnaire that contains sociodemographic aspects and mental health scales. We access more sociodemographic aspects than the WHO study and, in the same way, we access more mental health disorders instead (Figure 1) of only common mental disorders. Finally, our research had been projected to follow these universities' students, identifying some risk factors and consequences of mental health disorders.

The studies conducted in Brazil are mostly cross-sectional and their focus is on medical students [10]. The study by Miguel et al [10] showed higher rates of common mental disorders when in comparison to the WHO study [3]. Our study protocol describes a proposal to systematically and longitudinally survey the mental health of a large population of university students in Brazil. Our plan was based on methodological decisions that balance quality, precision, scalability, cost, and the likelihood of participant engagement.

Among the challenges encountered during the design of this web-based mental health survey, we have highlighted the need to assess a large number of potential participants and assess most psychopathological symptoms while aiming to be concise to achieve a maximum response rate and increase generalizability. Although university students are the majority in the digital world, they usually do not seek support [21]; therefore, another challenge is to engage them in web-based mental health surveys, through the many incentives we have described, we have accomplished a response rate of 2034 of 7455 (27.27%), which is relatively high compared to other web-based surveys.

Ethical considerations addressed here are related to the importance of interaction with the local health care services to provide assistance if cases of psychiatric emergency (ie, risk of suicide) are detected, as well as ensuring data privacy. We have also strived for this longitudinal study proposal to be as cost-efficient as possible considering financial constraints.

Our proposed use of an internet portal improved participant engagement and data integration and reduced longitudinal data collection's time and expense [22,23]. Indeed, automated data capture minimizes the need for paid researchers to run participants and enter data, while also reducing data entry errors [24]; as our survey involves multiple questionnaires, the platform allows for easier and more engaging access for potential participants [25]. Our dissemination plan has internal importance for promoting and preventing mental disorders at UniFAJ and UniMAX universities. The results of the research can be shared with the students themselves and with the university coordinators, guaranteeing confidentiality. Another of our dissemination plans is to share this data and results with the media and with the governments.

Finally, we believe that this protocol could be useful for monitoring mental health cross-sectionally and longitudinally in thousands of universities across Brazil, either to assess their mental health in a cost-efficient manner or guiding interventions such as preventive mental health programs or even screening students with high risk of having mental disorder. This would allow a positive impact on the burden of mental health in university students and ultimately in our communities.

Limitations

There are disadvantages associated with digital research. For example, open-ended questions cannot be explored with immediate follow-up questions and participants are unable to seek clarification of ambiguous items [26]. To address this issue, in the present survey, participants can easily email the project team with any questions they may have.

Selection bias presents another challenge for digital research. Internet access is affected by myriad variables including income, geographical location, mental health status, and age [27,28]. We do not anticipate serious issues with internet accessibility. UniFAJ and UniMAX have free internet access for all students. In addition, there were 181.8 million internet users in Brazil at the beginning of 2023, which means it is 84.3% of the

population [29]; and the southeast, where UniFAJ and UniMAX are, has an even greater user concentration. Our plan to remind participants via WhatsApp to finish their questions is sound, as WhatsApp is the most used social media by Brazilians, around 169 million [29]. Thus, though we cannot fully account for all these possibilities, the present strategy maximizes accessibility in a way that will mitigate these potential confounding issues and, consequently, increase the response rate.

After identifying participants, the present protocol contains strategies to maximize the probability that participants will continue to engage with and complete the survey. For example, one way to increase engagement is to provide participants with information about this study that (1) knows their interests, (2) helps them understand the importance of their participation in mental health research, and (3) increases their confidence about participating. To this end, the research team will hold meetings with UniFAJ and UniMAX course coordinators to transmit detailed study information so that it reaches the students. Furthermore, a 2-minute video will be sent to all participants. This video contains information about the research team, the reason for the research and its objectives, details about the questionnaires (application time, confidentiality, or freedom to decline), and the opportunity to ask questions via email. We intend to demonstrate the importance of participation in promoting mental health among the university population.

The security of collected data is ensured by the REDCap platform, a trusted and secure data collection and storage platform [30] used throughout the scientific community. The platform allows for the long-term reduction of research costs, the possibility of use on many devices, and rapid data entry, review, and analysis [31].

As noted in the Introduction section, there is a paucity of data that have been collected from low- and middle-income countries. Existing studies were carried out mainly with students from specific courses [32]. The data analysis will summarize the data collected and integrate information about the mental health of this population. It will allow us to better understand the mental health of the Brazilian university population This survey is a structured means for assessing this population's mental health given that it has been well established that preventive actions are feasible, cost-effective, and efficient in improving overall mental health [33] and this period of life represents a hub that critically impacts their responsibilities, mental health, values, and outcomes [34]. We believe that the results of this survey could in the future guide policy makers in the design and implementation of preventive programs destined specifically for this public group and ultimately have a positive impact on the mental health of our communities.

Conclusion

College and university students have high rates of mental health issues. We have developed and described a web-based mental health survey that will allow us to evaluate and detect these issues with low cost and reasonable response rate in a university in Brazil. These efforts will allow us, soon, to monitor and test the efficiency and impact of mental health preventive programs. The accurate and representative data about mental health disorders, their risk factors, and the quality of life of these universities' students can lead the path for new policies to ensure mental health and quality of life for these populations.

This model could be scaled up across other universities in Brazil to easily assess the mental health status of their students and have a significant impact on the mental health of our communities.

Acknowledgments

This study was supported with grants from the National Center for Research and Innovation in Mental Health (CISM): Grant Fundação de Amparo à Pesquisa do Estado de São Paulo (FAPESP; 2021/12901-9) and Banco Industrial do Brasil S/A. FAPESP also provided a grant to this study (2021/05332-8). This study also received financial support from Conselho Nacional de Desenvolvimento Científico e Tecnológico (Coordenação de Aperfeiçoamento de Pessoal de Nível Superior; CAPES) through scholarships.

Data Availability

Data sharing is not applicable to this article as no data sets were generated or analyzed during this study.

Authors' Contributions

All authors contributed to this paper. TDS contributed to the conceptualization, formal analysis, project administration, review and editing of the writing, and supervision. AGN carried out the formal analysis, writing of the original draft, and supervision. PF handled the conceptualization, investigation, data curation, review and editing of the writing, and supervision. VM worked on the writing of the original draft and supervision. GCAdA, CFPV, LCdO, LOdC, EMMK, and LAZG assisted in the writing of the original draft, software, and methodology. LDFC aided with the resources and visualization. VCCJ conducted the visualization, software, and methodology. EdCH was responsible for the validation and visualization. ECMF was involved in the funding acquisition, supervision, validation, and visualization. AC did the project administration, resources, funding acquisition, supervision, validation, and visualization.

Conflicts of Interest

None declared. AC has served as a consultant for Knight Therapeutics and Libbs, but this work is not related to the topic of this manuscript.

Multimedia Appendix 1
Instruments to be used in step 2.
[DOCX File , 17 KB - resprot_v14i1e63636_app1.docx]

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Abbreviations

CISM: Center for Research and Innovation in Mental Health
DSM-5: Diagnostic and Statistical Manual of Mental Disorders [Fifth Edition]
DSM-IV: Diagnostic and Statistical Manual of Mental Disorders [Fourth Edition]
ICF: informed consent form
PHQ-9: Patient Health Questionnaire-9
REDCap: Research Electronic Data Capture
UniFAJ: Centro Universitário de Jaguariúna
UniMAX: Centro Universitário Max Planck
WHO: World Health Organization

Edited by A Schwartz; submitted 25.06.24; peer-reviewed by RF Damiano, OE Santangelo; comments to author 18.10.24; revised version received 07.12.24; accepted 19.12.24; published 14.03.25.

Please cite as:
Di Santi T, Nascimento AG, Fukuti P, Marchisio V, Araujo do Amaral GC, Vaz CFP, Carrijo LDF, Oliveira LCD, Costa LOD, Mancini Marion Konieczniak E, Zuppi Garcia LA, Cabrelon Jusevicius VC, Humes EDC, Rossi Menezes P, Miguel E, Caye A
Measuring Mental Health in 2 Brazilian University Centers: Protocol for a Cohort Survey
JMIR Res Protoc 2025;14:e63636
URL: https://www.researchprotocols.org/2025/1/e63636
doi:10.2196/63636
PMID:40085140

Protocol

Estimating the Burden of Common Mental Disorders Attributable to Lifestyle Factors: Protocol for the Global Burden of Disease Lifestyle and Mental Disorder (GLAD) Project

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Abstract

Background: The Global Burden of Diseases, Injuries, and Risk Factors Study (GBD) collects and calculates risk-outcome data for modifiable lifestyle exposures (eg, dietary intake) and physical health outcomes (eg, cancers). These estimates form a critical digital resource tool, the GBD VizHub data visualization tool, for governments and policy makers to guide local, regional, and global health decisions. Despite evidence showing the contributions of lifestyle exposures to common mental disorders (CMDs), such as depression and anxiety, GBD does not currently generate these lifestyle exposure-mental disorder outcome pairings. This gap is due to a lack of uniformly collected and analyzed data about these exposures as they relate to CMDs. Such data are required to quantify whether, and to what degree, the global burden of CMDs could be reduced by targeting lifestyle

factors at regional and global levels. We have established the Global burden of disease Lifestyle And mental Disorder (GLAD) Taskforce to address this gap.

Objective: This study aims to generate the necessary estimates to afford the inclusion of lifestyle exposures as risk factors for CMDs in the GBD study and the GBD digital visualization tools, initially focusing on the relationship between dietary intake and CMDs.

Methods: The GLAD project is a multicenter, collaborative effort to integrate lifestyle exposures as risk factors for CMDs in the GBD study. To achieve this aim, global epidemiological studies will be recruited to conduct harmonized data analyses estimating the risk, odds, or hazards of lifestyle exposures with CMD outcomes. Initially, these models will focus on the relationship between dietary intake, as defined by the GBD, and anxiety and depression.

Results: As of August 2024, 18 longitudinal cohort studies from 9 countries (Australia: n=4; Brazil: n=1; France: n=1; Italy: n=3; The Netherlands: n=3; New Zealand: n=1; South Africa: n=1; Spain: n=1; and United Kingdom: n=3) have agreed to participate in the GLAD project.

Conclusions: Our comprehensive, collaborative approach allows for the concurrent execution of a harmonized statistical analysis protocol across multiple, internationally renowned epidemiological cohorts. These results will be used to inform the GBD study and incorporate lifestyle risk factors for CMD in the GBD digital platform. Consequently, given the worldwide influence of the GBD study, findings from the GLAD project can offer valuable insights to policy makers worldwide around lifestyle-based mental health care.

International Registered Report Identifier (IRRID): DERR1-10.2196/65576

(JMIR Res Protoc 2025;14:e65576) doi:10.2196/65576

KEYWORDS

mental health; depression; anxiety; diet; lifestyle; mental disorders; epidemiology; burden of disease

Introduction

Mental disorders rank among the top 10 leading causes of disease and economic burden worldwide. They account for 4.9% of global disability-adjusted life years [1] and it has been projected that by 2030 mental disorders will account for more than half of the economic burden attributable to noncommunicable diseases [2]. Given the recognized burden on individuals, communities, and economies [1,3], identifying risk factors for common mental disorders (CMDs), namely depression and anxiety disorders, is critical for early prediction, prevention, and treatment. While known risk factors such as genetics, childhood adversity, and family conflict have a significant impact on CMD risk [4], preventative efforts should also address potentially more modifiable factors that may have broader reach.

Over the past decade, evidence has emerged highlighting lifestyle behaviors as modifiable risk factors for CMDs. A recent meta-review, drawing from top-tier data such as meta-analyses of prospective cohort studies, Mendelian randomization studies, and randomized controlled trials, emphasized the significant role of lifestyle behaviors pertaining to diet quality, physical activity, smoking, and sleep in CMD risk [5]. Furthermore, current evidence indicates that targeting these lifestyle behaviors can ameliorate the risk of CMDs. For example, data involving adult participants from France estimate that 14% of incident cases of depression are attributable to a combination of unhealthful diet, weight, and smoking [6]. Promisingly, data from Norwegian adults show that 12% of de novo depression could be averted if an individual engages in at least 1 hour of physical activity per week [7]. Collectively, this evidence highlights the importance of lifestyle factors in mental health outcomes, which has implications regarding prevention and treatment.

Despite ample evidence supporting the inclusion of lifestyle-based mental health care in clinical recommendations and population-level strategies [8], exemplified by clinical practice guidelines from organizations such as the Royal Australian and New Zealand College of Psychiatrists [9], the global implementation of these strategies for addressing CMDs remains limited. Global nutritional recommendations focus largely on individual food groups or constituents, and not on the dietary patterns, such as the Mediterranean diet, that are commonly used in research. As such, the evidence regarding whether dietary components would be useful to the target population's mental health is unclear. Furthermore, it is widely acknowledged that numerous structural barriers hinder the improvement of lifestyle behaviors, including social, financial, and environmental determinants [10,11]. These barriers also exist in mental health treatment and care [12]. Therefore, there is merit in attempting to reduce the incidence of CMDs by improving lifestyle behaviors, not just at the individual level, but also through population and policy-level strategies. To inform such strategies worldwide, rigorous global data are required to quantify the contribution of lifestyle behaviors to the risk of population CMDs.

The largest epidemiological study worldwide, the Global Burden of Diseases, Injuries, and Risk Factors Study (GBD), provides important global health estimates that inform public health priority setting and policies. A critical tool used by the GBD to communicate the current state of health and disease for different countries is the digital platform, the GBD VizHub Data visualization tool [13]. This digital platform allows policy makers to quickly ascertain where the greatest improvements in public health could be achieved by targeting specific risk

factors. The GBD currently provides comprehensive estimates of lifestyle risks, such as diet, for a range of physical conditions, but has yet to incorporate estimates of these lifestyle risks for CMDs. This may be due to challenges in operationalizing and standardizing the measurement of lifestyle factors and CMD outcomes across studies, aligning them with GBD classifications and definitions, and establishing clear cause-and-effect relationships, particularly given the typical clustering of lifestyle risk factors [14-16]. In addition, studies investigating the associations between lifestyle risk factors and CMDs often face issues such as a lack of global representation, small sample sizes, inconsistent methodologies, residual confounding, and measurement error, particularly in regard to measuring dietary intake or ensuring adherence in intervention studies [17]. Consequently, while these factors are well-recognized risk factors for physical illnesses like heart disease and diabetes, the potential for lifestyle targets to be considered relevant to the population's mental health has historically been neglected [18].

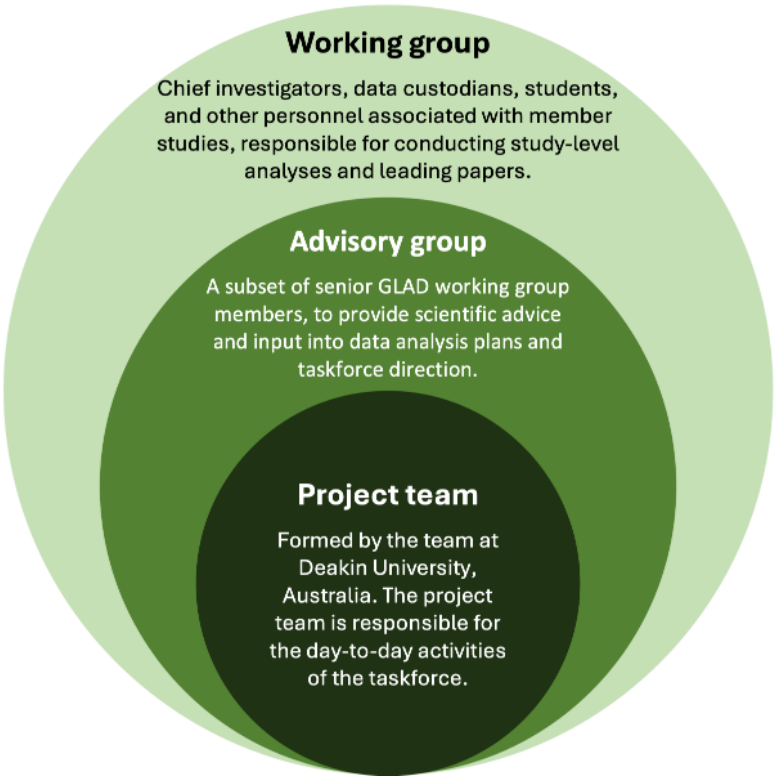
To include lifestyle exposures as risk factors for CMDs on the GBD digital platform, the Global burden of disease Lifestyle And mental Disorder (GLAD) Taskforce (a large-scale, coordinated, international collaborative effort) has been formed. The Taskforce comprises global epidemiological experts who will work with GBD representatives to oversee the comprehensive evaluation of the association of lifestyle risk factors with CMDs, starting with dietary intake as the exposure of interest (the GLAD project). These experts have developed a harmonized approach for individual studies to conduct analyses (the GLAD project) to enable the integration of lifestyle factors as a risk for CMDs in the GBD. This paper outlines the processes by which the GLAD project and participant member studies will execute this harmonized data analysis protocol on their own datasets and disseminate their results through peer-reviewed publications. The overarching aim of the GLAD project is to generate robust, comparable evidence on the global risk of CMDs attributable to lifestyle factors, ultimately enabling their inclusion as risk factors for CMDs within the GBD framework. We hypothesize that more healthful lifestyle factors, such as higher intakes of healthful dietary components (eg, fruits, vegetables, whole grains, and fiber) will be associated with a lower risk of CMDs. Conversely, we hypothesize that less healthful lifestyle factors, such as higher intake of less healthful dietary components (eg, processed meat, sugar-sweetened beverages, and sodium) will be associated with a higher risk of CMDs.

Methods

Recruitment

The GLAD project is a collective, multistudy initiative led by Deakin University's, Food and Mood Center, which is situated within the Institute for Mental and Physical Health and Clinical Translation, School of Medicine, Barwon Health, Geelong, Australia. The GLAD project will be completed by the GLAD task force, comprising the project team, the advisory group, and the working group containing all member studies (Figure 1).

Figure 1. The GLAD taskforce composition and responsibilities within the GLAD project. GLAD: Global burden of disease Lifestyle And mental Disorders.



To identify potential member studies for participation in the GLAD project, which would apply the harmonized data analysis protocol to their own datasets and contribute their results to the broader initiative, we used a multistep process. The first step was to identify epidemiological studies that had the necessary variables by which the study lead or representative could execute

our analysis plan (eg, food frequency questionnaires from which to derive GBD-defined dietary risks combined with mental health questionnaires to identify cases of depression or anxiety). This process involved a literature search to identify potentially eligible studies and key contacts to approach for invitation to participate in the GLAD project. To operationalize the dietary risk variables, we used previous GBD papers, which contained the definitions of each dietary exposure (Table 1) and depression and anxiety (Table 2) [1,19]. In addition to using the literature to identify potentially eligible datasets, we also drew on previous collaborations of the GLAD project team and researchers in the field of nutritional psychiatry (eg, via the International Society of Nutritional Psychiatric Research), as well as promoting the project on Food and Mood Center social media sites. Data custodians of identified studies were contacted, and those with relevant data and who had the capacity to participate in the GLAD project completed an expression of interest via the Food and Mood Center website.

To be eligible for inclusion, member studies must have dietary intake (Table 1) and depression and anxiety outcomes (Table 2) consistent with GBD definitions, or the ability to recode existing variables accordingly. Any deviations to these definitions must be reported and will be accounted for accordingly as reported below in "Future Directions: Meta-analyses." Any study design, in any location, with any sample size, is eligible to be a member study and can complete the required data analysis.

Table 1. Dietary exposure definitions and required coding for the GLAD project[a].

Dietary risk factor	GBD[b] exposure definition	Required coding[c]
Fruits	Average daily consumption of less than 310-340 g of fruit including fresh, frozen, cooked, canned, or dried fruit, excluding fruit juices and salted or pickled fruits.	grams/day
Vegetables	Average daily consumption of less than 280-320 g of vegetables, including fresh, frozen, cooked, canned, or dried vegetables and excluding legumes and salted or pickled vegetables, juices, nuts and seeds, and starchy vegetables such as potatoes or corn.	grams/day
Legumes	Average daily consumption of less than 90-100 g of legumes and pulses, including fresh, frozen, cooked, canned, or dried legumes.	grams/day
Whole grains	Average daily consumption of less than 140-160 g of whole grains from breakfast cereals, bread, rice, pasta, biscuits, muffins, tortillas, pancakes, and other sources.	grams/day
Nuts and seeds	Average daily consumption of less than 10-19 g of nuts and seeds.	grams/day
Milk	Average daily consumption of less than 360-500 g of milk including non-fat, low-fat, and full-fat milk, excluding plant derivatives.	grams/day
Red meat	Any intake of red meat including beef, pork, lamb, and goat but excluding poultry, fish, eggs, and all processed meats.	grams/day
Processed meat	Any intake of meat preserved by smoking, curing, salting, or addition of chemical preservatives.	grams/day
Sugar-sweetened beverages	Any intake of beverages with ≥50 kcal per 226.8-g serving, including carbonated beverages, sodas, energy drinks, and fruit drinks, but excluding 100% fruit and vegetable juices.	grams/day
Fiber	Average daily consumption of less than 21-22 g of fiber from all sources including fruits, vegetables, grains, legumes, and pulses.	grams/day
Calcium	Average daily consumption of less than 1.06-1.1 g of calcium from all sources, including milk, yogurt, and cheese.	grams/day
Seafood omega-3 fatty acids	Average daily consumption of less than 430-470 mg of eicosapentaenoic acid and docosahexaenoic acid.	milligrams/day
Polyunsaturated fatty acids	Average daily consumption of less than 7%-9% of total energy intake from polyunsaturated fatty acids.	total percentage of daily energy intake
Trans fatty acids	Any intake of trans fat from all sources, mainly partially hydrogenated vegetable oils and ruminant products.	total percentage of daily energy intake
Sodium	Average 24-hour urinary sodium excretion greater than 1-5 g.	grams/day
Ultra-processed foods (optional)	Any intake of ultraprocessed foods, as defined by the Nova system as any food item in Nova category 4 ("ultraprocessed food"), in grams [20].	grams/day

[a]Based on the GBD (Global Burden of Diseases, Injuries, and Risk Factors Study) risk exposure definitions (Pages 217-218 in Supplementary Appendix 1 in the study by the the GBD 2019 Risk Factors Collaborators [19]).

[b]GBD: Global Burden of Diseases, Injuries, and Risk Factors Study.

[c]Analyses using continuous exposures are required by the GLAD Taskforce. The units listed here are recommended, however, these may be rescaled to more meaningful units in papers (eg, per 10 g) provided the original units are available to the project team.

Table 2. Mental health definitions and recommended coding for the GLAD[a] project[b].

Mental disorder	Outcome definition	Diagnostic reference	Recommended coding[c]
Major depressive disorder	Involves the presence of at least one major depressive episode, which is the experience of either depressed mood or loss of interest/pleasure, for most of every day, for at least two weeks.	DSM-IV-TR[d]: 296.21–24; 296.31–34. ICD-10[e]: F32.0-9; F33.0-9.	0=no MDD[f]; 1= MDD
Anxiety disorders (any subtype)	Involves experiences of intense fear and distress, typically in combination with other physiological symptoms. Anxiety disorders will be modeled as a single cause for "any" anxiety disorder to avoid the double-counting of individuals meeting criteria for more than one anxiety disorder. Epidemiological estimates reporting an outcome for "any" or "total" anxiety disorders will be included if they reported on at least three anxiety disorders.	DSM-IV-TR: 300.0-300.3; 208.3; 309.21; 309.81. ICD-10: F40-42; F43.0; F43.1; F93.0-93.2; F93.8.	0=no anxiety disorder; 1=anxiety disorder

[a]GLAD: Global burden of disease Lifestyle And mental Disorders.

[b]The definitions and diagnostic references presented in this table are the current definitions used by the GBD (Page 4 in the Supplementary Appendix in the study by the GBD 2019 Mental Disorders Collaborators [1]). Since GLAD members may use alternative methods to ascertain disorder status, definitions or diagnostic references may vary slightly. For example, somatic forms of depression may be captured more by symptom scales, or studies using prescriptions may use Anatomical Therapeutic Chemical codes to determine incident depression and anxiety.

[c]Outcomes must be binary (condition present vs condition absent). For studies that only use symptom scales, validated cutoffs can be used to determine condition present versus condition absent (refer to Multimedia Appendix 1).

[d]*DSM-IV-TR*: *Diagnostic and Statistical Manual of Mental Disorders (Fourth Edition, Text Revision).*

[e]*ICD-10*: *International Statistical Classification of Diseases, Tenth Revision*.

[f]MDD: major depressive disorder.

Statistical Analysis

Overview

The GLAD project and the following methods have been prospectively registered on the Open Science Framework [21]. The methods outlined herewith are based on the most up-to-date definitions used by the GBD, at the time of writing this protocol. Given that the GBD is subject to change, future iterations may vary in accordance with such amendments. The initial iteration of the GLAD project will focus on dietary exposures, and the methods described within this protocol refer specifically to this first iteration. Subsequent updates to the protocol may be made when additional lifestyle risk factors are considered in future iterations of the GLAD project.

Exposure and Outcome Definitions

Definitions of dietary intakes and CMDs are based on definitions used by the GBD [1,18]. In addition to the 15 dietary intakes used by the GBD, ultraprocessed food intake will be included where practicable given the increasing literature in the field linking this dietary exposure to a wide range of health outcomes [22-25]. In doing so, we will use the most widely adopted food classification system based on the purpose and extent of industrial food processing, Nova, to define ultraprocessed foods [20]. Furthermore, we will follow best practice guidelines when categorizing foods according to the Nova food classification system [26].

CMDs can be measured differently across epidemiological studies. They are most commonly assessed using self-reported symptom scales with cutoffs for diagnosis, from medical records, or using diagnostic interviews. Multimedia Appendix 1 outlines some commonly used tools and their recommended cutoffs for identifying symptoms of depression and anxiety. The sensitivity, specificity, and diagnostic accuracy of these tools largely depend on the population. When undertaking meta-analyses, we may conduct a sensitivity analysis to determine if the magnitudes of associations change based on exposure and outcome measurement or ascertainment type.

Covariates and Confounders

To address the anticipated heterogeneity of member studies' available data, a set of core confounders are provided for the purpose of generating a consistent minimally adjusted analysis. The conduct of additional analyses (eg, using additional variables, fitting sensitivity models, or exploratory analyses) is at the discretion of the study author or authors based on available data and reviewer requests when studies are submitted for publication.

To be included in the GLAD project, member studies must adhere to the iteratively adjusted models (Textbox 1).

Textbox 1. The iteratively adjusted statistical models required for the Global burden of disease Lifestyle And mental Disorders (GLAD) task force.

- Model 1: Unadjusted model, with the dietary variable (as listed in Table 2) as the exposure and depression or anxiety as the outcome.
- Model 2: Minimally adjusted model, with the dietary variable of interest, depression or anxiety, and with baseline mental disorder status (or lifetime history of mental disorders for cross-sectional studies), age, sex, and a measure of socioeconomic status, such as household income, employment status, or education.
- Sensitivity model: Same as model 2, but with adjustment for total energy intake.

Of particular relevance in nutritional epidemiology are methods for adjusting for energy intake. Intake of specific nutrients are correlated with total energy intake, and so appropriate adjustment is required to disentangle the effect of the nutrient from the effect of energy. For example, an individual may alter intake of a specific nutrient by changing dietary composition, and not by changing total energy intake. As such, controlling energy intake can reduce confounding, and failure to appropriately control for total energy intake may nullify associations between nutrient intake and disease outcomes [27]. Given the correlation between nutrient intake and energy, the application of Willett's residual method is recommended to account for total energy intake [27]. This involves fitting a regression model with the dietary variable as the outcome and total energy intake as the exposure, predicting residuals from this model, and then using these predicted residuals in the analysis models [27].

Reporting Baseline and Demographic Characteristics

To describe participant characteristics, authors of member studies include a table containing descriptive statistics, given as n (%) for categorical variables, and mean (SD) or median (25th-75th percentile) for continuous variables. A column containing *P* values will not be included, as statistical tests do not meaningfully assess differences between samples or populations, nor should they be used as the basis for assessing confounders [28].

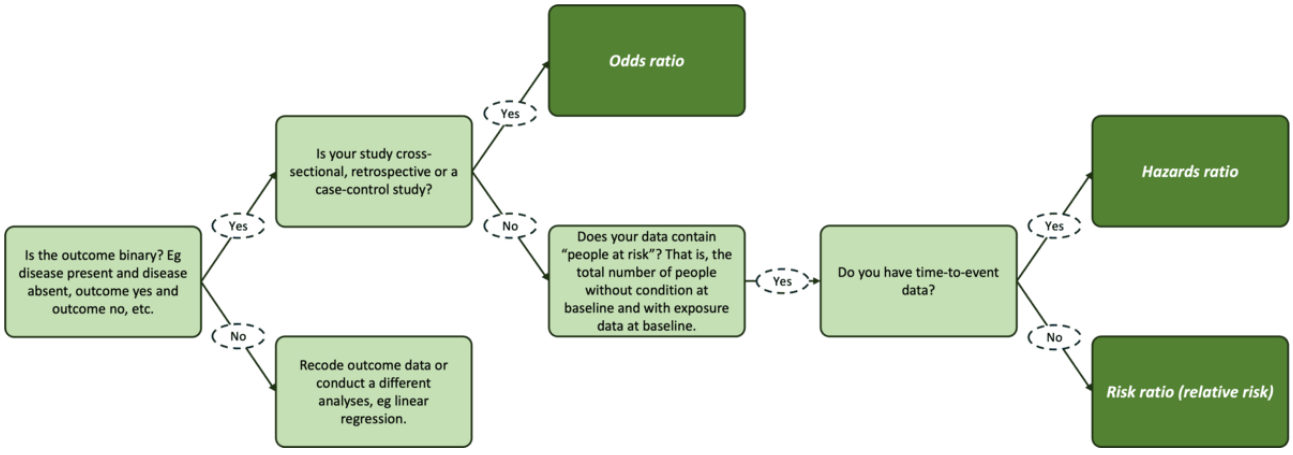
Estimating Risk Ratios, Odds Ratios, and Hazards Ratios

Each study is required to use risk ratios (estimated by Poisson regression with robust SE) as the primary means of assessing the association of dietary intake with CMDs. Risk ratios are based on incident cases, and so models will need to exclude participants with depression or anxiety at baseline. Furthermore, to determine incident risk, studies must have dietary exposures at baseline and depression, or anxiety measured at a subsequent time point. Where the estimation of a risk ratio is not possible (refer to Figure 2), for example, where the total number of people exposed at baseline is not available (such as for retrospective or case-control studies) [29], odds ratios are estimated using standard logistic regression techniques. Where only time-to-event data are available, hazard ratios are used, estimated by a Cox proportional hazards model. For rigor, all effect estimates will be accompanied by a 95% CI and exact *P* value [30].

Models can be fitted using any statistical analysis software, including R (R Core Team), SAS/STAT (SAS Institute Inc), Stata (StataCorp LLC), and SPSS (IBM Corp). Before fitting the relevant models, Member studies must assess model assumptions. Should any model assumptions be violated, an alternate approach to analysis may be selected. For example, the nonlinearity of continuous variables should be investigated, and transformations or nonlinear models fitted where necessary. Similarly, should any of the assumptions of Cox proportional hazards models be violated, alternative strategies will be deployed to account for these violations.

In addition to the models listed above, the following subgroups shall be fitted separately for each exposure-outcome pairing, where data allows: (1) sex, (2) age, (3) year (for longitudinal studies with multiple waves of follow-up), (4) country (for multicenter studies), and (5) all symptom scales and diagnostic measures (for studies with depression and anxiety measured via multiple measures. For age, studies should explore the relationship between the risk factors and mental disorders with age to see if a continuous measure is appropriate. Where a continuous measure is not appropriate, studies should generate appropriate age categories for their dataset by inspecting the frequency of outcomes by age groups. As a guide, the GBD currently uses 0-6 days (early neonatal), 7-27 days (late neonatal), 28-365 days, 1-4 years, 5-9 years, then 5-year intervals from 10-95 [31].

Figure 2. The types of ratio measures that can be obtained from binary outcome data. Odds ratios will be estimated using logistic regression, risk ratios will be estimated using Poisson regression with robust SE, and hazard ratios will be estimated using Cox regression.



Sensitivity Models

Multiple Testing

Given the need for multiple models to be fitted within each study, the GLAD Taskforce recommends a *P* value adjustment procedure, such as the Simes method, to minimize the chance of a type 1 error and determine whether multiple testing may be influencing results [32]. This should be applied to all models in a study where multiple models are required.

Outliers and Influential Data

Initial models include all available data points, with sensitivity analyses included for any influential or outlying observations. Influential observations are determined by predicting residuals, Cook's distance, or DFBETA after fitting the relevant model. Although several cutoff points have been proposed to identify influential observations, conventional cutoffs are applied: 3 for standardized residuals [33]; 4/(n-p) for Cook's Distance [34], where n=sample size and p=number of parameters in the model; and $2/\sqrt{n}$ for DFBETA [35].

Missing Data

Each study initially uses a complete-case model, whereby individuals with missing observations are excluded from the model. Member Studies with missing exposure, outcome, and covariate observations conduct a missing data analysis to determine the influence of missing data. While a multiple imputation approach is preferred, other methods such as k-nearest neighbor imputation or inverse probability weighting may be used where an imputation approach is not possible or appropriate [36-41].

Future Directions: Meta-Analyses

Upon completion of the analysis phase of the GLAD project (phase 2), the GLAD project team and advisory group will lead a meta-analysis (phase 3). A separate protocol will be created for this phase of the GLAD project. Briefly, the GLAD project team will conduct a systematic literature review to identify any relevant studies not already participating in GLAD. After screening abstracts and full text, data will be extracted from all identified studies and studies participating in GLAD. A random effects meta-analysis will be performed to pool results from all eligible studies. We will perform a meta-regression to quantify how the risk can vary by demographic factors, and methodological biases [42]. Where studies have used different assessment methods for mental health outcomes, different tools to ascertain dietary intake, any slight deviations to definitions, or where studies use different analysis strategies, we will perform cross-walking or sensitivity analyses to ensure comparability [43]. Papers using methods that deviate substantially from the methods described in this paper will be excluded from the meta-analysis. The resulting meta-analysis will be reported according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses).

Ethical Considerations

Each member study will have obtained informed consent from participants and had their study approved by institutional ethics review boards. Full details for ethics for each study can be found in previous studies [44-65] and a summary is provided below. This study is registered in the Open Science Framework (osf.io/zbg6x).

Results

As of August 2024, 18 longitudinal studies have agreed to participate in the GLAD project (Table 3). These studies have sample sizes ranging from 639 participants to 171,000 participants (Table 4).

The GLAD project comprises 3 essential phases, which will be repeated for other lifestyle exposures of interest: (1) conducting a systematic search to identify relevant studies and recruit study leads to contribute data, (2) generating estimates of study-level associations of dietary risk factors with CMDs using harmonized data analysis protocols developed by the GLAD Taskforce and approved by the GBD, and (3) pooling results from each study to provide the GBD with robust estimates to calculate the diet-CMD risk-outcome pairs in the first instance.

As of August 2024, phase 1 of the GLAD project has been completed, and phase 2 is due for completion in early 2025, at which time phase 3 of the GLAD project is due to begin (Figure 3).

Phase 1 includes searching for and recruiting studies with suitable data, harmonizing data definitions by ensuring member studies use the exposure definitions listed in Table 1 and the outcome definitions listed in Table 2, and harmonizing data analyses by ensuring member studies follow the statistical analysis plan presented in this paper.

Table 3. Details of the ethics approval for currently listed member studies[a].

Study name	Ethics review board
The African-PREDICT[b] study [44]	North West Department of Health and Health Research Ethics Committee of the North-West University.
Child to Adult Transition Study [45]	Royal Children's Hospital Human Research Ethics Committee.
Dunedin Study [46]	Health and Disability Ethics Committee, Ministry of Health.
Environmental Risk (E-Risk) Longitudinal Twin Study [47,48]	Joint South London and Maudsley and the Institute of Psychiatry Research Ethics Committee.
Fragility in the Elderly Lombardy Study [49]	Ethics committee of the University of Pavia.
Geelong Osteoporosis Study [50]	Barwon Health Human Research Ethics Committee.
Health4Life [51,52]	University of Sydney, NSW[c] Department of Education, University of Queensland, Curtin University, and relevant Catholic school ethics committees.
Healthy Life in an Urban Setting [53]	Ethical Review Board of the Academic Medical Center Amsterdam.
Longitudinal Aging Study Amsterdam [54]	Medical ethics committee of the VU University Medical Center.
Lothian Birth Cohort 1936 [55,56]	Multi-Centre Research Ethics Committee for Scotland and Lothian Research Ethics Committee.
Melbourne Collaborative Cohort Study [57]	Cancer Council Victoria's Human Research Ethics Committee.
Moli-sani Study [58]	Ethical committee of the Catholic University in Rome.
Netherlands Study of Depression and Anxiety [59]	Medical Ethical Committee of the Vrije Universiteit (VU) Medical Centre and medical ethical committees of the participating universities.
Northern Ireland Cohort of Longitudinal Ageing [60]	School of Medicine, Dentistry and Biomedical Sciences of Queen's University Belfast.
NutriNet Brasil [61]	Ethics committee of the School of Public Health from São Paulo University
NutriNet-Santé [62]	Ethics committee of the French National Institute for Health and Medical Research and by the National Commission on Informatics and Liberty.
Piccolipiù/Piccoli+/Piccolipiù in Forma [63]	Ethics committees of the Local Health Unit Roma E (management center), of the Istituto Superiore di Sanità (National Institute of Public Health) and of each local center.
REgistre GIroní del COR [64,65]	Institut Municipal d'Assistencia Sanitaria Ethics Committee

[a]Additional studies may be participating in or providing data for the GLAD project and not be listed here.

[b]African-PREDICT: African Prospective study on the Early Detection and Identification of Cardiovascular disease and Hypertension.

[c]NSW: New South Wales.

Table 4. Overview of the studies participating in the GLAD[a] project.

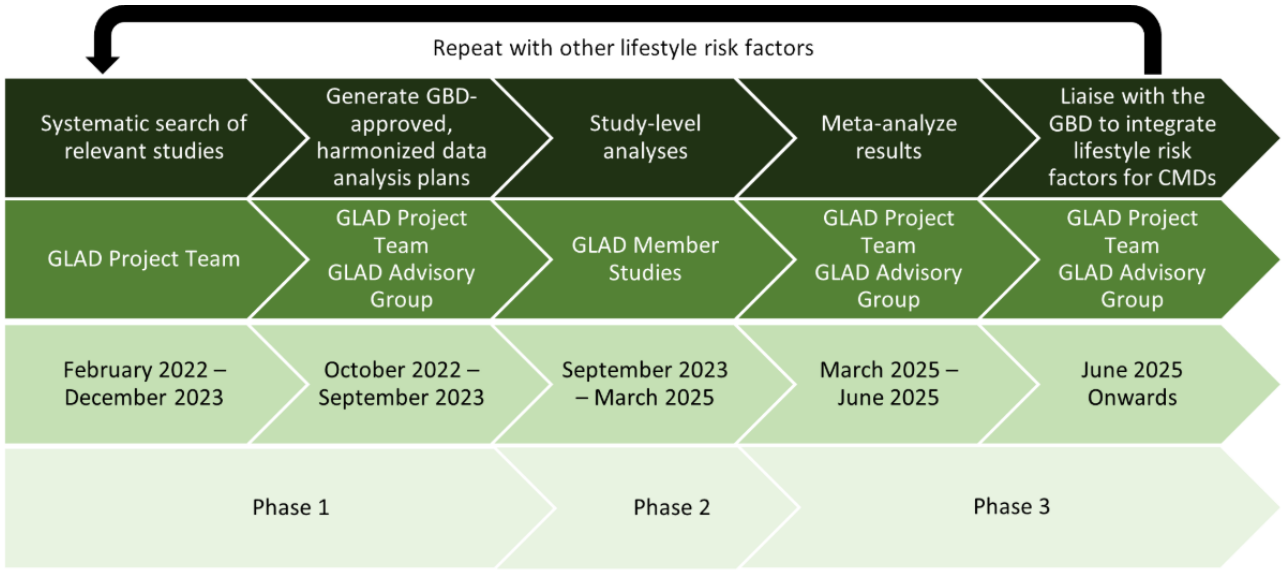
Study name	Study location	Maximum possible sample size[b], n	Age range
The African-PREDICT[c] Study [44]	South Africa	1202	20-30 years
Child to Adult Transition Study [45]	Australia	1239	Older than 8 years
Dunedin Study [46]	New Zealand	1037	0-45 years
Environmental Risk (E-Risk) Longitudinal Twin Study [47,48]	United Kingdom	2232	0-18 years
Fragility in the Elderly Lombardy Study [49]	Italy	639	Older than 65 years
Geelong Osteoporosis Study [50]	Australia	1518	Older than 30 years
Health4Life [51,52]	Australia	6639	11-13 years; 14-17 years
Healthy Life in an Urban Setting [53]	The Netherlands	24,789	18-70
Longitudinal Aging Study Amsterdam [54]	The Netherlands	3805	55-85 years
Lothian Birth Cohort 1936 [55,56]	United Kingdom	1091	Older than 60 years
Melbourne Collaborative Cohort Study [57]	Australia	41,500	Older than 40 years
Moli-sani Study [58]	Italy	24,325	Older than 35 years
Netherlands Study of Depression and Anxiety [59]	The Netherlands	3348	18-65 years
Northern Ireland Cohort of Longitudinal Ageing [60]	United Kingdom	8500	Older than 50 years
NutriNet Brasil [61]	Brazil	109,245	Older than 18 years
NutriNet-Santé [62]	France	171,000	Older than 18 years
Piccolipiù/Piccoli+/Piccolipiù in Forma [63]	Italy	3328	0-4 years
REgistre GIroní del COR [64,65]	Spain	11,158	Older than 26 years

[a]GLAD: Global burden of disease Lifestyle And mental Disorders.

[b]Maximum possible sample size refers to the largest reported sample size from study publications, study websites study protocol, or profile papers. The actual sample size to be included in the GLAD project may vary.

[c]African-PREDICT: African Prospective study on the Early Detection and Identification of Cardiovascular disease and Hypertension.

Figure 3. The tasks, responsible parties, phases, and expected timeline of the GLAD project. CMD: common mental disorder; GBD: Global Burden of Diseases, Injuries, and Risk Factors Study; GLAD: Global burden of disease Lifestyle And mental Disorders.



Discussion

Anticipated Impact

The GLAD project is a global collaboration designed to estimate the risk of CMDs attributable to lifestyle risk factors, with this protocol focusing on dietary risk factors. The anticipated results will provide the GBD with the required threshold of evidence for lifestyle risks to be causally related to CMDs, thereby enabling lifestyle-CMDs risk-outcome pairs to be integrated into the GBD framework. Specifically, the GLAD project will demonstrate that GBD-defined lifestyle risks (eg, diets low in fruit) will be associated with increased risk of CMDs. The GBD study is the largest and most comprehensive global epidemiological health study, providing metrics for 369 diseases and injuries and 87 risk factors [19,66]. These health metrics, including estimates such as the burden of disease and disability-adjusted life years, are publicly available via the GBD digital platform [13] and provide critical information for clinicians, researchers, and policy makers worldwide. While lifestyle risk factors, including dietary intake defined as per GBD-specific definitions, have been considered in the context of chronic physical conditions in the GBD study, they have not yet been linked with mental health outcomes. As the first global collaborative study to link these lifestyle risks with CMDs, using the definitions and methods concordant with the GBD, the results of the GLAD project can be used to link these lifestyle factors as risks for CMDs in the GBD. This effort will allow us to quantify the potential reduction or elimination of the CMD burden by targeting these risk factors at regional and global levels, and to ensure these data are available freely online via the GBD VizHub Data visualization tool.

Risk factors for CMDs in the GBD are currently limited, and so, the inclusion of these additional lifestyle risk factors will represent a significant expansion in the scope of the GBD, which will have global policy implications. Our work builds upon the previous efforts of studies that have successfully integrated novel risk factors for CMDs in the GBD. For example, bullying victimization has been successfully incorporated into the GBD as a level 3 risk and is now routinely integrated into GBD papers [67,68]. By emulating the successful integration of these other risk factors into the GBD, our comprehensive, collaborative approach to harmonized statistical analyses across multiple, internationally renowned epidemiological cohorts has the potential to establish a basis for evidence-backed preventive strategies focused on lifestyle risk factors to reduce the burden of CMDs. Furthermore, by operationalizing the definitions to be in line with the GBD, which are used to inform global policy guidelines, and by capturing data from different regions, sexes, and ages, these results have the potential to bring benefits to individuals and communities on a global scale.

There is substantial observational [69-71], intervention [72-76], and meta-analytical [5,77-79] evidence linking these lifestyle factors to CMDs globally, which suggests that lifestyle factors are potentially suitable (and importantly, modifiable) preventive strategies. This has been recognized by the Royal Australian and New Zealand College of Psychiatrists, with lifestyle treatments integrated into the recent clinical practice guidelines for mood disorders, including depressive disorders [9]. A 2020 meta-review identified that targeting lifestyle variables like physical activity and smoking can be used effectively in the prevention and treatment of CMDs [5]. However, there was less evidence for the role of targeting diet in preventing CMDs, particularly as defined by international policy guidelines or as per the GBD framework. In order to incorporate additional lifestyle factors into guidelines globally, we need comprehensive epidemiological evidence, with a particular focus on dietary risks. The GLAD project will address previous methodological limitations through global collaborations and following a rigorous methodological framework informed by the GBD.

Although mechanistic evidence is currently limited, the causal role of lifestyle risks for CMDs has been supported by shared biological mechanisms between lifestyle factors and CMDs. These pathways include inflammation, oxidative stress, epigenetics, hypothalamic-pituitary-adrenal axis regulation, and the gut microbiome [80]. Inflammation has been linked to CMDs previously, and physical activity, diet, sleep, and smoking have all been shown to impact inflammation [5]. As such, improving dietary intake, increasing physical activity, improving sleep, and smoking cessation may improve mental health via anti-inflammatory properties. Another mechanistic pathway shared by CMDs and many lifestyle risk factors (including diet, physical activity, sleep, and smoking) is the microbiome [80,81]. Many of the dietary risks listed in the GBD, including fruit, vegetable, whole grain, and fiber intake, have pre- and probiotic potential which has been shown to beneficially influence the gut microbiome, and other GBD-defined dietary risks, such as processed meats and sugar-sweetened beverages (which are markers for a high-fat diet), Western-style diet (have been shown to increase anxiety and depression via gut microbiome alterations) [80]. Despite the evidence linking lifestyle risk factors with CMDs, including studies identifying potential mechanisms of action, studies assessing the relationship between lifestyle risks as defined by the GBD with CMD outcomes are lacking. Further, to integrate lifestyle risks for CMDs in the GBD, evidence needs to be generated globally, and not just from individual studies. As a global collaborative project, the results from the GLAD project will therefore provide the necessary evidence to incorporate lifestyle as a risk factor for CMDs in the GBD, which will enable policy makers around the world to make policy decisions regarding the potential public health benefit of population-level lifestyle improvements to mental health.

Strengths and Limitations

Currently, the GBD is unable to include lifestyle exposures such as dietary intake as a risk for CMDs due to the following: difficulties determining directionality and causality, inconsistency in dietary variables and methods, small sample sizes, and lack of global representation. A strength of the GLAD project is that it will address all these methodological considerations. We will (1) prioritize prospective studies using incident cases (ie, excluding those with baseline CMDs) to obtain risks of CMDs attributable to dietary intake, and not the other way around (to determine directionality or temporality), (2) include all study designs (including from experimental or randomized controlled trials to strengthen causal conclusions),

(3) conduct harmonized data analyses approved by the GBD (to improve consistency between studies and specificity of the diet-CMD relationship), and (4) pool data from multiple studies from around the world (to address sample size and global representation).

Despite the clear strengths of the GLAD project, there are some limitations. First, the GBD study is an ongoing and dynamic study, and definitions and methods are constantly evolving. Every effort will be made to ensure the taskforce are following GBD-approved methods, however, some changes from the GBD may be unavoidable. Second, since the GBD does not currently include ultraprocessed food as a dietary risk factor, the definitions and methods used by the task force may not reflect those used in future iterations of the GBD. Finally, although food intakes provide a general overview of diet quality, people do not eat food items in isolation. The current methods used by the GBD do not currently consider dietary patterns. This may limit interpretations to specific food items and not to an overall dietary pattern.

Conclusion

This multicountry, 5-year project has the potential to highlight the role of modifiable lifestyle risk factors in the prevalence and incidence of CMDs. Given the global burden of depression and anxiety, new approaches and targets for their prevention and management are of unprecedented importance.

Acknowledgments

We would like to acknowledge all GLAD members, including the GLAD project team based at Deakin University, the GLAD advisory group, and the GLAD working group comprised of all member studies.

This work was supported by a National Health and Medical Research Council Emerging Leader 2 Fellowship (grant 2009295 to AON). FNJ is supported by a National Health and Medical Research Council Leader 1 Fellowship (grant 1194982). DNA is supported by a National Health and Medical Research Council Fellowship (2009295). MML is supported by a Deakin University Alfred Deakin Postgraduate Fellowship. RO is supported by a Deakin University Postgraduate Research Scholarship. LM is supported by the Italian Ministry of Health (Ricerca Corrente 34/2017) through funding made to the Institute for Maternal and Child Health - IRCCS Burlo Garofolo. CL is supported by a Ramon y Cajal fellowship funded by the Spanish Ministry of Science and Innovation (RYC2020-029599-I funded by MCIN/AEI /10.13039/501100011033 and the European Social Fund. DFS is affiliated with the Queensland Centre for Mental Health Research which receives core funding from the Department of Health, Queensland Government. AG is supported by the Italian Ministry of Health (Ricerca Finalizzata U40 2021, GR-2021-12375341 and Bando PNRR 2022, PNRR-MAD-2022-12375859). MB and SC are supported by the Italian Ministry of Health (Ricerca Corrente 2022-2024) through funding made to the IRCCS Neuromed; MB is supported by the Italian Ministry of Health (Bando PNRR 2022, PNRR-MAD-2022-12376167). SC is supported by the Italian Ministry of Health (Bando PNRR 2022, PNRR-MAD-2022-12376569).

Data Availability

The GLAD project is a multicountry collaborative effort for which individual collaborators apply a harmonized protocol developed by the task force to their own data. Data are not pooled in a shared repository or location, nor publicly available. The data custodians of each dataset may or may not make their data available upon request.

Disclaimer

The opinions, methods, and conclusions reported in this paper are those of the authors and are independent from the funding sources. This manuscript has been prepared in accordance with the requirements of the GLAD task force, as part of a global collaborative project to inform the GBD.

Authors' Contributions

AON and FNJ conceptualized the GLAD task force and project. AON acquired the funding for the project. DNA, RO, and MML contributed to the development of methodology, data curation, and project administration. DNA, RO, MML, FNJ, and AON contributed to the resources (provision of study materials), supervision of the project, and writing the original draft of the manuscript. All authors contributed to the validation of the methodology, and critically reviewing and editing the manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Commonly used tools and scales for assessing common mental disorders, and their cut-offs for indicative diagnosis.
[DOCX File , 62 KB - resprot_v14i1e65576_app1.docx]

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Abbreviations

CMD: common mental disorder
GBD: Global Burden of Diseases, Injuries, and Risk Factors Study
GLAD: Global burden of disease Lifestyle And mental Disorders
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses

Edited by T Leung; submitted 19.08.24; peer-reviewed by K Dobransky, WF Khaw, F Balieva; comments to author 29.11.24; revised version received 06.12.24; accepted 26.12.24; published 14.03.25.

Please cite as:
Ashtree DN, Orr R, Lane MM, Akbaraly TN, Bonaccio M, Costanzo S, Gialluisi A, Grosso G, Lassale C, Martini D, Monasta L, Santomauro D, Stanaway J, Jacka FN, O'Neil A
Estimating the Burden of Common Mental Disorders Attributable to Lifestyle Factors: Protocol for the Global Burden of Disease Lifestyle and Mental Disorder (GLAD) Project
JMIR Res Protoc 2025;14:e65576
URL: https://www.researchprotocols.org/2025/1/e65576
doi:10.2196/65576
PMID:

Protocol

Optimizing the Pharmacotherapy of Vascular Surgery Patients at Hospital Admission and Discharge (PHAROS): Protocol for a Quasi-Experimental Clinical Uncontrolled Trial

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Abstract

Background: Patient safety is essential in pharmacotherapy, especially in surgical contexts, due to the elevated risk of drug-related complications. Vascular surgery patients are particularly susceptible because of their complex medication needs and underlying health conditions. Improved safety monitoring and targeted pharmaceutical care in collaboration with physicians are crucial to minimize these risks and enhance patient outcomes.

Objective: This protocol evaluates whether structured pharmaceutical care interventions—including medication reconciliation, medication review, and patient education—can reduce the prevalence of drug-related problems at hospital admission and discharge in vascular surgery patients.

Methods: This prospective, uncontrolled study was conducted over 1 year in the Vascular Surgery Department at the National Institute of Cardiovascular Diseases in Bratislava, Slovakia. The study included adult patients with carotid artery disease or lower extremity artery disease who were on 3 or more medications, with an estimated sample size of approximately 100 patients. The primary intervention involved 3 key changes in practice: medication reconciliation at both admission and discharge, where hospital pharmacists review and verify medication lists; medication review to identify and address drug-related problems; and patient education at discharge. Pharmacist-proposed interventions were documented and communicated to the physician for treatment adjustments. The primary outcome is the change in drug-related problem prevalence from hospital admission to discharge. Secondary outcomes include the acceptance rate of pharmacist recommendations and patient understanding of pharmacotherapy. Data collection involved documenting the number, type, and frequency of drug-related problems; the anatomical therapeutic chemical classification of medications associated with drug-related problems; and patients' social, demographic, and clinical characteristics, with a focus on factors related to drug-related problems, comorbidities, and medication use. Data analysis will use the paired Wilcoxon signed-rank test to compare the prevalence of drug-related problems and medication counts between admission and discharge. Continuous variables will be presented as means (SDs), while categorical variables will be reported as counts and percentages. Patient understanding of pharmacotherapy will be evaluated using a 3-point scale, classifying understanding as good (2-3 points per medication), modest (1-2 points), or poor (0-1 point).

Results: Recruitment began in September 2021 and concluded in August 2022. Data collection occurred continuously during hospital stays, capturing demographics, comorbidities, pharmacotherapy, and drug-related problems at admission and discharge. Important milestones included the initial data review, which began in August 2023 to assess recruitment and data quality, including

an early evaluation of drug-related problems. The primary analysis was completed in January 2024, focusing on the reduction in drug-related problems, intervention acceptance, and patient understanding. The final report was to be prepared by June 2024, disseminating the findings on pharmacist-led intervention impacts.

Conclusions: This study should demonstrate that pharmacist-led interventions in collaboration with physicians can reduce pharmacotherapy risks and optimize medicine management for patient safety.

Trial Registration: ClinicalTrials.gov NCT04930302; https://clinicaltrials.gov/study/NCT04930302

International Registered Report Identifier (IRRID): RR1-10.2196/60728

(JMIR Res Protoc 2025;14:e60728) doi:10.2196/60728

KEYWORDS

pharmacotherapy; hospital pharmacy; vascular surgery; patient safety; risk reduction; pharmacist-proposed interventions

Introduction

Background

Pharmaceutical care was first defined in 1990 by Hepler and Strand [1] as "the responsible provision of drug therapy for the purpose of achieving definite outcomes that improve a patient's quality of life." Worldwide, pharmaceutical care is currently considered a patient-centered approach, replacing the previous product orientation (dispensing medications) [2,3]. The pharmacist actively cooperates not only with the patient but also with health care professionals in health promotion, disease prevention, evaluation, monitoring, and adjustment and initiation of drug use in order to ensure an effective and safe drug regimen, achieve positive clinical results, and reduce the economic costs of care [2,4].

Currently, patient safety in health care delivery is at the forefront of interest worldwide [5,6]. Patient safety is the absence of preventable harm to a patient during the process of providing health care and reduction of the risk of unnecessary harm associated with health care to an acceptable minimum. Hospital pharmacists [4,7] can make a significant contribution to the safe, effective, and rational use of medicines by hospitalized patients, especially high-risk medication and look-alike and sound-alike medications, through their close surveillance as well as advising on the most appropriate use of medicines [7]. Identification of drug-related problems (DRPs) and proposal of solutions for DRPs by hospital pharmacists is a tool to ensure safe and effective pharmacotherapy for patients [8,9].

The Pharmaceutical Care Network Europe Association (PCNE) defines a DRP as a problem, event, or circumstance related to pharmacotherapy that affects or has the potential to affect a desired therapeutic effect [10]. An example is the arbitrary withdrawal of metformin by patients due to persistent diarrhea [11]. The PCNE has developed a classification system as a tool to accurately identify DRPs. The current version is V9.00 as of 2019 [10]. This classification tool is used throughout our study to ensure consistency in identifying and categorizing DRPs.

DRPs are generally all problems related to the use of a drug [10]. DRPs include adverse drug reactions (ADRs), an unintended reaction after medication administration [11-14], medication errors, and any phenomenon that may lead to improper use of a drug under the control of a health care professional or patient [15-17].

Although it is not common practice in Slovakia to report all DRPs, this is not an issue unique to the country. Many nations face similar challenges, especially where comprehensive pharmacovigilance systems are still developing [18]. In 2019, only 1128 suspected ADRs were reported, of which only 8% were reported from pharmacists. Overall, up to 26% of reports were classified as severe (ie, required hospitalization of the patient or caused permanent harm to the patient). Although state authorities have seen an increase in the number of spontaneous reports, their number probably does not correspond to their actual occurrence. Currently, we do not have statistically evaluated health care costs due to medication errors in Slovakia [18].

We distinguish between intentional and unintentional DRPs [10,19,20]. There is no uniform classification of the severity of DRPs. It is necessary to focus on the identification and elimination of unintentional DRPs.

At the same time, according to current statistics, the average age of the population is increasing worldwide, which is directly related to the higher prevalence of polymorbidity and polypharmacy in the population [21-23].

There are certain indicators on the basis of which an increased incidence of unintentional DRPs can be expected. In a hospital environment, these are the high number of drugs, which is related to low adherence, potential interactions, accumulation of medication errors, more frequent hospitalizations, and increased treatment costs [24-27]; a low level of understanding of the therapy being used among patients [28-30]; older age of patients [21-23,28]; and absence of caregivers for older adult patients [29].

These indicators may be associated with the incidence of treatment errors related to primary care.

Prior Work

Pharmacists use several strategies to reduce DRPs, including medication reconciliation (MedRec), medication review (MedRev), and patient education [30-34]. Prescription errors during hospital admission are common, with studies showing that these errors occur in up to 67% of patients [35]. MedRec has been shown to identify at least one DRP in 60% of patients, with 18% being clinically significant [36]. The incidence of drug discrepancies during hospital transitions, especially at discharge, is high, with some studies showing significant discrepancies upon patient discharge [37,38]. According to a

2020 Organization for Economic Co-operation and Development report, pharmacy-led MedRec before discharge reduces drug discrepancies and the associated risks to patient health [39]. A meta-analysis conducted by Mekonnen et al [40] in 2016 found that pharmacist-led MedRec reduces hospital readmissions by 67%, emergency admissions by 28%, and hospitalizations by 19%.

MedRec involves obtaining a best possible medication history (BPMH) from various sources, including medical records, community pharmacies, and patient interviews. This is compared with the patient's current medication list to identify discrepancies, which are then discussed with health care professionals and resolved [32-34,41,42]. MedRev further optimizes pharmacotherapy by eliminating unnecessary medications, adjusting dosages, or addressing drug interactions [43].

Studies on pharmaceutical interventions typically focus on specific patient groups, such as those with cardiovascular diseases, renal failure, or older adult patients. For example, Stemer et al [44] identified 487 DRPs in 138 visits, with a 54.7% acceptance rate for pharmacist recommendations. Hohn et al [45] found a rate of 0.41 unintentional medication errors per patient in vascular surgery patients. In patients with chronic renal insufficiency, pharmacist interventions improved renal function, particularly in more severe cases [46]. Older adult patients also showed positive outcomes, with pharmacist interventions reducing hospital readmissions by 16% and hospitalization rates due to DRPs by 80% [47].

Overall, pharmacist-led interventions are effective in reducing DRPs, improving pharmacotherapy, and enhancing patient outcomes. However, the types and numbers of DRPs detected vary across studies, indicating the need for standardized definitions in research on DRPs [19,33,48].

Trial Objectives

This study aims to assess the impact of pharmaceutical care in collaboration with physicians on the prevalence of DRPs at hospital admission and discharge in patients with carotid artery disease or lower extremity artery disease hospitalized in the Department of Vascular Surgery. These patients often experience polypharmacy, making them particularly suitable for pharmacotherapy optimization through pharmacist-led interventions. MedRec, MedRev, and patient education provided by pharmacists are new interventions at our hospital and were not part of the standard of care prior to the study.

The key focus area of this project is the identification of DRPs, their occurrence, and their type. As part of further research, we want to analyze the degree of acceptance of the proposed changes in pharmacotherapy by physicians, document the Anatomical Therapeutic Chemical Classification (ATC) groups of drugs with the highest incidence of DRPs, and identify patients at highest risk for DRPs taking into consideration their personal and health information.

Trial Hypotheses

The null hypothesis is that pharmaceutical care provided at hospital admission and hospital discharge does not reduce the prevalence of DRPs in patients with carotid artery disease or lower extremity artery disease hospitalized in the Department of Vascular Surgery.

The alternative hypothesis is that pharmaceutical care provided at hospital admission and hospital discharge reduces the prevalence of DRPs in patients with carotid artery disease or lower extremity artery disease hospitalized in the Department of Vascular Surgery.

Methods

Study Design

This study is a single-center, prospective, uncontrolled biomedical clinical trial conducted over 1 year. The study took place in a hospital setting, specifically in the Department of Vascular Surgery at the National Institute of Cardiovascular Diseases in Bratislava, Slovakia. The intervention included MedRec, MedRev, and patient education, all performed by a trained pharmacist following the High 5s Project Standard Operating Protocol for Medication Reconciliation [24] and PCNE guidelines [10]. All pharmacist recommendations and proposed changes to therapy were documented in writing, recorded in the patient's medical record, and communicated to the attending physician.

Our study followed the Standards for Quality Improvement Reporting Excellence (SQUIRE) guidelines [49].

Study Population

Adult (≥18 years of age) vascular surgery patients with carotid artery disease or lower extremity artery disease admitted for hospitalization at the study setting during the course of the study were recruited.

Inclusion Criteria

To participate, patients needed to be ≥18 years old at the date of admission for hospitalization, taking at least 3 medications administrated systematically, and have carotid artery disease or lower extremity artery disease.

Exclusion Criteria

Patients were excluded for any of the following reasons: admitted for an acute condition; transferred from other hospitals or wards; not willing to sign the informed consent form for the study; not understanding the Slovak language; had any mental disorder affecting memory and recall ability (such as Alzheimer disease); any other reason, at the investigator's discretion, why he or she deemed the participant not eligible for study participation (all such reasons were recorded); or participating in another clinical study.

Study Sample Size

To calculate the sample size, we aimed to accept a type I error rate with a P value ≤.05. The study seeks to achieve 80% power to detect a small effect size of 0.3 using the Wilcoxon signed-rank test. Based on these assumptions, the required sample size was calculated as 94 patients. To account for potential dropouts, the sample size was increased to 120 patients. The sample size calculation was performed using G*Power

software version 3.1 [50]. Similar studies published in this field have comparable sample sizes [51].

Data Sources and Measurements

Data were drawn from the hospital information system (HIS), medical and nursing reports, patient interviews, and contacting outpatients.

Primary Outcomes

The primary outcome is a change in the prevalence of DRPs at hospital admission versus hospital discharge.

Secondary Outcomes

The secondary outcomes are the acceptance rate of the pharmaceutical intervention by physicians and patient understanding of their pharmacotherapy.

Variables

The variables collected include the number, type, and frequency of DRPs; ATC of drugs causing DRPs; medical, social, and demographic characteristics of patients; health condition of patients; comorbidities; and patient understanding of their pharmacotherapy assessed on a 3-point scale at hospital admission.

We assessed the patients' basic social, demographic, and clinical characteristics, with a particular emphasis on evaluating their pharmacotherapy and the incidence of DRPs. Additionally, we examined the degree of acceptance of pharmacists' recommendations by physicians and the outcomes of DRP resolutions. Our analysis will also identify the medications most frequently associated with the occurrence of DRPs. Patients' understanding of their pharmacotherapy was also be evaluated.

Time Points for Intervention

At Hospital Admission

Current Condition at Patient Admission

A vascular surgery patient with carotid artery disease or lower extremity artery disease comes for a planned hospitalization with a report from the attending physician, with or without an internal preoperative examination. The physician, in cooperation with the nurse, examines the patient on admission, draws information from the patient's medical records, and in the case of rehospitalization, from the HIS and internal preoperative examination. The physician will prepare an admission report, which will record the patient's previous illnesses, the current state of health, the reason for hospitalization, and all associated illnesses. Patients often bring a list of medications they are taking; the physician will consult with the patient on the completeness of this list. He or she detects then records possible allergies to drugs and food and other forms of intolerance or allergic manifestations. He or she is interested in the use of addictive substances, alcohol, and drugs of abuse and the frequency of their use. The patient signs informed consent that he or she consents to hospitalization and treatment. The admission report, which also includes the drug course (current drug record, which is updated once a day; if necessary, it is possible to insert notes, consultation examinations, orders for laboratory tests, and other information), will be prepared both in the HIS and in printed form. Each hospitalized patient has a printed medical record that is more comprehensive and contains more detailed information than the HIS records. It contains all the patient's health results, required examinations, daily drug courses, all daily updated nursing records, records of the patient's diet, and more. Based on the prescription of medications in the course, the nurse prepares and administers medications to the patient, and a sudden change in pharmacotherapy by the physician is reported to the nurse orally then recorded in the course. Some patients keep some of their medication with themselves and dose it themselves according to the physician's instructions.

MedRec by Pharmacists at Patient Admission

The patient is normally admitted to a planned hospitalization by the physician in cooperation with the nurse, as aforementioned. If the patient is older than 18 years, takes more than 3 medicines, speaks and understands the Slovak language, and has signed informed consent to participate in biomedical research, after being placed in a bed, a pharmacist comes to the patient's bedside and performs a MedRec. During the MedRec, the pharmacist creates a record of the patient's therapy, the original of which is placed in the patient's medical record, and a copy is placed in the pharmacist's records.

The steps in the MedRec involved the following. As part of the invitation for the hospitalization (by telephone or in writing), the patient was asked to bring all their medications and a complete medication list, which was used in consultation with the pharmacist regarding their proper use. The BPMH was completed.

The source of information can be a drug record, an admission report, hospital records, historical records from the HIS, or information from the patients or their family member. A BPMH is different and more complex than the routine history of primary treatment (which is often a rapid history of patient treatment). The BPMH includes the name of the medicine, dose, and frequency and administration route of the medicines that the patient is currently taking, although it may differ from what was actually written in the drug list.

The types of drugs that need to be recorded in the BPMH include prescription drugs, over-the-counter drugs, nutritional supplements, herbal medicines, medicinal teas, recreational drugs, and regular consumption of certain foods (eg, grapefruit). Special emphasis should be placed on specific forms of medicines, such as inhalers, eye drops, topical semisolid medicines, or medicines taken every few weeks (bisphosphonates).

One of the recorded parameters is patient understanding. This is evaluated in 3 steps and scored as 0 or 1: The patient knows (1) or does not know (0) the name of the drug, the patient knows (1) or does not know (0) the indication of the drug, and the patient knows (1) or does not know (0) the dosage of the drug. The 3-point scale was based on previously published studies by Cline et al [52], Boonstra et al [53], and Marfo et al [54], who evaluated patients' knowledge based on their understanding of the drug name, dosage, duration of treatment, indication, relationship of the drug to food, duration of therapy, or route

of administration. If the patient was unable to attend the interview, other sources were used to obtain a medical history or to clarify conflicting information. Other resources should never be a substitute for a thorough conversation with the patient or family members.

Regarding verification and documentation of the BPMH, the BPMH list should be verified by more than one other source. Sources for the initial acquisition of an overview of pharmacotherapy are the admission report, the history of hospitalization, outpatient reports, HIS, and the course at admission.

According to the World Health Organization standard operating procedure, a retroactive MedRec model was used for our biomedical research. In a retroactive model, in accordance with the aforementioned method, the patient is admitted by a physician in cooperation with a nurse by default, and a drug course—a daily prescription of drugs for the patient – is created. In this case, the BPMH is determined after admission by a physician or nurse.

The result of the MedRec is a comparison of medicines prescribed to and actually used by patients (BMPH) with marked discrepancies.

During the process of obtaining the BPMH, the pharmacist informs patients to always share their doubts about the correct use of the medication with the medical staff.

MedRev With Pharmaceutical Intervention at Patient Admission

The basis for patient therapy optimization is the acquisition of the BPMH and patient factors, such as the reason for hospitalization, current health status, comorbidities, height, weight, heart rate, blood pressure, and the results of examinations of biochemical and hematological parameters.

The detected BPMH is written in the case report form. It is then analyzed in the context of the patient's overall health condition, and DRPs are identified. Each detected discrepancy is assigned an alphanumeric code according to the PCNE V9.00 classification. The patient's personal data are anonymized.

Discrepancies in therapy should be consulted with the treating physician within 24 hours of admission.

Evaluation of Therapy Based on DRPs and PCNE Classification

After receiving the BPMH and a detailed study of the reason for hospitalization, current medical condition, and any patient comorbidities, the pharmacist collects information about the patient's weight, height, heart rate, and blood pressure from the admission report. Subsequently, the results of biochemical and hematological examinations are studied. The pharmacist focuses on the results of examinations related to pharmacotherapy and the determination of the function of elimination organs. These are mainly the levels of serum potassium, serum creatinine, serum uric acid, liver transaminases, lipidogram, and C-reactive protein. Renal function is calculated based on the Cockcroft and Gault creatinine clearance estimate.

Duplicate Treatment

The pharmacist controls duplication in the drugs used, considering the use of the same substance in 2 drugs, use of the same substance in 2 dosage forms, use of 2 substances from the same pharmacological group, and double inhibition of the renin-angiotensin-aldosterone axis by angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers.

Duplicity is recorded in written form in the final evaluation of the patient's pharmacotherapy; duplication is discussed with the patient, who confirms or refutes the actual use of the duplicate drugs, and the most appropriate procedure is proposed in collaboration with the attending physician.

Indications of Used Drugs and Contraindications

The pharmacist checks the indications of the drugs used according to the patient's comorbidities. The pharmacist checks whether all comorbidities are treated according to evidence-based medicine and according to treatment procedures developed by local, national, or international authorities. The result of this step is the identification of missing drugs in the patient's pharmacotherapy.

Furthermore, drugs whose use has no clear indication are identified. In older adult patients (≥65 years), the pharmacist also considers the use of potentially inappropriate drugs. The pharmacist follows the EU (7)-PIM list [55], which was designed for patients aged 65 years and older. The result of this step is the identification of drugs that do not have a clear indication or are inappropriate due to the patient's age.

The pharmacist also checks whether the prescribed drug is appropriate for the specific patient.

Drugs that the patient should and should not take, drugs whose indications are not clearly known from the available data, and contraindicated drugs are recorded in the final evaluation of the patient's pharmacotherapy, in cooperation with the attending physician; subsequently, the most appropriate procedure is proposed.

Drug Management

The pharmacists verify compliance with maximum recommended doses, considering patient-specific factors, and records any excess in the pharmacotherapy evaluation. They assess the suitability of dosage forms, administration practices (including infusion components, timing, and food interactions), and screen for potential drug interactions using LexiComp and other resources, documenting any clinically significant findings. All observations and recommendations are reviewed with the attending physician to determine the appropriate course of action.

Adverse Drug Reactions

If a newly manifested ADR not documented in the patient's medical history is suspected, the pharmacist evaluates the degree of causality between the drugs used and the manifestations of the ADR, which is proven on the basis of laboratory parameters or the patient's subjective complaint. The pharmacist reports suspicions of ADR to the State Institute of Drug Control via an electronic form available from [56].

ADRs are recorded in the final evaluation of the patient's pharmacotherapy.

The individual DRP findings shall be entered in the form as an appropriate code according to the PCNE classification [10].

The result of the pharmacist's intervention at patient admission is the completion of the MedRec form at admission and creation of an accurate list of medicines taken by the patient. All comments on pharmacotherapy with the proposed solutions are written in the form of a summary report and undergo consultation with the physician.

At Hospital Discharge

Current Condition at Patient Discharge

When discharging a patient, the attending physician evaluates the patient's state of health and prepares a discharge report with complete information about the procedures that the patient underwent during hospitalization. The discharge report also includes the current results of the patient's laboratory examinations, an overview of current pharmacotherapy, and recommendations to the patient's general practitioner. The nurse explains the regimen measures in relation to his or her state of health to the patient and gives the patient medication for the 3 days following discharge.

MedRec by Pharmacists at Patient Discharge

The pharmacist performs MedRec when discharging a patient from the hospital, similar to the process at admission. When evaluating a patient's pharmacotherapy on discharge from hospital, the BPMH obtained at the patient's admission will be used as a source of information. The BPMH is then compared with the list of medicines that are recorded in the release report. The pharmacist will compare 2 lists of medicines, focusing on the identification of DRPs with special regard to the re-introduction of the chronic therapy the patient was taking before hospitalization. As part of this research, the pharmacist met with the patient during his or her discharge from the hospital and discussed with him or her the management of further pharmacotherapy. Pharmacists provided an understandable summary list of a patient's medicines explaining the importance and the correct use of the medicine.

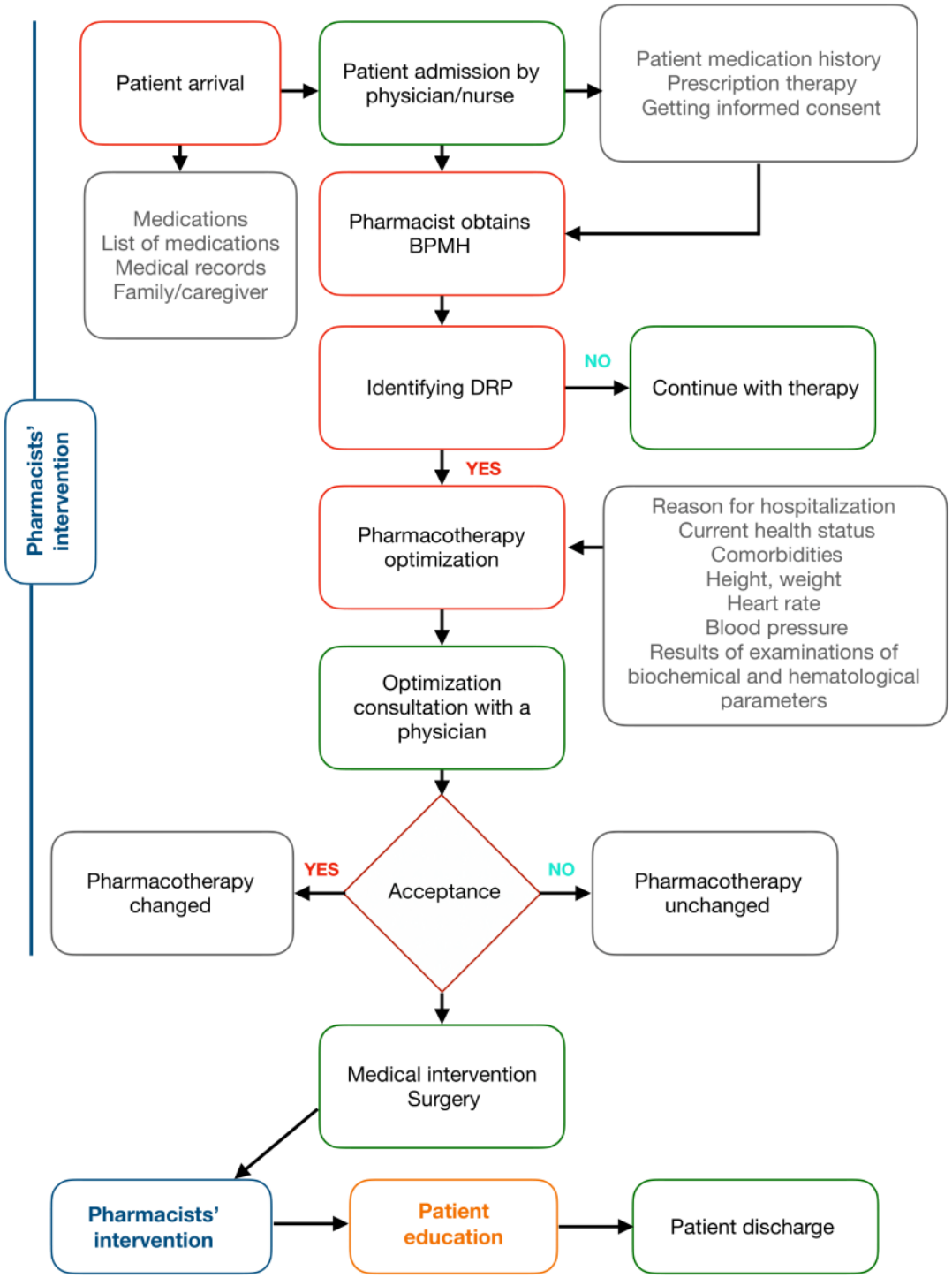
MedRev With Pharmaceutical Intervention at Patient Discharge

The pharmacist analyzes the pharmacotherapy in the context of the patient's state of health and the results of laboratory tests, similar to the patient's admission, as described in the previous sections. Detected DRPs are then consulted with the treating physician and recorded in the case report form.

The result of the pharmacist's intervention at discharge is the completion of the MedRec form for discharge and the documentation of all comments on pharmacotherapy in the form of a summary report. Discrepancies and comments are consulted with the physician.

The complete scheme of the procedure can be seen in Figure 1.

Figure 1. Procedure scheme.



Ethical Considerations

Human Subject Ethics Review Approvals

The study was approved by the Ethics Committee of the National Institute of Cardiovascular Diseases (approval number 1625/21; May 26, 2021) and registered on ClinicalTrials.gov (trial registration number NCT04930302; June 16, 2021). All research procedures adhered to the ethical standards of the institutional and national research committees and were conducted in accordance with the 1964 Helsinki Declaration and its later amendments or comparable guidelines.

Informed Consent

Written informed consent was obtained from all participants before any research-related activities were initiated. The consent form, approved by the Ethics Committee, was provided in Slovak to ensure participants' understanding. By signing the consent form, participants consented to the publication and presentation of their pseudonymized data.

Privacy and Confidentiality

Patients' personal data were anonymized to ensure confidentiality. The Participant Identification Sheet was securely

stored at the study center, alongside other documentation. Anonymized data were entered into the case report form in the MIA DMS online database, which operates within Europe.

Compensation Details

No compensation was provided to participants for their involvement in this study.

Results

This protocol outlines the planned study design and anticipated timeline for the PHAROS trial, aimed at evaluating the impact of pharmacist-led interventions on DRPs in patients undergoing vascular surgery. The key stages of the trial and their anticipated completion dates are described in the following sections.

Study Initiation and Recruitment

Patient recruitment began in September 2021 and was completed in August 2022. The target sample size of 100 patients was reached.

Data Collection

Data collection occurred continuously during each patient's hospital stay, including assessments at admission and discharge to document patient demographics, comorbidities, pharmacotherapy details, and DRPs. These data will help evaluate the prevalence and types of DRPs, intervention acceptance rates, and changes in patient understanding of pharmacotherapy.

Analysis and Reporting Milestones

For the initial data review, preliminary data analyses began in August 2023 to assess recruitment efficacy and data integrity. This phase includes an initial assessment of DRPs and intervention types recorded during patient admission.

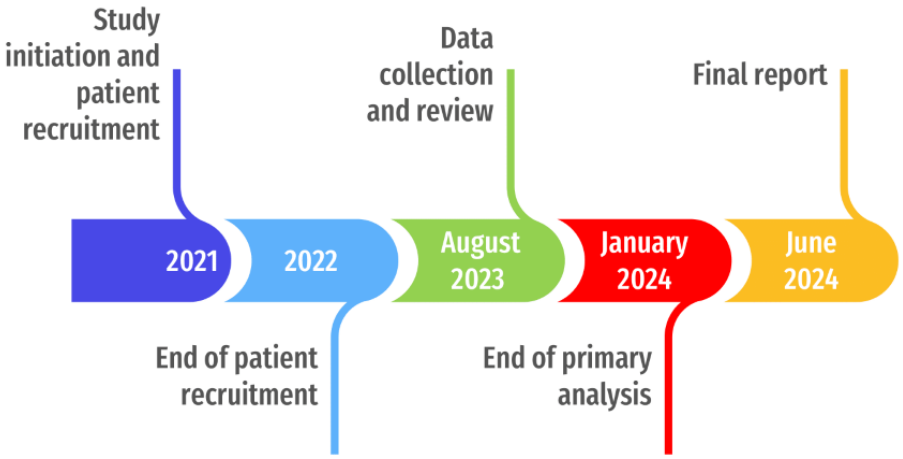
The primary analysis, including full data analysis encompassing outcomes related to DRP reduction, intervention acceptance, and patient pharmacotherapy understanding, was completed in January 2024.

For the final report and dissemination, the study findings, including the impact of pharmacist interventions on patient outcomes, were compiled and prepared for dissemination by June 2024.

A timeline of the PHAROS trial (Figure 2) illustrates each phase of the study, from patient recruitment through final analysis and reporting.

These timeline indicators and progress markers will enable ongoing tracking of study completion and ensure that each stage of data collection and analysis aligns with the study's objectives.

Figure 2. Timeline of the PHAROS trial.



Statistical Methods

Continuous variables will be characterized as the mean with standard deviation. Categorical variables will be expressed as numbers and percentages.

To compare the number of drugs, active substances, and DRPs at hospital admission and discharge, the paired Wilcoxon signed-rank test will be used due to the non-normal distribution of differences between the 2 time points. Normality will be assessed with the Shapiro-Wilk test. To determine the effect size of the intervention, Cohen *d* will be calculated and categorized as small, medium, or large based on established intervals. Patients' understanding of their pharmacotherapy at hospital admission will be evaluated using a 3-point scale. The average score per medication will be calculated, categorizing patients into groups based on their understanding: good (2-3 points per medication), modest (1-2 points per medication), and poor (0-1 point per medication).

Discussion

Importance

The PHAROS study is the first prospective clinical trial in Slovakia to evaluate pharmacist-led interventions on DRPs in vascular surgery patients. Our findings add to the growing body of evidence that pharmacist involvement can reduce the prevalence of DRPs, improve patient understanding of medications, and enhance overall pharmacotherapy outcomes for hospitalized patients.

Comparison With Prior Work

Several studies have examined the role of pharmacists in preventing and managing DRPs across various clinical settings [57], including vascular surgery. Hohn et al [45] and Martínez López et al [51] documented a decrease in DRPs due to pharmacist-led interventions, reporting an average of 1.3 and 1.7 DRPs per patient, respectively. These studies support the role of pharmacists in reducing DRPs and improving medication safety in hospitalized patients. Findings from Schmelzer et al [58] and other international studies also demonstrated a significant reduction in DRPs at discharge.

The impact of pharmacist-led interventions on vascular surgery patients specifically has not been extensively studied. However, studies in other settings, such as those by Hohn et al [45] and Rychlíčková et al [59], have shown positive outcomes from pharmacist interventions. Singh et al [60] highlighted the underprescription of statins in patients with peripheral artery disease, attributing this to clinician-related barriers such as concerns about adverse effects. The PHAROS study aims to contribute to this literature by demonstrating that pharmacist involvement in MedRec and MedRev supports DRP management and optimizes pharmacotherapy, underscoring the importance of pharmacist intervention in promoting guideline-adherent care.

An important aspect of the PHAROS study is its focus on patient education. Based on the prior literature, educating patients about their medications is strongly associated with better adherence and a reduction in DRPs [31,32,61,62]. Including patient education as part of the pharmacist's role is intended to support informed patient participation in their treatment.

Challenges and Barriers

Despite the promising outcomes of pharmacist-led interventions, challenges remain in their implementation. One significant barrier is resistance to change among health care professionals, especially in settings where the role of pharmacists in medication management is not well established. As noted by Hohn et al [45], physicians may be hesitant to accept pharmacist recommendations, particularly in complex cases involving polypharmacy and comorbidities. Successful pharmacist-led interventions require clear protocols, comprehensive training, and effective collaboration with other health care professionals. The lack of legislative requirements for MedRec and MedRev in Slovakia demonstrates the need for policy changes to integrate pharmacists systematically into patient care transitions. This is particularly important, as international guidelines, such as those from the European Association of Hospital Pharmacists [63], emphasize the role of MedRec in ensuring safe and effective care.

Future Directions

Building on the results of this pilot study, future research should seek to validate these findings through a larger, randomized controlled trial, which would allow for a more rigorous assessment of pharmacist-led interventions on DRPs. Such studies could incorporate a control group, a larger sample size, and postdischarge follow-up to evaluate long-term effects. Expanding research to diverse health care settings and patient demographics could provide insights into optimizing pharmacist interventions across various clinical contexts.

Limitations of the Study

Our study has several limitations. First, it was conducted as a single-center trial and performed in specific departments and with specific indications; therefore, the results may not be applicable under different conditions. Second, the study did not include a control group. Although all investigators were trained in all study processes, some degree of subjectivity is possible in the assessment of DRPs. Moreover, the number of patients was limited. However, trained hospital pharmacists strengthened the methodology used in our trial.

Conclusions

The study should determine that pharmaceutical care provided at hospital admission and at hospital discharge could reduce the prevalence rates of DRPs in our study setting. The pharmacist-led interventions upon hospital admission and discharge, followed by patient education, might be implemented in daily practice in health care in our hospital.

Acknowledgments

This study would not have been possible without the support of the Chief of the Vascular Surgery Department, Ján Tomka, MD, PhD, as well as the cooperation of the physicians from this department.

Data Availability

Only investigators from the National Institute of Cardiovascular Diseases have access to all patient data. They maintain an accurate and comprehensive list of biomedical research participants, along with the alphanumeric codes assigned to them, all documented in the "Participant Identification Sheet." Both the completed Participant Identification Sheet and all research data are securely stored. Anonymized personal data are entered into the case report form in the online MIA document management system (DMS) database and are accessible only to investigators. The data sets used and analyzed during the study are available from the corresponding author upon reasonable request.

Authors' Contributions

All authors contributed equally to the study conception and design. All authors read and approved the final manuscript. TT is responsible for the overall content as the guarantor.

Conflicts of Interest

None declared.

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Abbreviations

ADR: adverse drug reaction
ATC: Anatomical Therapeutic Chemical Classification
BPMH: best possible medication history
DRP: drug-related problem
HIS: hospital information system
MedRec: medication reconciliation
MedRev: medication review
PCNE: Pharmaceutical Care Network Europe Association

SQUIRE: Standards for Quality Improvement Reporting Excellence

Edited by A Schwartz, T Leung; submitted 20.05.24; peer-reviewed by M Wilcock, J Walsh; comments to author 05.11.24; revised version received 14.11.24; accepted 21.02.25; published 19.03.25.

Please cite as:
Porubcova S, Lajtmanova K, Szmicsekova K, Slezakova V, Tomka J, Tesar T
Optimizing the Pharmacotherapy of Vascular Surgery Patients at Hospital Admission and Discharge (PHAROS): Protocol for a Quasi-Experimental Clinical Uncontrolled Trial
JMIR Res Protoc 2025;14:e60728
URL: https://www.researchprotocols.org/2025/1/e60728
doi:10.2196/60728
PMID:

Protocol

Vaping, Acculturation, and Social Media Use Among Mexican American College Students: Protocol for a Mixed Methods Web-Based Cohort Study

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Abstract

Background: The tobacco industry has a history of targeting minority communities, including Hispanic individuals, by promoting vaping through social media. This marketing increases the risk of vaping among Hispanic young adults, including college students. In Texas, college enrollment among Mexican Americans has significantly increased over recent years. However, little research exists on the link between social media and vaping and the underlying mechanisms (ie, outcome expectations, attitudes, and beliefs) explaining how vaping-related social media impacts vaping among Mexican American college students. Moreover, there is limited knowledge about how acculturation moderates the association between social media and vaping. Hispanic individuals, particularly Mexican Americans, are the largest ethnic group in Texas colleges; thus, it is crucial to understand the impact of social media and acculturation on their vaping behaviors.

Objective: We outline the mixed methods used in Project Vaping, Acculturation, and Media Study (VAMoS). We present descriptive analyses of the participants enrolled in the study, highlight methodological strengths, and discuss lessons learned during the implementation of the study protocol related to recruitment and data collection and management.

Methods: Project VAMoS is being conducted with Mexican American students attending 1 of 6 Texas-based colleges: University of Texas (UT) Arlington, UT Dallas, UT El Paso, UT Rio Grande Valley, UT San Antonio, and the University of Houston System. This project has 2 phases. Phase 1 included an ecological momentary assessment (EMA) study and qualitative one-on-one interviews (years 1-2), and phase 2 includes cognitive interviews and a 4-wave web-based survey study (years 2-4) with objective assessments of vaping-related social media content to which participants are exposed. Descriptive statistics summarized participants' characteristics in the EMA and web-based survey.

Results: The EMA analytic sample comprised 51 participants who were primarily female (n=37, 73%), born in the United States (n=48, 94%), of middle socioeconomic status (n=38, 75%), and aged 21 years on average (SD 1.7 years). The web-based survey cohort comprised 1492 participants self-identifying as Mexican American; Tejano, Tejana, or Tejanx; or Chicano, Chicana, or Chicanx heritage who were primarily female (n=1042, 69.8%), born in the United States (n=1366, 91.6%), of middle socioeconomic status (n=1174, 78.7%), and aged 20.1 years on average at baseline (SD 2.2 years). Of the baseline cohort, the retention rate in wave 2 was 74.7% (1114/1492).

Conclusions: Project VAMoS is one of the first longitudinal mixed methods studies exploring the impact of social media and acculturation on vaping behaviors specifically targeting Mexican American college students. Its innovative approach to objectively measuring social media exposure and engagement related to vaping enhances the validity of self-reported data beyond what national surveys can achieve. The results can be used to develop evidence-based, culturally relevant interventions to prevent vaping among this rapidly growing minority population.

International Registered Report Identifier (IRRID): DERR1-10.2196/63584

(JMIR Res Protoc 2025;14:e63584) doi:10.2196/63584

KEYWORDS

vaping; social media; Mexican American; college students; marketing; acculturation; protocol; artificial intelligence

Introduction

Background

The tobacco industry has a history of targeting marketing campaigns toward specific minority groups [1,2]. In particular, Hispanic individuals, especially young adults and college students, are increasingly subjected to effective vaping promotions on social media, which raises their risk of e-cigarette use, commonly referred to as vaping [1,2]. Hispanic individuals are the largest and fastest-growing ethnic minority in the United States, comprising 19.1% of the total population, with 58.9% of this demographic being of Mexican heritage, primarily identifying as Mexican American [3]. In Texas, a majority-minority state with the second-largest Hispanic population in the United States, Hispanic individuals are the largest ethnic minority group, nearly 90% of whom are of Mexican heritage [4]. Moreover, the youthful profile of the Hispanic population, with approximately 50% aged <29 years, makes them a particularly appealing target for e-cigarette marketing [5,6]. One limitation of previous research is the study of Hispanic individuals as a homogeneous group. Despite variations in tobacco use behaviors by country of origin, there is a lack of ethnic-specific studies on Mexican Americans [7]. Moreover, little research has explored the link between social media and vaping among Hispanic college students even though national data show that they vape at rates comparable to those of their White peers and their use of social media is high [8].

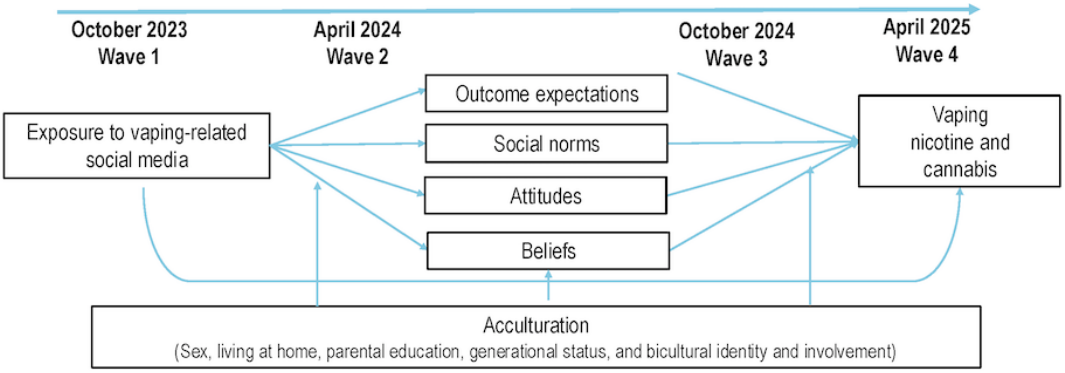
Social media plays a crucial role in the acculturation process as it provides a platform for language practice, information seeking, and social interaction, all of which are integral to acculturation [9]. Social media facilitates cultural exchange by enabling users to connect, share content of cultural significance, and influence each other's perspectives, thereby playing a pivotal role in shaping evolving cultural norms, beliefs, and identities within communities [10]. Of concern, Mexican American college students who are less acculturated yet use English-language social media might be more prone than their more acculturated peers to adopt the intrapersonal outcome expectations (eg, "e-cigarettes help me look cool and stay slim"), social norms (eg, perceived peer and family use and e-cigarettes being socially acceptable), and attitudes and beliefs (eg, e-cigarettes are safer and more convenient than cigarettes) promoted on social media, which elevates their risk of vaping [10]. Therefore, it is crucial to understand how social media influences intrapersonal mechanisms and mediators and, in turn, vaping behavior among individuals with varying levels of acculturation. This knowledge is important to developing evidence-based, culturally relevant interventions aimed at preventing vaping among this rapidly growing, vulnerable minority population.

Objectives

The primary goals of Project Vaping, Acculturation, and Media Study (VAMoS) are to (1) identify mechanisms underlying vaping-related social media exposure and engagement and vape use among Mexican American young adults and (2) examine the role of acculturation as a moderator of these mechanisms. Project VAMoS has 3 aims, which will be implemented in 2 phases and addressed using multiple methods. Aim 1 seeks to characterize vaping-related social media and vape use from the perspective of Mexican American college students using ecological momentary assessments (EMAs) and one-on-one qualitative interviews and was completed in years 1 and 2 (phase 1). Aim 2 seeks to identify intrapersonal mediators of the relationship between exposure to vaping-related social media and subsequent vaping, and aim 3 seeks to determine the moderating role of acculturation on the direct and mediated paths of aim 2. Aims 2 and 3 are addressed using a 4-wave, biannual web-based survey in years 2 to 5 (phase 2).

Guided by social cognitive theory [11,12], we hypothesize that outcome expectations, social norms, and attitudes and beliefs will mediate the association between social media and vaping. Guided by acculturation theories [13,14], we further hypothesize that these mediated associations will be moderated by acculturation such that they will be stronger for those who use English-language media and for less acculturated students, including first-generation college students and female individuals [15,16]. Figure 1 presents the conceptual framework used to guide this study as well as the data collection timeline.

Figure 1. Data collection timeline and conceptual model.



Methods

Overview

Project VAMoS is a 5-year study examining the independent and combined influences of social media exposure and engagement and acculturation on the vaping behaviors of a longitudinal cohort of Mexican American college students aged 18 to 29 years in Texas. VAMoS is a study that is conducted entirely on the web, including participant recruitment, data collection, and incentive delivery to participants. In this paper, we describe the protocol and present the planned mixed methodologies to be used in Project VAMoS. We present descriptive analyses of the participants enrolled in the study, focus on methodological strengths, and discuss lessons learned during the implementation of the study protocol related to recruitment and data collection and management.

Sampling

Sampling frames were constructed by requesting names and email addresses of full- or part-time undergraduate students through Texas's Public Information Act from the public information officers at 6 universities (University of Texas [UT] Arlington, UT Dallas, UT El Paso, UT Rio Grande Valley, UT San Antonio, and the University of Houston System). These 6 universities were selected because they are designated as Hispanic-serving institutions and all have large proportions of Hispanic students [17].

We received 100% of the requested information from all 6 colleges. Simple random samples using probability-based sampling frames of student names were drawn from each of the 6 colleges to minimize self-selection bias and improve generalizability [18]. The EMA study, qualitative interviews, and web-based surveys were and will be conducted in English, consistent with the cross-sectional web-based survey we conduct annually at Texas colleges as part of the tobacco prevention program [19]. However, participating students had the option to submit vaping-related social media content in Spanish, and our team had expertise to analyze such data.

Study Procedure and Participants

Phase 1: EMA Study (Years 1-2; March 2023 to May 2023)

An introductory invitation email explaining the study's objectives was sent to random samples of 5000 students at 5 of the 6 universities in the study (UT Arlington, UT El Paso, UT Rio Grande Valley, UT San Antonio, and the University of Houston), totaling 25,000 students, between March 24, 2023, and May 3, 2023. Eligibility criteria for the EMA study included (1) self-identifying as Mexican Americans, (2) being a degree-seeking college student, (3) being aged between 18 and 25 years, (4) being an active user of at least 2 social media platforms in the previous 30 days, (5) vaping in the previous 30 days, and (6) owning a smartphone and being willing to download the LifeData RealLife Exp mobile app.

Those who met the eligibility criteria were guided to a web-based consent form, and those who consented completed a baseline survey administered using the Qualtrics platform (Qualtrics International Inc). After completing the baseline survey, participants were invited to download the EMA app onto their smartphones via a QR code granting them access to the EMA study. Participants were provided with detailed study instructions that explained data collection procedures and offered step-by-step tutorials on how to use the app's features to complete the daily EMAs.

In total, 2 types of EMA data were collected over the 14-day-period: daily diary and event-based assessments. Daily diaries were delivered at 10 AM each day on weekdays and at noon each day on weekends. In both cases, participants had 8 hours to complete the survey, with up to 3 reminders delivered every 2 hours. The mobile EMA system alerted participants to complete the surveys through an in-app push notification, which rang and made the phone vibrate. Event-sampling assessments were initiated by participants and were available via a button on the app home screen. Participants were instructed to initiate an event-based assessment when they (1) encountered a vaping-related post on social media or (2) vaped. For the vaping-related social media post assessments, participants had the option to upload a screenshot or photo of the post. All assessments were date and time stamped.

Qualitative Interviews (Years 1-2; May 2023 to November 2023)

A total of 37% (19/51) of the students who participated in the EMA also completed a 1-hour, one-on-one qualitative interview that occurred between May 2023 and November 2023. The purpose of the qualitative interviews was to more deeply understand how vaping-related social media to which participants were exposed and with which they engaged during the 14 days shaped their outcome expectations, social norms, and attitudes and beliefs (ie, mediators) and, in turn, their vaping behaviors. For example, we showed participants a set of three screenshots of vaping-related content, which was in both English and Spanish and included (1) an advertisement for various flavors of vapes, (2) a video outlining tips to quit vaping, and (3) a humorous skit about locating a friend based on the scent of their vape.

We probed their reactions to the intended message of the content; its appeal to both the interviewee and other e-cigarette users; and whether, how, and why the content enticed vaping. Findings from the qualitative interviews also provided the basis for the measures and items in the web-based survey, ensuring culturally relevant content and terminology. For example, we identified and verified the terminology used for social media concepts and vaping products and verified that the vaping products and social media platforms that we planned to assess (eg, Instagram, TikTok, and YouTube) were appropriate. If participants identified other platforms or newly emerging tobacco products, our plan was to also assess those.

The interviews were conducted in English by trained bilingual staff (to capture "Spanglish" terminology) who were either college students attending one of the participating colleges (ie, UT Rio Grande Valley) or recent graduates of the University of Texas Health Science Center (UTHealth) Houston School of Public Health. The interviews were digitally recorded and transcribed, and transcripts were analyzed using a thematic

approach. Several members of our team audited the themes to ensure appropriate inferences. Each of the 19 participants was assigned a code number so that data from the EMA study and qualitative interviews could be deidentified. The code number was used to link data across the 14-day EMA study and the qualitative interviews.

Phase 2: Cognitive Interviews (Year 2; July 2023 to September 2023)

While designing the web-based survey, we conducted 1-and-a-half–hour cognitive interviews with 10 participants who had completed both the EMA and qualitative interviews. The purpose of the cognitive interview was to refine and finalize all measures and items for the web-based survey [20,21]. All cognitive interviews were conducted by trained staff through Microsoft Teams (Microsoft Corp) and were digitally recorded. We directed participants to complete the survey while on Microsoft Teams with both their own and project staff's cameras off and then let us know when they finished the survey; following completion, the staff walked through each question and the participants' answers, asking them to use the "think-aloud" method articulating their thought processes as each question was reviewed. Furthermore, the cognitive interviews incorporated specific, customized questions or "probes" regarding the survey questions. These probes yielded more detailed information than the think-aloud responses. This approach provided clarity on how participants formulated their answers as well as an estimate for approximate completion time.

4-Wave Web-Based Survey Study (Years 2-5; October 2023 Until 2025)

Following the incorporation of changes and recommendations from the cognitive interviews, we began to recruit for the web-based survey. An invitation email was sent to 165,966 undergraduate students across the 6 schools describing the study and providing a link with a brief eligibility screener survey between October 2023 and December 2023. Eligibility criteria for the survey included (1) self-identifying as Mexican American, (2) being a degree-seeking college student, and (3) being aged between 18 and 29 years. Those who met the eligibility criteria were guided to a web-based consent form that included the purpose and timeline of the study and described the incentive structure. Those who consented completed a baseline survey and established the cohort for Project VAMoS.

The survey was programmed in Qualtrics and was distributed using the built-in Qualtrics Mailer. Each participant received a unique link to the survey, which could only be completed once [22]. During data collection, participants' names, emails, and other information from the contact list were automatically saved to a secure server. Each participant was assigned a unique ID number, which allowed us to track student progress on each survey and match their data across waves without inclusion of personally identifying information in our survey database. Thus, we were able to track responses in progress and send reminders and thank-you messages to participants. In addition, this link automatically saved participants' data as they progressed through the survey. If they needed to leave the survey before finishing, a participant could return to it at any time before the survey closed. Participants who did not complete the baseline or wave-1 survey after receiving the initial email invite received up to 4 follow-up reminders to their school email addresses.

Measures

Phase 1: EMA Measures

Daily EMA measures captured data across 3 main constructs: acculturation, social media use, and vaping. For acculturation, participants provided information on their language preferences, engagement in cultural practices, and sense of ethnic identity. Regarding social media use, participants detailed how often they accessed social media per day, the time spent daily (in hours) on social media, the platforms they engaged with, the type of social media interactions they had (eg, comments, follows, likes, and shares), and their encounters with vaping-related content or advertisements. Participants also reported daily vaping behaviors, including frequency of use; device features; nicotine concentration; flavor preferences; use of other tobacco products, cannabis, and alcohol; and social contexts in which they vaped. All EMA questions were structured to capture participants' behaviors and experiences specifically for the previous day, allowing for a comprehensive understanding of their activities over a 24-hour period. Multimedia Appendix 1 shows the constructs assessed and example measures.

Qualitative Interview Guides

To provide a general outline for the qualitative interviews, we drafted a qualitative interview guide consisting of questions and follow-up probes to prime participant responses. The qualitative interview guide was informed by responses obtained from the EMA study. Participants were asked about vaping and use of social media. Probes sought to determine exposure to and engagement with vaping-related social media content over the previous 14 days and how this influenced their outcome expectations, social norms, and attitudes and beliefs (ie, mediators), subsequently affecting their vaping. After conducting 10 qualitative interviews, we observed that many participants disclosed vaping not only nicotine but also cannabis or tetrahydrocannabinol (THC), with some exclusively using cannabis or THC. Therefore, we revised the guide to explore the differences that participants perceived between vaping cannabis or THC and vaping nicotine. Specifically, these questions served to tease out distinctions in use patterns, contexts, and perceptions between the 2 substances. For example, we asked questions such as the following—"Are there places where and/or times when you use nicotine versus THC?"—to better understand the situational and behavioral differences in vaping these products.

Phase 2: 4-Wave Web-Based Survey Study

At wave 1 (baseline), participants completed a self-report survey consisting of 142 measures. Measurement selection was guided by the conceptual model in Figure 1, informed by the EMA and qualitative interviews, and refined through the cognitive interviews. Vaping measures were selected or adapted from national surveys, including the Population Assessment of Tobacco and Health Study, the Behavioral Risk Factor Surveillance System, the Youth Tobacco Survey, and the

National Survey on Drug Use and Health [23-26] (Multimedia Appendix 1).

The constructs assessed included sociodemographic characteristics, susceptibility to vaping, patterns of nicotine and cannabis or THC use, symptoms of dependence, cessation, outcome expectations from vaping, prevailing social norms, attitudes and beliefs, exposure to and engagement with social media, social media use patterns, and potential problems with social media [27]. We also assessed acculturation using proxy measures such as country of birth [28] and scaled measures such as the American Identity Measure [29-31] and included correlates of quality of family interactions and relationships [32]. Covariates assessed confounders and included use of other tobacco products and alcohol, experiences of racial or ethnic discrimination [33], and symptoms of depression [34] and anxiety [35].

At wave 2, we made several revisions. First, we shortened the survey by removing all items that would not change over time, such as sex at birth. We also did not ask participants to respond to "ever use" items at wave 2 (eg, ever used e-cigarettes) if they responded affirmatively at wave 1. Second, we included a limited number of new items; for example, we collected participants' race as defined by the US Census Bureau and intrapersonal measures of impulsivity, sensation seeking, and social anxiety [36-39]. Third, we asked participants to provide their personal social media handles or usernames for YouTube, Instagram, X (formerly known as Twitter), and Reddit to objectively assess the vaping-related social media content to which participants were exposed. We also asked participants to share 3 subreddits to which they subscribed and with which they frequently engaged also for objective assessment of vaping-related social media content. Consistent with our previous research [40,41], these data will be collected via the YouTube application programming interface (API) and web scraping for Instagram and X [42]. We will search for publicly available posts, videos, and hashtags with which our participants engage. We will not have access to the posts that participants see in their feeds or "for you" pages as these are not publicly available data and, thus, are outside the scope of our institutional review board (IRB) protocol.

Before analysis, all personally identifying information will be replaced with a unique ID number that matches the participants' ID number for the web-based survey, allowing us to link all the data for analysis. Custom-developed Python scripts (Python Software Foundation) will be used for API data collection from YouTube, and the Selenium toolkit [43] or Zeeschuimer [44] will be used for all browser-based web scraping (Instagram, YouTube, and X). The Python Reddit API Wrapper [45] will be used to collect data from Reddit. Depending on the platform, the date range of available posts will vary. We will scrape as much publicly available data as possible. The collected social media data will be studied computationally (with manual content analysis used to check validity). In terms of the former, we will use topic modeling, a computational natural language processing technique that we have successfully used in previous work [46], to identify statistically significant themes from (1) the posts of each user, (2) the aggregated posts of all users, and (3) the posts from subreddits that users follow and that they provided to us. Particularly for the latter, the data will be voluminous. Previous work has established the utility of generative artificial intelligence as a topic modeling tool to discover latent themes in large volumes of unstructured textual data [47]. We will adapt prompts developed and tested by others for topic modeling using ChatGPT (OpenAI) [48] to provide up to 5 themes for each user, 15 themes for all aggregated users, and 15 themes for each subreddit. We will then conduct a manual content analysis of a random sample of 150 posts from the aggregated posts of all users and the posts from subreddits that users follow to evaluate the robustness of the ChatGPT-based results. Our use of generative artificial intelligence will provide objective assessments of vaping-related social media content, which will allow us to characterize content that appeals to and entices Mexican American college students to use vapes**.**

Ethical Considerations

Human Participant Ethics Review Approvals

The IRB at UTHealth Houston (HSC-SPH-19-0796) approved all aspects of the study protocol. UT Austin approved the reliance on the UTHealth Houston IRB.

Informed Consent

All eligible participants in this study provided electronic informed consent before their participation in the 2 phases. Participants were informed about the study's objectives, procedures, potential risks, and benefits. They were informed that their participation was voluntary and that they could withdraw from the study at any time.

Privacy and Confidentiality

All collected data were deidentified to protect participants' privacy at the baseline wave. Personal information is removed before analysis, and the data are securely stored, with access restricted to authorized personnel.

Compensation Details

Phase 1

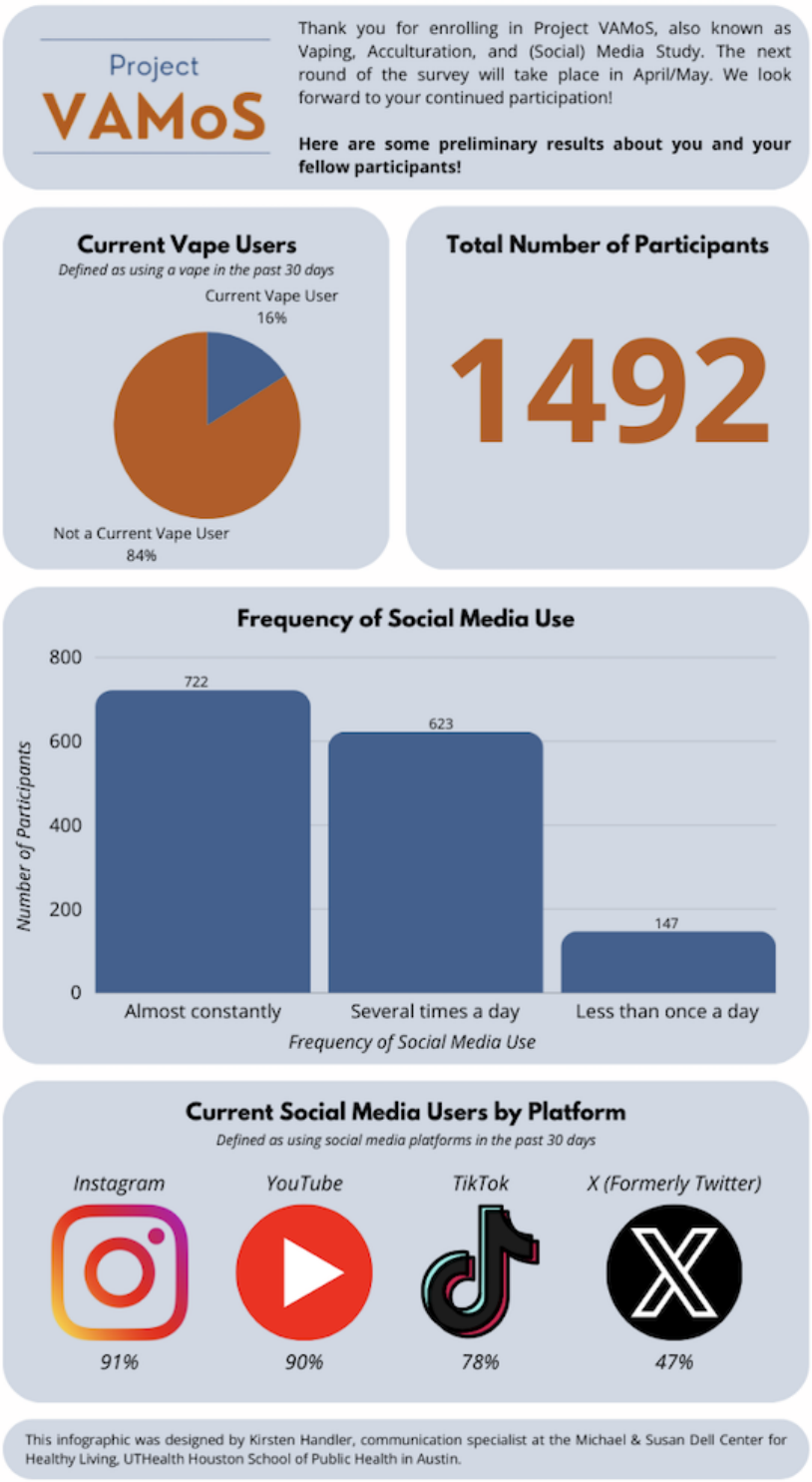
Participants who completed the EMA study were compensated with e-gift cards (US $10-$50) based on the percentage of daily diary assessments completed over the study period, with a minimum requirement of 50% of assessments completed to receive an incentive. Those who completed at least 7 daily diaries over the 14-day period received US $10 in e-gift cards (5/51, 10% of the participants), those who completed at least 10 daily diaries received US $35 in e-gift cards (13/51, 25%), and those who completed ≥13 of their daily diary EMAs received US $50 in e-gift cards (28/51, 55%). Participants were not compensated for event-based EMAs so as not to encourage false reporting of vaping or encounters with vaping-related social media content. Participants who completed the qualitative interviews were compensated with a US $50 e-gift card. Individual incentives were distributed within 2 weeks of completing the EMA and qualitative interviews.

Phase 2

Participants who completed the cognitive interviews were compensated with a US $50 e-gift card, which was distributed within 2 weeks of completing the interview. Individual

incentives were and will be offered at each of the 5 waves of the web-based survey. Students receive a US $25 e-gift card for completing each of the first 4 waves (totaling US $100) and a larger e-gift card of US $30 for completing the fifth and final wave. In addition, to maximize retention, we send an infographic with preliminary results between each survey (see Figure 2 for the infographic distributed between waves 1 and 2). Individual incentives are distributed within 2 weeks of survey completion.

Figure 2. Infographic distributed between baseline and wave 2 of the web-based survey.



Data Integrity and Security

We used rigorous protocols and advanced security measures to protect the integrity of the web-based survey data against bots and fraudulent respondents. First, we created a contact list with email addresses provided by each college and then distributed the survey using a unique, 1-time-use link for each participant in Qualtrics [22]. This setting prevented multiple survey completion attempts from the same individual by placing a

cookie on the participant's browser when they submitted a response. Participants are only able to complete the survey once; if the respondent clicks on the survey link after completing it, the presence of the cookie will prevent them from beginning a new survey. In addition, we incorporated a Completely Automated Public Turing Test to Tell Computers and Humans Apart (CAPTCHA) to ensure that surveys are completed by humans, not automated bots. Other strategies used to maximize the validity of the web-based survey data include the use of skip patterns within and across waves, which minimize participant fatigue and eliminate inconsistent responses; the use of "soft prompts" in most survey pages so that participants who skip questions are asked to verify their intent to leave the question blank; and the display of a limited number of items per screen or page [49,50]. In addition, participants are given the option to review and modify their responses using a Back button to enhance data accuracy. At wave 2, we added a human and attention check item to further ensure data validity and reliability [49].

Data security in Qualtrics is supported through advanced technological measures and robust policy enforcement. Qualtrics uses transport layer security encryption (also known as HTTPS) for all transmitted data. Qualtrics services are hosted by trusted data centers that are independently audited using the industry standard Statement on Standards for Attestation Engagements 18 method [49]. Access to datasets containing personal or identifying information is strictly limited to authorized members of the research team. These individuals undergo training in data privacy, confidentiality, and security protocols. Furthermore, they must use secure, complex passwords to access the Qualtrics data servers.

Final Data Quality Checks

Additional data quality checks were and will continue to be implemented to ensure the highest-quality survey data. Our team thoroughly reviews the survey responses for evidence of poor data quality. For example, we search for discrepancies in responses, such as participants providing contradictory answers to questions that should logically correlate or displaying a potentially problematic pattern of responses (eg, straight lining or selecting the same answer option several times in a row and a completion time of <10 minutes). Despite the exclusion of 0.2% (4/1824) of the participants at wave 1 due to these quality concerns, these participants received their incentive for taking part in this phase of the survey after we verified that a proper email address had been provided.

Maximizing Retention

To optimize retention across all waves of data collection, our team (1) fosters participant identification with the study by using our project name on all materials and correspondence [50-52]; (2) makes participation convenient by allowing participants to respond to the survey on a computer, smartphone, or other personal devices anywhere and at any time during the survey period [50]; (3) shares key study results via an infographic every 6 months; (4) sends multiple reminders (starting at wave 2, we sent reminders via email and SMS text message); and (5) keeps the survey open for up to 6 weeks to accommodate students' school and work schedules.

Results

Overview

Funding for Project VAMoS began in August 2022 and will conclude in March 2027. Data collection for phase 1 (EMA and qualitative interviews) was completed by June 2023. Phase 2, wave 1, was completed between November 2023 and December 2023; wave 2 was completed between April 2024 and May 2024. Wave 3 was completed between October 2024 and November 2024, and wave 4 will be completed between April 2025 and May 2025 (Table 1).

Table 1. Vaping, Acculturation, and Media Study timeline. Timeline: August 1, 2022-March 31, 2027.

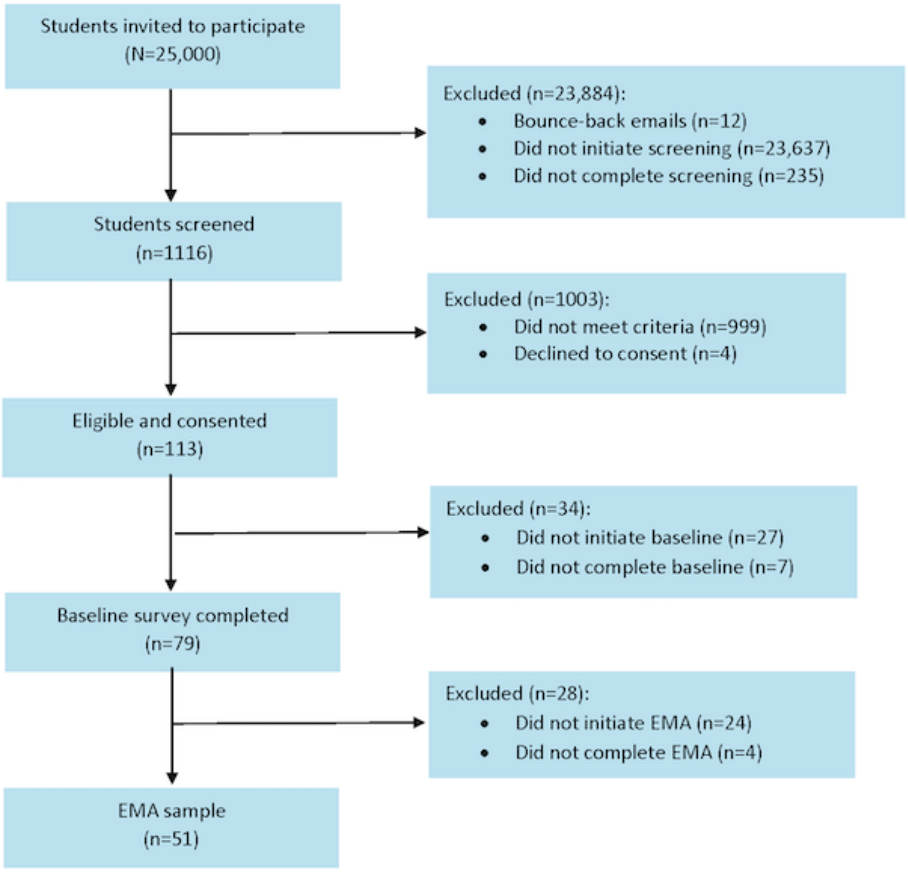
	Year 1 (2022-2023)		Year 2 (2023-2024)		Year 3 (2024-2025)		Year 4 (2025-2026)		Year 5 (2026-2027)	
	August-January	February-July	August-January (wave 1)	February-July (wave 2)	August-January (wave 3)	February-July (wave 4)	August-January	February-July	August-January	February-March
Phase 1: survey development and qualitative interviews										
Survey development	✓	✓								
Ecological momentary assessment		✓								
Qualitative interviews		✓	✓							
Phase 2: cognitive interviews and data collection										
Cognitive interviews		✓	✓							
Survey refinement		✓	✓							
Recruitment of participants			✓							
Survey data collection			✓	✓	✓	✓				
Data collection from social media				✓	✓	✓	✓			
GenAI[a] classification					✓	✓	✓	✓	✓	
Participant retention				✓	✓	✓				
Cleaning and analyzing data		✓	✓	✓	✓	✓	✓	✓	✓	✓

[a]GenAI: generative artificial intelligence.

EMA Eligibility and Completion Rates

In spring 2023, a total of 25,000 invitations were sent to potential participants, and 1116 (4.5%) students were screened to participate in the EMA study, of whom 113 (10.1%) were eligible and 79 (7.1%) completed a baseline survey that collected information on their demographics, social media use, and tobacco use behaviors. Of the 79 eligible participants, 24 (30%) did not proceed with the EMA study, and 4 (5%) were dropped due to inactivity (ie, did not complete the daily assessments). Thus, 45.1% (51/113) of the participants took part in the 14-day EMA study to address aim 1 (Figure 3). Completion rates were calculated to determine the feasibility of EMA as a means of obtaining daily data among Mexican American college students. Of a possible 714 prompts, a total of 608 (85.2%) were sent to participants over 14 days; this discrepancy is due to some participants disabling the LifeData app before the study concluded, meaning that they were not able to receive further prompts. Of the 608 prompts sent, we received 583 (95.9%) complete responses. Of the overall sample of 51 participants, 5 (10%) completed at least 10 daily diaries, 13 (25%) completed at least 11, and 28 (55%) completed ≥13 of the daily diary EMAs. The average completion rate was 83.2% (SD 24.9%; range 7%-100%).

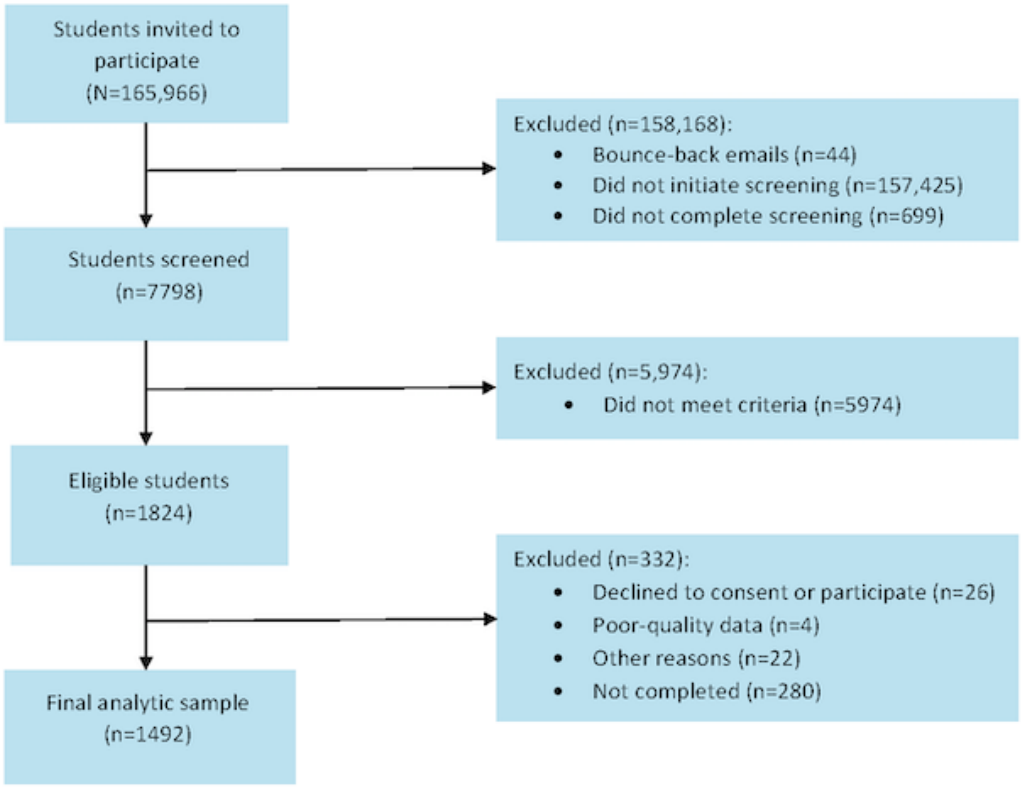
Figure 3. Flow diagram of ecological momentary assessment (EMA) participant recruitment.



4-Wave Web-Based Survey Eligibility and Retention Rates

In fall 2023, a total of 165,966 invitations were sent to potential participants, and 7798 (4.7%) students were screened to participate, of whom 1824 (23.4%) were eligible (Figure 4). Of those 1824 eligible participants, 26 (1.4%) declined to consent, 4 (0.2%) were excluded due to poor-quality data, 22 (1.2%) did not meet the age criteria and were excluded, and 280 (15.4%) did not complete the survey. Thus, 81.8% (1492/1824) of Mexican American students were recruited from all 6 participating universities to establish our cohort and address aims 2 and 3 (Figure 4). Of the baseline cohort, the retention rate in wave 2 was 74.7% (1114/1492).

Figure 4. Flow diagram of web-based survey participant recruitment.



Sample Characteristics

For the purposes of this paper, descriptive statistics were used to summarize the characteristics of the EMA study participants (Table 2) and the baseline characteristics of the participants who form the cohort for the web-based survey (Table 3). The final EMA analytic sample comprised 51 current vaping and social media users who were of Mexican American heritage. Participants (Table 3) were primarily female (37/51, 73%), born in the United States (48/51, 94%), of a middle socioeconomic status (38/51, 75%), and aged 21 years on average (SD 1.7 years). The final sample for the web-based survey included 1492 participants who were of Mexican American; Tejano, Tejana, or Tejanx; or Chicano, Chicana, or Chicanx heritage. Participants (Table 3) were primarily female (1042/1492, 69.8%), born in the United States (1366/1492, 91.6%), of a middle socioeconomic status (1174/1492, 78.7%), and aged 20.1 years on average (SD 2.2 y).

Table 2. Descriptive statistics for the ecological momentary assessment sample (N=51).

Characteristic	Values
Age (y), mean (SD)	21 (1.7)
Sex, n (%)	
Male	14 (27)
Female	37 (73)
Country of birth, n (%)	
United States	48 (94)
Mexico	3 (6)
Socioeconomicstatus, n (%)	
Low (1-3)	4 (8)
Middle (4-7)	38 (75)
High (8-10)	9 (18)
Socioeconomic status, mean (SD)	5.9 (1.7)
Federal Pell Grant, n (%)	
Yes	40 (78)
No	11 (22)
School attended, n (%)	
UT[a] Arlington	11 (22)
UT El Paso	12 (24)
UT San Antonio	10 (20)
UT Rio Grande Valley	10 (20)
University of Houston System	8 (16)

[a]UT: University of Texas.

Table 3. Descriptive statistics for the survey sample at wave 1 (N=1492).

Characteristic	Values
Age (y), mean (SD)	20.1 (2.2)
Sex, n (%)	
Male	450 (30.2)
Female	1042 (69.8)
Country of birth, n (%)	
United States	1366 (91.6)
Mexico	114 (7.6)
Other	12 (0.8)
Socioeconomicstatus, n (%)	
Low (1-3)	260 (17.4)
Middle (4-7)	1174 (78.7)
High (8-10)	56 (3.8)
Socioeconomic status, mean (SD)	4.9 (1.5)
Federal Pell Grant, n (%)	
Yes	474 (31.8)
No	1018 (68.2)
School attended, n (%)	
UT[a] Arlington	264 (17.7)
UT El Paso	240 (16.1)
UT San Antonio	405 (27.1)
UT Rio Grande Valley	321 (21.5)
University of Houston System	195 (13.1)
Year in college, n (%)	
Freshman	522 (35)
Sophomore	368 (24.7)
Junior	295 (19.8)
Senior	307 (20.6)

[a]UT: University of Texas.

Discussion

Expected Findings

Project VAMoS is one of the first longitudinal mixed methods research projects to explore the influences of social media and acculturation on vaping behaviors focusing exclusively on Mexican American college students. The results of this project will provide evidence for the roles of intrapersonal mediators (eg, outcome expectations and social norms) in the associations between vaping-related social media content and subsequent vaping. The results will also determine the moderating role of acculturation in the association between vaping-related social media content and subsequent vaping, as well as in the mediated paths between vaping-related social media content and subsequent vaping. In turn, results can inform the tailoring of culturally relevant interventions and the development of countermarketing policies to prevent vaping among Mexican American college students [53].

Project VAMoS is innovative in 3 key areas. First, unlike many studies that consider Hispanic individuals as a homogeneous group, this project specifically focuses on Mexican Americans, acknowledging the diversity within this population, particularly in tobacco use patterns related to country of origin and acculturation levels [54]. Second, the project delves into the underlying mechanisms or mediators—such as outcome expectations, social norms, and attitudes and beliefs—that influence how exposure to vaping-related social media content affects vaping behavior. These mediators are identified through an EMA study and one-on-one qualitative interviews and are empirically examined in a comprehensive, 4-wave survey study. Finally, in addition to subjective assessments, the project conducts objective assessments of the social media content that participants actually view and engage with on popular platforms

such as Instagram, TikTok, and YouTube. This approach minimizes the biases often associated with self-reported data [55].

Refining and Finalizing the Web-Based Survey

Some items were developed or refined based on findings from the EMA study and one-on-one interviews and then tested through cognitive interviewing to ensure their appropriateness for the study population [11,12]. For example, given the diverse range of substances that can be vaped, we incorporated options such as cannabis, THC, or delta-9; delta-8 THC; cannabidiol; caffeine; essential oils; vitamins; and more to include more potential vaping choices. In addition, we refined survey questions to ensure that they specifically addressed the substances that participants are vaping by including the terms "with nicotine" or "with cannabis/THC" without assuming exclusive consumption of either substance. As another example, we added response options such as "I do not know" or "neutral," along with time frames such as "When you were younger?" or "currently" to some acculturation measures. Moreover, we amended and will continue to amend items that are and are not included in subsequent waves in response to findings from the baseline survey wave. We will also add items in response to changes in the marketplace, such as the introduction of a new vaping device type, or in the policy landscape, such as a state or federal ruling regarding vapes or the marketing and promotion of these products.

Items were also added in response to the 2023 Surgeon General Report titled Social Media and Youth Mental Health [56], which concluded that there are gaps in current knowledge related to "the mental health impacts posed by social media" and that, currently, we cannot conclude that social media is sufficiently safe for young people. Accordingly, at wave 1, we assessed symptoms of depression, suicidal ideation, and anxiety [34,35]. At wave 2, we added measures to assess sensation seeking and impulsivity [38,39]. Symptoms of depression and anxiety increase risk of vaping both nicotine and cannabis or THC [57,58], whereas sensation seeking is associated with the uptake of vaping nicotine [59,60] and impulsivity increases risk of current vaping [61]. Therefore, the inclusion of these mental health and personality constructs complements existing measures assessed in Project VAMoS and will enable us to examine their role as potential mediators and moderators of the association between social media use and vaping.

Lessons Learned

Recruiting participants to join the EMA took more time than planned. Thus, we revised the eligibility criteria from vape use in the previous week to use in the previous 30 days. Similarly, recruiting participants to join the web-based survey took longer than planned; thus, we expanded the age range eligibility criteria from 18 to 25 years to 18 to 29 years and expanded recruitment from freshman students to all undergraduate levels, and we sent up to 4 email reminders rather than just 3. However, recruitment for the EMA study was completed in 6 weeks, and recruitment for the web-based survey was completed in 8 weeks. These adjustments broadened our participant pool, thereby creating a more representative cohort of college students. These challenges might be due to the specific nature of the inclusion criteria, such as being Mexican American [62]; potential hesitancy among young adults to participate in substance use research studies [62-65]; or the omission of incentive details from the invitation emails sent to participants to comply with IRB requirements.

This project provides an opportunity to better understand how Mexican American college students self-identify across racial categories. In wave 1, a total of 78.2% (1167/1492) of the participants identified solely as Hispanic when responding to a combined race and ethnicity question, whereas only 20.2% (301/1492) specified their race (data not shown). In response, at wave 2, we adopted a best practice approach aligning with the US Census Bureau's guidelines [66,67]. Specifically, we separated the race and ethnicity question into 2 items on the survey to allow participants to identify with a specific race while also recognizing their Hispanic ethnicity. Such an approach ensures that our data more accurately reflect the diverse racial backgrounds within the Mexican American population, enhancing our understanding of the associations among race, ethnicity, and social factors in the Mexican American community [66,67].

Strengths and Limitations

This project has many strengths. A major strength is the focus on Mexican American college students. Most studies have examined Hispanic populations as a single group, overlooking the differences in vape use patterns influenced by country of origin and acculturation levels. In addition, the Mexican American population in Texas is on the rise, with an increasing number of young individuals from this group enrolling in college annually [68]. Another major strength is the innovative approach in objectively measuring both exposure to and engagement with social media related to vaping. These objective assessments optimize the validity of self-reported social media exposure and engagement data and represent a distinct advantage that cannot be replicated by national surveys such as the Population Assessment of Tobacco and Health Study [23]. Furthermore, our EMA study and in-depth semistructured interviews enhance our research by enabling us to uncover culturally pertinent terms and concepts for evaluation in our web-based survey. Finally, the longitudinal design of our web-based survey allows for mediation tests to identify the intrapersonal factors that explain whether and how baseline levels of vaping-related social media content impact subsequent vape use at follow-up [69].

The project is not without limitations. First, we focused on college students, which limits generalizability. Nonetheless, this drawback is somewhat mitigated by the rapidly growing rate of college enrollment among Mexican American young adults. Second, we only recruited participants from Texas. However, Texas is a majorly minority state with the second-largest Hispanic population in the United States, predominantly consisting of Mexican Americans [4]. Moreover, Texas has the second-largest population of Hispanic college students in the United States [68]. This demographic profile enables us to concentrate on the largest Hispanic subgroup in the country.

Implications

The results of this research will offer unique insights into the prevalence, patterns of use, and determinants contributing to vaping among Mexican American college students. This information will inform the development of evidence-based, culturally relevant prevention interventions and policies specifically for the growing population of Mexican American college students. Moreover, results from mediation analyses will pinpoint the most effective intervention targets (namely, significant mediators), and the outcomes of such analyses will highlight which subgroups (namely, significant moderators) are most at risk from the impacts of exposure to and engagement with vaping-related social media content.

The results gathered from the EMA study, in-depth semistructured interviews, and objective assessment of social media content will reveal the vaping messaging that attracts Mexican American college students to vaping and influences them to vape. These insights will then serve as a foundation for developing economical counteradvertising and health messaging strategies. These strategies can be effectively disseminated through social media platforms to reduce vape use among Mexican American college students, thereby lowering their risk of tobacco-related morbidity and mortality. Finally, research in this area contributes to the broader goal of health equity by ensuring that the health needs of ethnic minority groups are adequately addressed. By understanding and addressing the specific health behaviors and their determinants within minority communities, public health initiatives can move toward reducing health disparities.

Acknowledgments

The research protocol described in this publication was supported by the National Institutes of Health under award R01MD017280 to AL and AVW.

Data Availability

The datasets generated or analyzed during this study are not publicly available as the study is ongoing but are available from the corresponding author on reasonable request.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Examples of ecological momentary assessment and web-based survey measures.
[DOCX File , 23 KB - resprot_v14i1e63584_app1.docx]

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Abbreviations

API: application programming interface
EMA: ecological momentary assessment
IRB: institutional review board
THC: tetrahydrocannabinol
UT: University of Texas
UTHealth: University of Texas Health Science Center
VAMoS: Vaping, Acculturation, and Media Study

Edited by A Schwartz; submitted 25.06.24; peer-reviewed by M Strowger; comments to author 06.09.24; revised version received 05.10.24; accepted 27.12.24; published 24.03.25.

Please cite as:
Bataineh BS, Marti CN, Murthy D, Badillo D, Chow S, Loukas A, Wilkinson AV
Vaping, Acculturation, and Social Media Use Among Mexican American College Students: Protocol for a Mixed Methods Web-Based Cohort Study
JMIR Res Protoc 2025;14:e63584
URL: https://www.researchprotocols.org/2025/1/e63584
doi:10.2196/63584
PMID:

Protocol

Exploring Climate Change's Impact on the Cardiopulmonary Health of Adults Living in the Canton of Valais, Switzerland: Protocol for a Development and Usability Pilot Study

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Abstract

Background: Climate change is affecting public health and well-being. In 2016, Swiss emergency departments (EDs) treated 1,722,000 cases, with 4718 daily admissions. In 2023, the ED of Sion Regional Hospital recorded 75,000 consultations. The links between climate change and health are complex, necessitating urgent research on its impact on cardiopulmonary health in Valais, Switzerland. Raising awareness among frontline professionals is crucial for developing health promotion and disease prevention strategies.

Objective: This study explores the preliminary effects of climate change on cardiopulmonary health in Valais and assesses adult patients' knowledge of its health consequences. Findings will inform adaptations in patient care, health promotion, and disease prevention at Sion Hospital's ED. The feasibility of patient selection and data collection will also be evaluated.

Methods: Using a convergent, parallel, mixed methods design, data will be collected from September 21, 2024, to September 20, 2025, with a target sample of 60 patients. The quantitative phase will examine patient recruitment feasibility, consultation reasons, and triage levels, correlating them with climate variables (temperature, nitrogen dioxide, particulate matter, sulfur dioxide, and ozone). It will also analyze sociodemographic profiles. The qualitative phase will explore patients' knowledge of climate change and its potential links to their ED visits. The feasibility and acceptability of the study process will be assessed. The protocol follows the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) Extension for Pilot and Feasibility Trials.

Results: Data collection started on September 21, 2024, following the approval by the ethical commission. Data collection will take place over 1 year, until September 20, 2025.

Conclusions: This study will test the feasibility of a larger investigation and examine potential associations between Valais' changing microclimate and population health. Findings will establish patient profiles and explore their perceptions and knowledge of climate change, informing future health interventions.

International Registered Report Identifier (IRRID): DERR1-10.2196/67128

(JMIR Res Protoc 2025;14:e67128) doi:10.2196/67128

KEYWORDS

climate change; global warming; emergency department; emergency nursing; sustainable care; ecological medicine; cardiopulmonary; cardio health; Valais; Switzerland; pilot study; study protocol; humanity; air pollution; impact; comorbidities; adults; mixed methods design; feasibility; health promotion; disease prevention; acceptability

Introduction

The planet's climate crisis is directly damaging human health. Globally, 3.6 billion people live in areas highly sensitive to climate change. Rising temperatures, extreme weather events, air pollution, and the spread of infectious diseases are just some of the major health threats exacerbated by climate change [1]. Climate change has many other direct and indirect effects on human health, including physical and mental disorders. Projections for 2025 estimate that climate change will be responsible for 250,000 additional deaths per year between 2030 and 2050 [2,3]. Worldwide, 9 out of 10 people breathe poor-quality air, and more than 7 million people die every year because of this pollution [4]. Greenhouse gas emissions, particulate matter (PM), nitrogen dioxide (NO_2), tropospheric ozone (O_3), and sulfur dioxide (SO_2) are the pollutants with the most significant impact on human health. There has been a concurrent 57% increase in heatwave episodes since 2010. Heat-related deaths among people >65 years of age have risen by 70% in 2 decades [5].

In recent years, several studies have been conducted on the various components of the relationship between health and climate change in Switzerland, particularly via the Swiss Study on Air Pollution and Lung and Health Diseases in Adults cohort [6]. A review of 22 studies by Cicci et al [7] highlighted positive associations between high temperatures and ischemic heart disease, acute myocardial infarction, the risk of congestive heart failure, and the number of emergency department (ED) consultations. Indeed, increasing numbers of ED admissions [7,8] hospitalizations for respiratory and cardiovascular diseases have been linked to nonoptimal temperatures and exposure to pollutants and unconventional natural gas development, while more cases of decreased lung function or chronic obstructive pulmonary disease have been linked to exposure to SO_2, NO_2, and PM_{10} [9-11]. Finally, climate change is leading to global warming, that is, the phenomenon of increasing average air temperatures near the Earth's surface [12]. This prolongs plant growth and pollination seasons and often increases the overall amount of pollen produced. This phenomenon can lead to increased respiratory allergies, rhinitis, and asthma in sensitive patients with immunoglobulin E–mediated allergic reactions [13,14].

In addition to its impacts on health, climate change can compromise many social determinants of good health, exacerbating the inequalities in morbidity and mortality that particularly threaten vulnerable populations. Indeed, environmental risk factors, such as demographics, geography, biology, health, sociopolitical and socioeconomic status, health system capacity, and overall equity, are responsible for 80% of common illnesses and 25% to 33% of the total disease burden [15]. Vulnerability has 4 primary features: integrity (a person's sense of soundness), challenge (vulnerability is experienced when there is a perceived challenge to one's integrity and uncertainty about how to respond to it), capacity for action (the perceived ability to withstand, integrate or cope with the challenge), and multidimensionality (how vulnerability varies from one person to another and from one experience to another) [16,17]. Older adults, infants from the age of 0-1 year, people with chronic diseases, those living in urban environments with low socioeconomic status or experiencing social isolation [5,18], and people living at higher altitudes [7] are all considered to be population groups vulnerable to climate change. Finally, regarding biological sex, Bayentin et al [19] and Gebhard et al [20] found that hospitalizations for ischemic heart diseases and myocardial infarction were higher among younger women than among younger men. Women have a higher core temperature, skin temperature, heart rate, and blood pressure than men, which can lead to decreased heat tolerance. However, men have a 33% higher incidence of stroke and a 41% higher prevalence of stroke than women [7].

EDs are gateways to the health care system. Their mission is to provide immediate specialist care to patients with urgent or life-threatening needs. Despite their heterogeneous profiles, EDs must provide patients with efficient, high-quality care, which the Institute of Medicine defines as the ability of a health service to increase the likelihood of achieving desired health outcomes in line with current professional knowledge [21]. Quality of care is a multidimensional concept that implies safe, responsive, effective, efficient, equitable, and patient-centered care [21]. In Switzerland, the National Ordinance on Quality of Care and Patient Safety sets out how health care facilities, institutions, and health care professionals must be actively committed to ensuring the quality of care and promoting patient safety. Moreover, through their collaboration, patients contribute to achieving the defined objectives of high-quality care and safety.

Ever more attention is being paid to the relationship between the environment and health. Climate change is causing health problems that did not exist before, leading to new health care needs. It is, therefore, essential to explore preliminary associations between climate variables and sociodemographic and health variables. Specifically, the primary outcome of the quantitative phase is the systematic assessment and analysis of the feasibility of patient recruitment, the reasons for their consultation, and their triage level. This first outcome will be correlated with climate variables (maximum and minimum temperature and concentrations of NO_2, PM, SO_2, and O_3) to investigate whether climate variables influence hospital admissions. The secondary outcome is an exploration of the sociodemographic profiles of adult patients consulting at Sion Hospital's ED. For the qualitative stage, the primary outcome is evaluating the level of acceptability of an interview guide to explore patients' knowledge about climate change and its potential links with their ED visits, and the secondary outcome is an exploration of patients' knowledge about climate change. Given the nature of the study, we decided to focus solely on cardiorespiratory comorbidities. As part of a larger study, other comorbidities should be explored, such as metabolic comorbidities (metabolic syndrome; type 2 diabetes, often associated with cardiovascular disorders; hypercholesterolemia; and hyperuricemia or gout), psychiatric comorbidities (depression, anxiety disorder, schizophrenia, and bipolar disorder), musculoskeletal comorbidities (osteoarthritis, fibromyalgia, and osteoporosis), endocrine comorbidities

(hypothyroidism and hyperthyroidism), or gastrointestinal comorbidities (celiac disease and inflammatory bowel disease).

Nurses are pivotal in recognizing and addressing the direct health impacts of climate change. They are uniquely positioned to promote overall health with their sensitivity to patients' vulnerabilities and emerging health needs. This includes identifying how climate change affects health in their daily practice, educating patients and communities about related risks, and fostering environmentally sustainable behaviors [22]. To achieve this, studies must be conducted on climate change and its health consequences. The first step is to assess the feasibility of the methods and procedures for a future large-scale study.

Methods

Design

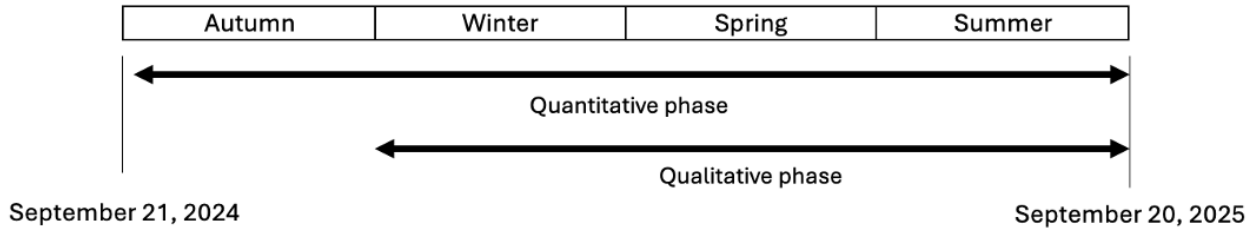
Achieving this development and usability pilot study's objectives requires a convergent, parallel, mixed methods design. Pilot studies are commonly used in health-related research in disciplines such as nursing and medicine [23], frequently to generate data for sample size calculations. This seems especially relevant when there are no data from previous studies to inform the process [24-26].

Quantitative Phase

Overview

Data collection will occur from September 21, 2024, to September 20, 2025 (Figure 1).

Figure 1. Pilot project's quantitative and qualitative phases.



The quantitative phase's objectives are to assess and analyze patient recruitment's feasibility, the reasons for adult patients' consultations at Sion's ED, their triage level, and their sociodemographic profiles. These variables will be analyzed with climate variables (maximum and minimum temperatures and concentrations of NO_2, PM, SO_2, and O_3) to investigate potential associations between hospital admissions and various climate variables. The secondary outcome is an exploration of the sociodemographic profiles of the adult patients consulting at Sion's ED.

A sample size of 40 to 60 adult patients is planned, that is, 15 per season. Pilot studies are often conducted to generate data for sample size calculations. This seems especially sensible when there are no data from previous studies to inform this process. This is the case in the context of this study. It is the first time such a study has been carried out in the canton of Valais. A general rule of thumb is to take 30 patients or greater to estimate a parameter [24,26]. During the triage process, the triage nurse recruits patients for the quantitative phase. Then, the nurse in charge collects the variables of interest.

Inclusion Criteria and Data Collection

We will include all adult patients aged 18 years and older, who consulted at Sion's ED and have cardiopulmonary comorbidities (ischemic heart disease, hypertensive heart disease, heart arrhythmias, heart failure, chronic obstructive pulmonary disease, asthma, obstructive sleep apnea, pneumonia, pulmonary fibrosis, and pulmonary cancer) sorted into levels 3, 4, or 5 according to the Valais triage scale. According to the Valais Swiss sorting scale, level 3 is considered semiurgent with a maximum response time is 60 minutes. Levels 4 and 5 are nonurgent, with a waiting time of 120 and 180 minutes, respectively (nonurgent). The patient must be able to speak, understand, and read French and sign the informed consent form with full knowledge of the facts. Eligible participants who sign this form but die during or after their ED consultation will be included in the study. The exclusion criteria are patients classified at levels 1 or 2 on the triage scale or who do not possess the capacity for discernment (as diagnosed by an ED physician). A level-1 classification on the Valais triage and severity scale implies a life-threatening condition. The patient's pathological situation could lead to death or the loss of an organ or a limb if care is not provided immediately. The patient must be transferred to an emergency care unit immediately. A level-2 triage classification requires urgent treatment since the pathological situation is not life-threatening but is susceptible to rapid deterioration. The patient must be transferred to an emergency care unit and assessed by a physician as quickly as possible. We believe it is, therefore, inadvisable to involve patients triaged at levels 1 and 2 in the pilot study as their rapid care is vital. Finally, Sion's ED does not accept patients under 18 years of age, as they are referred directly to the pediatric ED.

The variables to be analyzed can be divided into two categories: (1) sociodemographic data such as sex, age, place of residence (commune and postal code) and marital status (single, married, divorced, widowed, separated, or in a couple); and (2) medical and clinical data collected during ED visits, such as triage level, reason for the consultation, diagnosis based on the *ICD-10(International Statistical Classification of Disease, Tenth Revision*) classification, medical or surgical history, smoking status, and ED readmissions in the last 6 months. All these questions, except for ED readmissions in the last 6 months, will be collected by the nurse in charge during history taking and other exchanges with the patient. In this way, the data collection

process for the study's variables of interest will not prolong emergency care or diminish its quality.

Sociodemographic, medical, and clinical data will be analyzed in conjunction with climate data, for example, O_3 concentrations and air pollution data (Table 1). Data come from MétéoSuisse, Switzerland's official meteorological service, under the Federal Office of Meteorology and Climatology, and from RESIVAL, the Valais network collecting information on local climatic parameters.

Table 1. Databases and variables of interest for meteorological data.

Databases	Variables of interest								
	T_{max}	T_{min}	T_{mean}	NO_2[a]	PM_{25}[b]	PM_{10}	SO_2[c]	O_3[d]	Pollen
MétéoSuisse [27]	✓	✓	✓						✓
RESIVAL [28]			✓	✓	✓	✓		✓	

[a]NO_2: nitrogen dioxide.

[b]PM: particulate matter.

[c]SO_2: sulfur dioxide.

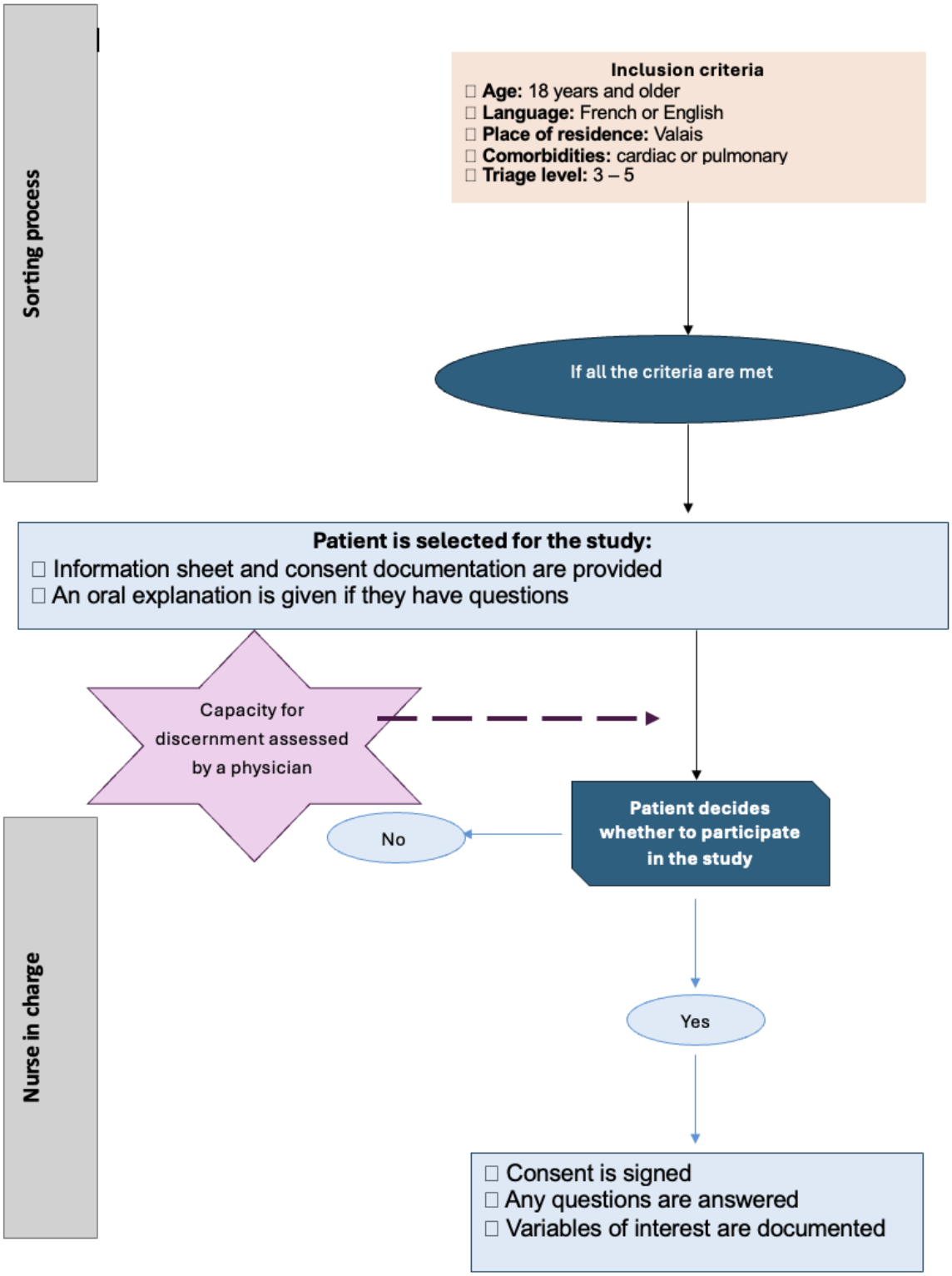
[d]O_3: tropospheric ozone.

Recruitment Procedure in Triage

The procedures for participant recruitment will be carried out by triage nurses—the first nursing staff patients meet when they arrive at the ED—and the nurse in charge. The principal investigator will explain the participant selection process to all the ED nurses at 2 team meetings (each 45 minutes long at the ED) and through an email containing a Microsoft PowerPoint presentation with a voiceover that will be sent out before those meetings. This will enable nurses to ask pertinent questions about their understanding of the recruitment algorithm. The triage nurses' role is to prioritize the patient's health status for their ED stay. They will be responsible for identifying whether patients meet all the inclusion criteria and, thus, for initiating the selection process. The nurse in charge or the triage nurse will then ask the patient whether they consent to participate in the study. If they agree, the nurses will collect the signed consent form. If the patient wishes, they can be given a 24-hour period to reflect. In this case, a stamped addressed envelope with the consent and information sheet will be given to them. As a reminder of the process and to ensure that it is carried out homogeneously, the participant selection algorithm (Figure 2) will be posted in every triage station and at the door of each cubicle. Indeed, nursing care in emergency contexts is often represented using an algorithm, so it is a visual tool that professionals in this field are familiar with. This will promote adhesion to and understanding of the algorithm.

The triage nurse or the nurse in charge will explain the study's purpose and the patient's contribution. They will then provide the patient with the study information document and the consent form. These additional explanations will not significantly lengthen triage time nor compromise the quality of care. The patient will have time to read the documents before entering the cubicle. When patients are given their discharge papers home (eg, a prescription, a follow-up appointment, a potential sick note for their employer, or other recommendations), the nurse in charge and the charge nurse, who oversees the operations of their specific nursing unit during a set period while working alongside the team, will ascertain the patient's decision to participate in the study. If the patient agrees, they will collect the signed consent and the document with the variables of interest. Their primary role is to ensure that all nursing functions within the department run smoothly and efficiently, verify whether they have decided to participate in the study, and collect their signed consent form if this is the case. They will answer any patient questions and remind them that their data will be coded and that they may receive a telephone call from the principal investigator.

Figure 2. Patient selection algorithm.



Measuring Temperatures and Pollution

In Valais, the RESIVAL measurement station network monitors and analyzes air pollution levels and calculates mean daily air quality parameters (24 hours from 0 Coordinated Universal Time to 0 Coordinated Universal Time) all across the canton [28]. Daily temperature variables (T_{min}, T_{max}, and T_{mean}) and pollen variables will be taken from MétéoSuisse, Switzerland's official federal national weather and climate service that operates under the Swiss Federal Department of Home Affairs. It is responsible for weather forecasting, climate monitoring, meteorological research, data collection, and public weather-related services [27].

Qualitative Phase

Overview

The qualitative phase's primary outcome is to explore patients' knowledge about climate change and its potential links with

their ED visits. The secondary outcome is an exploration of patients' knowledge about climate change. Indeed, factors outside of medical care, such as health beliefs, knowledge, attitudes, and behaviors such as smoking, are categorized as social determinants of health [29].

The inductive approach will guide the qualitative phase. A thematic analysis will be carried out independently by 2 researchers (OPS and PJPA). The level of theme identification will be latent or interpretative. During the pooling, disagreements will be settled by the intervention of the third researcher (HV).

Criteria and Data Collection

A nonprobability sample of patients participating in the study's quantitative phase will be selected for inclusion in the qualitative phase. The exclusion criterion established is the patient's incapacity for discernment, according to the patient's family doctor or family, or having a severe psychiatric disorder. The qualitative phase will be documented through individual interviews of 30-45 minutes until data saturation is reached. Data saturation will be reached when the data collected no longer yields any new significant or thematic information relevant to answering the research question. The theoretical number of interviews required is approximately 10-15. At least 6 weeks after the ED consultation, the principal investigator will contact participants on an aleatory basis by telephone to ask them to participate in a 30-45-minute interview. Six weeks were chosen so as to be far enough removed from any potential hospitalization that followed the index ED consultation. More information will also be collected and explored regarding the social determinants of health, categorized into five domains: (1) neighborhood and environment (where patients live, work, and play), (2) health and quality of access to health care (patients' use of health services to achieve the best health outcomes), (3) the social and community context (people with whom patients communicate and connect), (4) patients' access to education, and (5) economic stability (patients' financial resources). These domains can affect wellness, illness, and disease conditions [30]. By recognizing how social determinants impact health outcomes, nurses can play a key role in addressing health disparities and promoting health equity. Indeed, health disparities—variations in health linked to social, economic, and environmental disadvantages within a society [31], are pressing issues that demand immediate attention. Each area will be explored through a question and a follow-up question. Thus, the semistructured interview guide (Multimedia Appendix 1) consists of 5 questions and 5 follow-up questions. The aim is for the patient to share information about their daily life in relation to these 5 areas.

Withdrawal and Discontinuation

In the event of the patient's withdrawal from the study's quantitative phase, their data will not be included in the analysis. However, if the patient withdraws from the qualitative phase, their data will still be incorporated into the analysis of the quantitative phase. Participants withdrawing from the qualitative phase will be replaced in order to maintain the estimated number of interviews required. Participants can withdraw from the qualitative phase at any time, which could be due to a change of mind or to any complication resulting in a loss in their capacity for discernment or ability to understand and speak French (eg, an altered state of consciousness, intubation, tracheostomy, and tracheotomy).

Statistical Analysis

Statistics calculated in a pilot study are used to assess the feasibility of the full-size study and refine its methodology. A variety of methods can be used to address the objectives established for a pilot study, and these need not be statistical [23,26]. Indeed, statistical uncertainty must be taken into consideration before any of the pilot study's findings are generalized. The goal of publishing results from pilot studies is not to focus on their statistically significant findings but rather to provide their estimated effects on all the measures of interest and to describe the lessons that have been learned and will be informative in planning subsequent studies [23,32].

Factors such as the population's sociodemographic characteristics, economic conditions, and access to outpatient and hospital care facilities may confound the relationship between climate variables and hospital admissions.

More specifically, numerical and qualitative data will be analyzed according to good clinical research practices. Statistics will be generated from the raw data collected from the ED's patient records and the appropriate meteorological and air pollution websites (MétéoSuisse and RESIVAL). A database gathering sociodemographic variables (sex, age, place of residence, and marital status), health variables (triage level, reason for the consultation, diagnosis based on the *ICD-10* classification, medical or surgical history, smoking status, and ED readmissions in the last 6 months), meteorological (maximum and minimum temperature), and air pollution data (NO_2, $PM_{2.5}$, PM_{10}, SO_2, O_3, and pollen concentrations) will be prepared on a Microsoft Excel spreadsheet. They will be imported into and analyzed using SPSS software (version 29.0; IBM Corp). Descriptive statistics such as mean and SD (for quantitative variables) and frequency and percentages (for qualitative variables) will be calculated. Parametric statistical tests will be applied to normally distributed variables. Nonparametric statistical tests will be used for variables with non-Gaussian distributions. This data analysis will enable us to better describe the study participants' profiles. To estimate the effects of meteorological, sociodemographic, and health data, we will calculate a conditional quasi-Poisson regression and distributed lag nonlinear models. The model will estimate the association between hospital admissions and predictor variables (sociodemographic, health, meteorological, and air pollution variables). One advantage of the Poisson pseudomaximum likelihood estimator is that the scale of the dependent variable does not affect the parameter estimates [10]. In this type of regression model, a pseudolikelihood is applied to properly scale the SD of the coefficients proportionally to the potential overdispersion. We will use overdispersed generalized additive models with random effect meta-analysis to investigate the associations between variables [8]. ANCOVA models will also be developed to compare the means of a continuous dependent variable (hospital admissions) across multiple factor variables (autumn, winter, spring, and summer) and to determine

covariates' effects (sociodemographic, health, meteorological, and air pollution variables). This approach ensures a more nuanced understanding of how various factors and covariates collectively influence hospital admissions. Finally, the participant inclusion rate and study retention or drop-out rates will also be estimated, as will the total sample size required for the full-scale study.

The statistical significance threshold will be set according to the number of variables and the size of the database developed (2-sided *P* values<.01 will be considered statistically significant, with 95% CIs and Bonferroni adjustments for multiple comparisons).

Feasibility and Acceptability Phase

Feasibility refers to the practicality and appropriateness of the processes involved in patient selection and data collection within the pilot study. It evaluates the ability to recruit and retain participants, the functionality of inclusion and exclusion criteria, the adequacy of recruitment methods, and the efficiency, reliability, and acceptability of data collection tools and procedures [33,34]. Acceptability refers to the extent to which the study recruitment and data collection procedures, and interventions are considered appropriate, satisfactory, and appealing to participants, and other stakeholders. It evaluates the willingness of participants and involved personnel to engage with and adhere to the study's requirements [33,34]. The acceptability will be explored through an inductive approach. Three focus groups, each consisting of 4-6 ED nurses, will be conducted to explore variables such as time, objectives of the pilot study, implications, satisfaction, potential barriers, and facilitators to collect data, and ease of the process through open-ended questions. Finally, patients' level of acceptability of the interview guide will be explored through an open-ended question at the end of the individual interview "Do you feel that the guide enabled you to share meaningful insights?"

Feasibility will be assessed through 2 different approaches. The first approach will assess feasibility through the same focus groups used to assess acceptability. On a scale of 1="don't agree at all" to 5="completely agree," nurses will rate the process of the communication and training process to which they have been subjected (study protocol, mentoring, printed selection algorithm, principal investigator's feedback, and communication about the project). The second approach will consist of the proportion of expected data and data collected.

Ethical Considerations

The research protocol (2024-00900) for this pilot project was presented to its different partners. A request for authorization to proceed was presented to Swiss Ethics. The cantonal ethical commission for research on human beings, represented by Jean-Marie Annoni, gave its final approval on October 23, 2024. The support of the University of Applied Sciences and Arts Western Switzerland is assured. Participation in the study will be voluntary and pose no risk to the patients. In the context of this study, it is highly unlikely that participants will be exposed to any inconvenience or risk. Whether they participate in the study will in no way alter their care pathway or the quality of the care and follow-up they receive. Should the participant request them, the principal investigator will send them the pilot study's results by email or post. Participation in this study will be of no direct benefit to the patient. However, the results may help improve the overall delivery of care by providing emergency medicine that is better adapted to the patient's health status and needs. Finally, the preliminary results of the development and usability pilot study will enable the research team to propose a larger-scale study.

Given the nature of the variables to be collected, personal data will be coded to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of the people participating in the research. The coding process will be based on the best-practice recommendations found in Article 29 of the Working Group on Data Protection (the independent European advisory body on data protection and privacy). A collaboration agreement has been drawn up with Hôpital du Valais in the canton's French-speaking area. The principal investigator will be granted access to data obtained with patient consent for the duration of the study. The data collection process will be carried out in compliance with the appropriate data protection, human research, and ethical principles, thus ensuring respect for patients' rights and the confidentiality of their medical information. The coding key will be kept separate from the study data.

For the purposes of this development and usability pilot study, data will be stored on the Haute École de Santé Valais-Wallis' OneDrive server. The coding key between personal data and the numerical code, as well as the transcripts of each individual interview, will be kept by the principal investigator.

Results

Data collection started on September 21, 2024, following approval by the ethical commission. Data collection will take place over 1 year, until September 20, 2025. After 1 season of data collection, that is, between September 21, 2024, and December 21, 2024, a total of 60 patients were screened. The quantitative phase will begin in February 2025.

Discussion

Principal Results

The results of this development and usability pilot study will enable us to assess the feasibility of its methods and procedures with a view to carrying out a larger study. Indeed, it is important to adapt the patient selection algorithm to the clinical field's requirements and frontline carers' needs. By definition, the flow of patients coming to EDs cannot be predicted. The selection algorithm must be simple and not significantly delay a patient's treatment or slow its commencement. Our assumption is that we will have to make changes in 2 stages. These will still be communicated to managers and the entire care team. Concerning sociodemographic profiles, the hypothesis is that cardiovascular disease, active smoking, previous smoking, and diabetes are factors of vulnerability to climate change. In conjunction with the qualitative part, we hypothesize that vulnerable patients are aware of reduced quality of life during extreme temperatures or pollution peaks. However, little, if any, action is taken to

anticipate and prevent this. Patients' levels of technical literacy are, therefore, potentially low. Finally, we hypothesize that the qualitative interview guide's acceptability level is high. The interview guide has been pretested, and the exchange lasts no more than 45 minutes [32].

The results of the present development and usability pilot study could constitute a first step toward developing sustainable, ecological care. Indeed, today's duality of a health care system that provides benefits to patients and the population but has deleterious environmental consequences is becoming less and less acceptable. Finally, this development and usability pilot study will establish guidelines for a future larger-sized study.

Limitations

Data will be collected over 1 year so that all 4 seasons and their particularities—especially regarding climatic variables—can be studied. This development and usability pilot study is a single-center study and will only represent results from the Hôpital du Valais' ED in Sion. Finally, its objective is to assess and analyze the potential for adult patient recruitment, the reasons for patients' consultations, and their level of triage. It will also test the acceptability of an interview guide to explore patients' knowledge of climate change and its links with their ED visits. These preliminary results will constitute the first milestone in the assessment of the practicality of recruiting and retaining participants and in the determination of the most appropriate participant selection process to ensure stakeholder adherence for a full-scale study.

Conclusions

Climate change is a central concern for the discipline of nursing. Nurses are strategically placed to respond to the impacts of climate change through their practice, research, and training in developing, implementing, and sustaining innovation for climate change mitigation and adaptation. To do so, they must be given the tools to come to grips with the global health emergency, that is climate change. Taking stock of the current situation, particularly in the alpine canton of Valais, in Switzerland, will require a thorough assessment. This development and usability pilot study's preliminary results will be used to inform a future large-scale study whose findings we may be able to generalize and identify climate change's impact on the environment and the health of Valais' population.

Acknowledgments

HV is thanked for his valuable help in developing this protocol. The authors thank Amélie Borgeat, a specialist in Internal Medicine and Allergology and Clinical Immunology at the Hôpital du Valais, and Vanessa Azzi Virgini, allergist and pneumonologist, for contributing to the selection of the 16 pollinic variables best suited to this research. The authors also thank Jean-March Fracheboud, air specialist, Department of Mobility, Territory and Environment, for his contribution to the selection of variables proposed by RESIVAL.

Data Availability

All data generated or analyzed during this study are included in this published article.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Interview guide.
[PDF File (Adobe PDF File), 23 KB - resprot_v14i1e67128_app1.pdf]

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Abbreviations

ED: emergency department
ICD-10: International Statistical Classification of Disease, Tenth Revision
PM: particulate matter
NO2: nitrogen dioxide
O3: tropospheric ozone
SO2: sulfur dioxide
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials

Edited by A Schwartz; submitted 03.10.24; peer-reviewed by R Salgado, O Ramos; comments to author 14.11.24; revised version received 21.11.24; accepted 07.02.25; published 25.03.25.

Please cite as:
Portela Dos Santos O, Alves PJP, Verloo H
Exploring Climate Change's Impact on the Cardiopulmonary Health of Adults Living in the Canton of Valais, Switzerland: Protocol for a Development and Usability Pilot Study
JMIR Res Protoc 2025;14:e67128
URL: https://www.researchprotocols.org/2025/1/e67128
doi:10.2196/67128
PMID:

Protocol

Supporting Physical and Mental Health in Rural Veterans Living With Heart Failure: Protocol for a Nurse-Led Telephone Intervention Study

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Abstract

Background: Heart failure (HF) remains a disease of notable disparity for rural veterans, despite recent advancements in clinical treatment. Managing HF in the home is stressful and complex for rural veterans who experience unique barriers to optimal physical and mental health, necessitating adequate support and problem-solving skills.

Objective: This study aims to (1) adapt, to the rural sociocultural context, a culturally sensitive, tailored, telephone support and problem-solving intervention (CARE-HF [Supporting Physical and Mental Health in Rural Veterans With Heart Failure]) using findings from preliminary qualitative research and (2) evaluate the effects of CARE-HF on problem-solving and physical and mental health outcomes among rural veterans with HF.

Methods: This study involves a repeated-measures, single-group design. The intervention content was adapted and tailored to the rural sociocultural context using preliminary qualitative data and guided by the Theories of Social Problem-Solving and Stress, Appraisal, and Coping. Veterans are recruited from Veterans Administration home-based cardiac rehabilitation clinics, cardiology clinics that serve veterans, veterans-based community resource centers, and social media campaigns. Veterans with HF (N=100) receive the CARE-HF intervention. This nurse-led intervention comprises 8 telephone sessions that use a five-step, problem-solving process to manage common HF problems in the home: (1) identifying the problem and viewing it in a positive manner, (2) goal setting, (3) generating potential strategies for problem management, (4) choosing and implementing strategies to manage the problem, and (5) evaluating strategy effectiveness. Veterans receive initial problem-solving training during the first session, with follow-up sessions focusing on problem-solving skill reinforcement and assisting veterans in applying these principles to manage self-identified, HF-related problems experienced in the home. Data are collected at baseline and 3, 6, 12, and 18 months from baseline on problem-solving and outcomes of interest (ie, HF self-care; HF symptoms; health care utilization; depressive symptoms; anxiety; HF-specific, health-related quality of life; stress; resilience; and coping). Demographic data will be analyzed using descriptive statistics and multilevel growth curve modeling with restricted maximum likelihood estimation to compare a series of models using Akaike information criteria and Bayesian information criteria fit indices while controlling for covariates.

Results: Recruitment started in April 2023. As of December 2024, we have enrolled 56 veterans. Recruitment is anticipated to end in June 2025, with data collection continuing until all enrolled veterans have completed the 18-month follow-up period.

Conclusions: Adapting and testing a culturally sensitive, tailored, telephone intervention to aid support and problem-solving in the home has the potential to provide individualized care to rural veterans where they reside, thereby reducing travel burden while also increasing access to evidence-based care programs. If effective, telephone support and problem-solving interventions could be a low-cost, accessible method to improve physical and mental health in rural veterans with HF.

Trial Registration: ClinicalTrials.gov NCT05839067; https://clinicaltrials.gov/study/NCT05839067

International Registered Report Identifier (IRRID): DERR1-10.2196/63498

(JMIR Res Protoc 2025;14:e63498) doi:10.2196/63498

KEYWORDS

heart failure; veterans; problem-solving; self-care; heart failure symptoms; depression; anxiety; HRQOL; health-related quality of life; stress; resilience; coping; mental health; nurse-led intervention; social support; telehealth; chronic disease management

Introduction

Background

Heart failure (HF) is a chronic, progressive disease of notable disparity for rural veterans despite recent advancements in clinical treatments [1] and overall improvements in HF-related outcomes [2]. Incidence, hospitalization, and mortality rates continue to be highest in rural versus urban individuals with HF [2,3]. In rural veterans, specifically, HF is the second leading cause of cardiovascular-related hospitalization, accounting for about 30% of total hospitalizations [4]. Lower levels of health literacy, higher rates of food insecurity, the presence of food deserts, the lack of community support services, poverty, and limited health care access contribute to the disparities in HF-related outcomes in rural veterans [5-7] and influence physical and mental health [7].

Rurality impacts patients' ability to maintain optimal HF self-care and disease management in the home. Specifically, rural veterans with HF experience unique challenges, which are stressful, such as difficulties in obtaining fresh fruits and vegetables and low-sodium foods, which are a vital component of the HF dietary regimen [8]. The lack of local health care services and pharmacies, as well as public transportation, adds to the complexity of managing HF in a rural area [8] and increases the travel burden for veterans associated with receiving medical care [9]. In fact, only 9% of physicians practice in rural areas, which is significant given that 20% of the population in the United States lives in rural areas [6]. These rural-related social determinants of health play a crucial role in the ability to maintain optimal HF self-management and influence patient outcomes in rural veterans with HF [7].

Likewise, depression and anxiety are influenced by the progression of HF [10], with increased symptoms and decreased physical functioning contributing to poor mental health [11,12], and are associated with higher mortality and hospitalization rates [10,13]. Notably, depression and suicide rates are highest in rural patients compared to their urban counterparts, yet only 10% of mental health professionals practice in rural areas, leaving many rural veterans without access to mental health care [14] and placing them at even greater risk for poor HF outcomes [10,13]. Thus, rural veterans living with HF lack substantial support in aiding disease management and mitigating the negative emotions that often accompany living with HF, necessitating the development of novel interventions to support physical and mental health in the home.

Social support and problem-solving are essential coping resources that aid stress management, support resiliency, and enhance coping processes [15,16]. In rural veterans with HF, social support and problem-solving skills are critical to maintaining physical and mental health [8,17,18]. Patients with HF need to appraise and manage diverse symptomatology, adhere to dietary restrictions, cope with negative emotions, and negotiate daily activities [11,12]. Rural veterans with HF also need to successfully address rural-related challenges and barriers that undermine overall health [7]. Previous research suggests that the use of rational, systematic problem-solving strategies to manage HF-related problems is associated with better HF self-care [8,17] and may reduce HF symptom severity [18] and mental distress [17]. However, rural veterans often lack access to support and problem-solving interventions in their communities. Furthermore, when such services are available, they typically are not tailored to the rural sociocultural and educational context, nor are they able to address the specific emotional needs of veterans [19].

Culturally sensitive, tailored interventions that provide support and focus on enhancing problem-solving skills [16] hold considerable promise for increasing uptake in rural veterans with HF. Tailored support and problem-solving programs may be beneficial for veterans who need more assistance outside of a "standardized, one-size-fits-all" disease self-management program. Furthermore, the use of telephones allows for an easy-to-access, cost-effective, and successful modality for delivering such interventional programs to rural areas where access to broadband internet may still be problematic [20-22].

Our previous research assessed the preliminary efficacy of a 12-week, nurse-led, tailored, telephone-based, problem-solving and support intervention (Coping in Heart Failure [COPE-HF] Partnership) for patients with HF on changes in self-care, HF symptoms, depressive symptoms, and health care utilization in a three-arm randomized clinical trial [17,18]. Participants in the COPE-HF Partnership were all recently discharged from an acute care facility for issues related to HF and resided primarily in urban areas. A trained nurse interventionist partnered with the patient to manage HF-related self-care and disease management problems encountered in the home. Data were collected at baseline and 5, 9, and 13 weeks. The intervention was associated with improvements in self-care management;

notably, patients had less health care utilization over the intervention period versus the other groups [17]. Patients who received the intervention also reported fewer HF symptoms, with a significant decrease in HF symptom severity over the intervention period [18]. Although not significant, improvements in depression were also found in the intervention group [17].

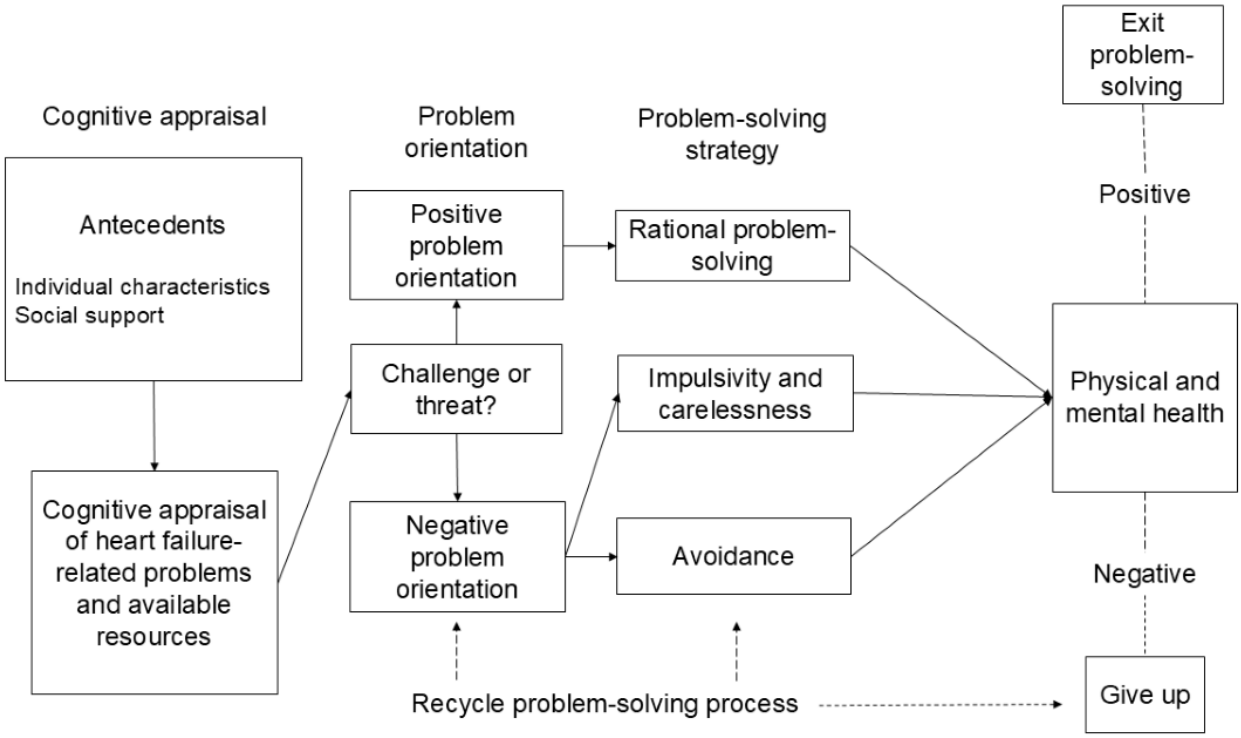
To prepare for the sociocultural adaptation of the CARE-HF (Supporting Physical and Mental Health in Rural Veterans With Heart Failure) intervention to the rural population, we conducted a qualitative study with rural patient–care partner dyads living with HF (n=11) to identify and describe the problems experienced in the home related to HF and associated management strategies [8]. The findings of this study showed that rural residents with HF experience significant problems related to self-care and disease management adherence due to the rural environment and lack of resources, as well as differences in cultural and personal values and beliefs related to health care. These problems resulted in a variety of physical and mental health sequelae and strained interpersonal relationships. However, most dyads developed effective workarounds and management strategies to overcome these challenges [8]. The problems and management strategies identified in this study provide the basis for the adaptation of intervention content for the rural population included in the CARE-HF intervention.

The CARE-HF also builds upon the COPE-HF Partnership intervention, in that it includes self-care and disease management components [17,18]. However, it differs in that the CARE-HF intervention is more holistically focused, also incorporating mental health, interpersonal, and social components. In addition, all components of the CARE-HF intervention are adapted to the rural sociocultural context and include specific problems and management strategies pertaining to physical and mental health drawn from the rural setting [8]. Because of the expanded focus of the CARE-HF intervention, additional study outcomes, not examined in the parent intervention, are included in the CARE-HF study.

Conceptual Framework

The Theories of Social Problem-Solving [16] and Stress, Appraisal, and Coping [15] provide the foundation for the CARE-HF intervention (Figure 1). Rural veterans with HF encounter a unique variety of problems that require cognitive appraisal and appropriate problem-solving to successfully cope with HF-related challenges. The two-fold cognitive appraisal process is influenced by individual characteristics and consists of primary appraisal (determination of the significance of the problem) and secondary appraisal (evaluation of available resources) [15]. Effective problem-solving requires a positive problem-orientation approach which elicits rational problem-solving versus avoidance, impulsivity, and carelessness. Problem-solving involves accurate problem identification, generation of appropriate strategies, active decision-making, and strategy implementation and evaluation [16]. The goal of the CARE-HF intervention is to move rural veterans with HF toward a positive problem orientation and use of rational problem-solving strategies, thereby supporting a more adaptive problem-solving style and enhancing physical and mental health [15,16].

Figure 1. Conceptual model based on the Theories of Social Problem-Solving and Stress, Appraisal, and Coping.



Purpose, Aims, and Hypotheses

The overall purpose of this study is to adapt to the rural sociocultural context and test the efficacy of a tailored, telephone-based intervention (CARE-HF) to support the physical and mental health of rural veterans by enhancing disease self-management and coping processes. To accomplish this goal, our research aims are to:

1. Adapt the CARE-HF intervention content to the rural sociocultural context using findings from preliminary qualitative research.
2. Examine the effectiveness of the CARE-HF intervention on study outcomes (HF self-care, HF symptoms, health care utilization, depressive symptoms, anxiety, health-related quality of life, stress, resilience, and coping), process (problem-solving), and antecedent (social support) in a sample of rural veterans with HF (N=100) at baseline and 3, 6, 12, and 18 months from baseline.

Our hypotheses are as follows:

- Hypothesis 2a: Increases in HF self-care, health-related quality of life, resilience, coping, and problem-solving will be noted at 3 months from baseline and sustained throughout the 18-month follow-up period.
- Hypothesis 2b: Decreases in HF symptoms (frequency, severity, and interference with physical activity and enjoyment of life), health care utilization, depressive symptoms, anxiety, and stress will be seen at 3 months from baseline and sustained throughout the 18-month follow-up period.

Methods

Cultural Adaptation

To address aim 1, before recruitment and study initiation, steps were taken to adapt the CARE-HF intervention content to the rural sociocultural context using some aspects of the ADAPT-ITT (Assessment, Decision, Adaptation, Production, Topical Experts, Integration, Training, and Testing) model [23]. Specifically, qualitative findings from preliminary research in rural patients with HF [8,12] guided the context of problems and potential strategies included in the program materials and telephone intervention sessions. The problems presented during the card sorting task, a component of the sessions, are drawn directly from this preliminary rural research [8,12]. In addition, during the telehealth sessions, veterans' values and beliefs are assessed and inform the potential strategies identified in the problem-solving process to enhance adherence and tailor the program to the unique needs of each rural veteran.

Ethical Considerations

This study was approved by the Florida State University Institutional Review Board (protocol STUDY00003764) to collect verbal consent via the telephone according to the principles of the Declaration of Helsinki, with potential participants maintaining the opportunity to opt out of the study. Telephone sessions are recorded to monitor intervention fidelity. However, all participant data are deidentified and stored in accordance with the General Data Protection Regulation Rules to maintain privacy and confidentiality. Veterans enrolled in the study receive compensation in the form of US $20 gift cards to a superstore following each completed data collection point, for up to a total of US $100 in gift cards if the entire study is completed. No identifiable information or images of research participants will be included in research reports. The CARE-HF protocol is registered at ClinicalTrials.gov (NCT05839067).

Design and Sample

This study includes a repeated-measures, single-group design. Veterans are recruited from Veterans Administration home-based cardiac rehabilitation clinics, cardiology clinics that serve veterans, veterans-based community resource centers, and social media campaigns using study flyers. Veterans with HF (N=100) will be recruited over 3 years, with the anticipated enrollment of 5 or more veterans per month. The desired sample size was based on a power analysis for repeated-measures ANOVA with 5 time points, α=.05, a medium effect size (f=0.25), and 80% power, plus oversampling for potential attrition (20%) estimated from studies involving patients with HF [17,18]. Veterans are eligible for participation if they (1) have a diagnosis of HF; (2) are aged 18 years or older; (3) have New York Heart Association functional class II-IV HF; and (4) can read, write, and communicate verbally in English, and excluded if they have a history of cognitive impairment.

Data Collection

Telephone data collection is conducted by a trained research assistant who verbally asks each item and records participants' responses in an online HIPAA (Health Insurance Portability and Accountability Act)–compliant Qualtrics database. Data are collected at baseline and 3, 6, 12, and 18 months from baseline. In addition to a sociodemographic and clinical survey (age, gender, comorbidities, education, and HF class), a set of self-report surveys is used to measure the study variables (Table 1). We also collect data on standard Veterans Administration Office of Rural Health metrics.

Table 1. Study variables.

Variables	Baseline	3 months	6 months	12 months	18 months
Covariates					
Social support	✓				
Process					
Problem-solving	✓	✓	✓	✓	✓
Outcomes					
HF[a] self-care	✓	✓	✓	✓	✓
HF symptoms	✓	✓	✓	✓	✓
Health care utilization		✓	✓	✓	✓
Depressive symptoms	✓	✓	✓	✓	✓
Anxiety	✓	✓	✓	✓	✓
HF-specific, health-related quality of life	✓	✓	✓	✓	✓
Stress	✓	✓	✓	✓	✓
Resilience	✓	✓	✓	✓	✓
Coping	✓	✓	✓	✓	✓

[a]HF: heart failure.

Study Measures

Social Support

The 12-item Interpersonal Support and Evaluation List measures perceived belonging, tangible, and appraisal support. The 3 subscales will be combined to obtain a single index of perceived support, in addition to the evaluation of the individual subscales. Scores range from 0-36, with higher scores suggesting a higher perception of available support [24]. Previous studies support its construct validity using the original 40-item version [24] and its internal consistency reliability (α=.90) [25].

Problem-Solving

The 25-item Social Problem-Solving Inventory Revised-Short measures problem orientation and problem-solving style using 5 subscales: positive and negative problem orientation, rational problem-solving, impulsivity and carelessness, and avoidance styles. The 5 subscales will be combined to provide a total score, with higher scores representing more of an adaptive problem-solving style and lower scores suggesting more of a maladaptive style. Higher scores on the individual subscales suggest more of the problem-solving characteristics [26]. Research supports its validity [16,26] and its reliability (α=.91) [25].

HF Self-Care

The 39-item Self-Care of Heart Failure Index v 7.2 measures HF self-care across 4 subscales: self-care maintenance, symptom perception, symptom management, and self-efficacy (α=.73-.88 across all subscales) [27,28]. Scores are standardized (0-100), with higher scores on each subscale suggesting better self-care principles. Scores ≥70 on each subscale are considered adequate; improvement of ≥8 is considered clinically significant [27].

HF Symptoms

HF symptoms are measured using the Heart Failure Symptom Survey. This survey contains 14 common symptoms of HF, which are rated on an 11-point scale (0–10) across 4 domains (frequency, severity, interference with activity, and interference with quality of life) based on the last 7 days. Higher scores indicate more of the respective domain in relation to the specific symptom [29]. Empirical evidence supports its content validity [29] and reliability (α=.96) [25].

Health Care Utilization

Health care utilization is determined by the frequency of emergency department visits and readmissions for HF and assessed via self-report. There are acceptable levels of agreement between self-report and medical record data [30].

Depressive Symptoms

Depressive symptoms are measured using the 20-item Center for Epidemiological Studies—Depression Scale. Overall scores range from 0 to 60, with higher scores indicating the presence of more depressive symptoms. A cutoff score of 16 indicates an individual is at risk for some degree of depression. Previous studies support its validity (Radloff [31]) and reliability (α=.90) [25].

Anxiety

The Generalized Anxiety Disorder-7 scale is a valid and reliable (α=.92) 7-item scale that assesses the presence of anxious symptoms over the past 14 days, using a Likert scale to rate the frequency of the symptoms (0=not at all, 1=several days, 2=more than half of the days, and 3=nearly every day). Total scores range from 0 to 21, with higher scores indicating more severe anxiety symptomatology [32]. In this study, the following recommended anxiety severity categories will be used: none or

normal (0-4), mild (5-9), moderate (10-14), and severe (15-21) [32].

Health-Related Quality of Life

The multidimensional 21-item Minnesota Living with Heart Failure Questionnaire measures the physical, socioeconomic, and emotional dimensions of HF-specific, health-related quality of life. This self-report survey asks respondents to evaluate the way they have felt in relation to the specific dimension over the last 4 weeks. Scores for the individual dimensions, as well as a total score, are obtained by summing the individual items. Higher scores suggest worse health-related quality of life relative to the specific dimension or overall. A change of ≥5 points is considered clinically meaningful [33]. Previous studies support its validity [33] and reliability (α>or=.80 across dimensions) [34].

Stress

The valid and reliable 10-item Perceived Stress Scale measures stress and includes questions relative to feelings and thoughts experienced during the last month using a Likert scale with scores ranging from 0 (never) to 4 (very often). Higher scores indicate higher levels of acute stress [35].

Resilience

The 25-item Five-by-Five Resilience Scale has 5 subscales that measure adaptability, emotion regulation, optimism, self-efficacy, and social support on a 5-point Likert scale (1=very inaccurate to 5=very accurate). Higher scores represent higher levels of resilience relative to the specific facet. Previous research shows adequate validity and reliability (α=.81-.93 across subscales) [36].

Coping

The Brief Coping Orientation to Problems Experienced is a 28-item scale that measures 14 coping strategies over 3 subscales (active emotional coping, avoidant emotional coping, and problem-focused coping) on a 4-point scale ranging from 1 (I haven't been doing this at all) to 4 (I have been doing this a lot). Higher scores on the subscales suggest more use of the specific type of coping strategy [37]. Previous research has indicated the measure is valid [37] and reliable (α=.78) [38].

Procedure and Intervention

CARE-HF

Veterans are trained to use social problem-solving skills to manage common HF-related problems in the home during 8 telephone sessions led by a trained registered nurse interventionist (NI).

Initial Telephone Session

Before the first session, veterans are mailed program materials and a manual presented at a sixth-grade reading level. To start the first telephone session, participants receive an overview of the program manual, tailored to the rural context, which includes information about social problem-solving principles. The manual also includes detailed real-life examples drawn from the rural setting of how to use the five-step, problem-solving process to evaluate and manage HF-related problems based on previous research (Table 2) [8]. Each example includes a positive problem-orientation approach and rational problem-solving strategies to address these HF-related problems. The NI uses fatigue as an example when discussing how to apply the iterative five-step, problem-solving process to manage actual HF-related problems. The five-step, problem-solving process is based upon the "Theory of Social Problem-Solving" and rational problem-solving principles and includes (1) identifying the problem and viewing it in a positive manner, (2) setting a goal related to problem management, (3) generating potential strategies to address the problem, (4) choosing and implementing one to two strategies to manage the problem, and (5) evaluating the effectiveness of chosen strategies [16].

Veterans are then asked to participate in a card-sorting task. Veterans are given a set of cards portraying HF-related problems identified in previous research (Table 2) [8,12] and asked to prioritize the cards from the highest priority problem to the lowest. Then, the NI will guide veterans in applying the problem-solving process to the HF-related problem identified as the highest priority. Next, the NI describes the benefits of reframing the problem in a positive manner and facilitates the selection of preliminary strategies to manage them. In doing so, the NI explores through discussion with the participants how their values and beliefs can be incorporated into potential strategies. Participants then choose one to two strategies on which to focus, the results of which are reviewed at the next session. The five-step, problem-solving process is reinforced throughout the intervention period in the follow-up telephone sessions.

Table 2. HF[a]-related problems and examples.

Problem categories	Examples
Monitoring and managing HF symptoms	• Fatigue (tiredness) • Forgetfulness • Edema (swelling) • Activity intolerance • Difficulty breathing (shortness of breath)
Staying on your special diet program	• Access to suitable foods • Shopping for and cooking correct foods • Limiting fluids (if recommended) • Barriers to eating foods with less salt • Personal food likes and dislikes • Not sure how to read and understand food labels
Staying on your HF treatment program	• Take daily weights • Exercise regularly (as recommended) • Keep regular health care visits • Get immunizations (flu, RSV[b], pneumonia, and COVID-19) • Use oxygen (as directed) • Stop smoking
Dealing with unhelpful emotions	• Sadness • Anxiety • Decreased quality of life • Depression • Anger • Negative life changes
Social isolation and loneliness	• Unable to do normal activities (community, church, family, and friends) • Fewer or no invitations to social events with friends and family • Feeling as if you have no one to turn to for support • Feeling alone
Medicine management	• Difficulty in obtaining medicine • Unable to pay for medicine • Problems in preparing medicine • Trouble in taking medicine on time • Taking several medicines for other health problems
Health beliefs	• How you view your health and wellness (accept, do not accept, positive, or negative) • How well you think you can do health activities for yourself (good, ok, or not well) • Your view of how well the heart medicine and treatment works (works well, no change, or does not help)
Caring for yourself (self-autonomy)	• You want to do everything for yourself and or make health care decisions whether you can or not • Family or friends want to do everything for you and or make health care decisions whether you can or not
Social support and community resources	• Family or friends who live close by • Church members and social group friends • Neighbors • Local senior center • Home health • Grocery store or grocery delivery programs nearby • Food pantry • Pharmacy nearby • Public transportation
Managing HF and other health issues	Managing HF and: • Diabetes • Neurological disorders

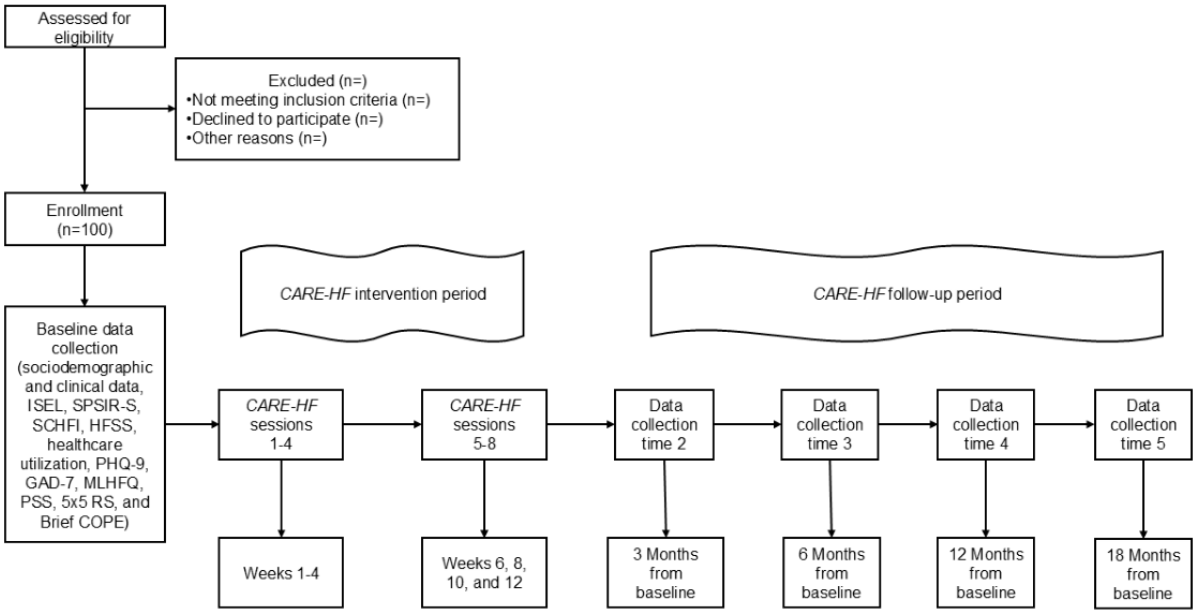
[a]HF: heart failure.

[b]RSV: respiratory syncytial virus.

Follow-Up Telephone Sessions

Seven follow-up telephone sessions occur weekly for the first month (sessions 2-4) and then biweekly for the second and third months (sessions 5-8). Each session begins with an evaluation of the previous week's problem, including the veterans' perceptions of the effectiveness of the strategies used. If needed, problem-solving guidance is provided or reinforced via verbal feedback from the NI. If the problem improves and no further problem-solving is required, the NI works with the veterans to establish a maintenance plan using rational problem-solving strategies. Veterans then repeat the card sorting task to identify new problems and the iterative five-step, problem-solving process starts over. Both current and new problems are identified by the veterans and examined during each follow-up telephone session. Each follow-up session lasts approximately 30 minutes. Figure 2 provides an overview of the study and associated major activities.

Figure 2. Study overview.



Intervention Fidelity

Strategies to enhance intervention fidelity are based upon the National Institutes of Health Behavior Change Consortium recommendations [39]. Standardized training for research staff who are conducting inclusion and exclusion screening, data collection, and intervention sessions occurred before study implementation to ensure adequate skill acquisition for the defined roles. The primary investigator trained staff initially until a minimum of 90% accuracy was achieved in covering the key elements of the defined role using role-playing, scenarios, and scripts. Fidelity checks of eligibility screening and informed consent, data collection contacts, and intervention sessions are also performed by the primary investigator every three months using a checklist of key elements for the specific activity to ensure that 90% of core elements are being consistently performed. Retraining of research staff occurs as needed to ensure that they meet the 90% criterion.

Data Analysis

Preliminary Analyses

Descriptive statistics will be computed on all time-invariant and time-varying study variables. Cronbach α values will be calculated for all measures containing multiple items to assess internal consistency. In the case that internal consistency is low ($\alpha<0.6$), an if-item-deleted analysis will be performed, and items that are not a good indicator for the underlying construct will be excluded.

Main Analyses

Multilevel growth curve modeling will be used for the testing of aim 2 or the evaluation of the effectiveness of CARE-HF. For each outcome variable, a series of models will be estimated and compared using incremental fit indices, including the Akaike information criteria and the Bayesian information criteria. The first model is an intercept-only model. Then, a growth curve model with a linear growth component will be estimated. Finally, a model with a quadratic growth component will be tested. The multilevel modeling and restricted maximum likelihood estimation method will be used in R (R Foundation for Statistical Computing) [40]. This method can deal with dropouts and missing data without excluding incomplete cases. In addition to fixed effects, random effects will be estimated.

Covariates

Several covariates will be considered for inclusion: age, biological sex, race and ethnicity, and educational attainment. Only covariates that are statistically significant predictors of at least one outcome will be included. That is, the same covariates will be used in all analyses for the primary aim.

Expected Outcome

We anticipate that the CARE-HF intervention will improve problem-solving, HF self-care, health-related quality of life, resilience, and coping and decrease HF symptoms, health care utilization, depressive symptoms, anxiety, and stress across all time points from baseline.

Results

Funding for this study was received in October 2022, and recruitment started in April 2023. As of December 2024, a total of 56 veterans have been enrolled, 4 veterans have completed the study, and the remaining veterans are in varying phases of intervention or follow-up. Recruitment is anticipated to end in June 2025, with follow-up data collection continuing until all enrolled veterans have completed the 18-month follow-up data collection period. Data analysis is forthcoming and will be conducted after the study completion.

Discussion

Significance of This Study

In recognition of the extraordinary challenges that rural patients encounter in maintaining optimal health, the American Heart Association [22] recently recommended the use of telehealth to increase health equity and provide vital access to cardiovascular supportive care in this population. Although mobile apps and virtual platforms are popular telehealth modalities for intervention delivery, their use in rural populations is plagued by technological challenges [22]. However, the use of telephones to deliver support and problem-solving interventions to rural patients with HF eliminates these technological issues and has been effective in optimizing HF self-care [17,18] and reducing depressive symptoms [41].

With an increasing focus on innovative methods to support physical and mental health and enhance health equity among rural veterans with HF, this study will provide important evidence on the effectiveness of an innovative, telephone-based, support and problem-solving intervention on HF self-care, HF symptoms, health care utilization, depressive symptoms, anxiety, health-related quality of life, stress, resilience, and coping. The CARE-HF intervention has the potential to improve the clinical care of rural veterans with HF, as well as be expanded to other populations. If this novel intervention is found to be effective and sustainable, it can be further tested in a larger randomized clinical trial, with the long-term goal of translating this intervention into clinical care for veterans with HF to enhance HF disease self-management and mental health.

Limitations

This study has some limitations. First, enrollment is restricted to rural veterans with HF; therefore, generalization of findings may be limited. Second, this is a single-group study that lacks a comparison group, reducing our ability to make meaningful comparisons across outcomes. Third, a lengthy follow-up period is included to examine the sustainability of the intervention effect and assess the need for booster sessions, but this may also contribute to a higher-than-desired attrition rate. Despite these limitations, this study will provide valuable insights for program evaluation and improvement, as well as intervention adherence and sustainability of effect to inform future research.

Conclusions

This study adapts to the rural sociocultural context and tests a tailored, telephone-based, support and problem-solving intervention designed to help rural veterans manage HF-related problems experienced in the home. If the intervention is effective, it will provide support for a highly accessible, low-cost method to aid rural veterans in maintaining optimal physical and mental health. This study fills an important research gap but, more importantly, provides the basis for future work to evaluate potentially effective and accessible services for rural veterans living with HF.

Acknowledgments

The authors would like to thank the following members of the research team: Rachel Abbott, RN, BSN; Armita Amiri, research assistant; Erik Rawls, PhD; and Kimberly Mattox, MS, research coordinator. The authors of this study would like to acknowledge the Veterans Administration Office of Rural Health, Gainesville Veteran Health Resource Center (VRHRC-GNV) (#008927), and the Florida Blue Center for Rural Research and Health Policy for the funding to conduct this study. We confirm that the protocol was subject to independent peer review as part of the review process conducted by the VRHRC-GNV.

Data Availability

The datasets generated or analyzed during this study are available from the corresponding author on reasonable request.

Authors' Contributions

LJG performed conceptualization, funding acquisition, project administration, supervision, methodology, writing – original draft, and writing – review and editing. LA handled funding acquisition, supervision, writing – original draft, and writing – review and editing. JH conducted investigation, methodology, and writing – original draft. TL managed funding acquisition, formal analysis, methodology, writing – original draft, and writing – review and editing. MBH contributed to funding acquisition, project administration, investigation, methodology, writing – original draft, and writing – review and editing.

Conflicts of Interest

None declared.

Multimedia Appendix 1
SPIRIT Checklist.
[PDF File (Adobe PDF File), 122 KB - resprot_v14i1e63498_app1.pdf]

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Abbreviations

ADAPT-ITT: Assessment, Decision, Adaptation, Production, Topical Experts, Integration, Training, and Testing

CARE-HF: Supporting Physical and Mental Health in Rural Veterans With Heart Failure
COPE-HF: Coping in Heart Failure
HF: heart failure
HIPAA: Health Insurance Portability and Accountability Act
NI: nurse interventionist

Edited by A Schwartz, T Leung; submitted 21.06.24; peer-reviewed by L Park; comments to author 06.12.24; revised version received 16.12.24; accepted 23.02.25; published 26.03.25.

Please cite as:
Graven LJ, Abbott L, Hodgkins JV, Ledermann T, Howren MB
Supporting Physical and Mental Health in Rural Veterans Living With Heart Failure: Protocol for a Nurse-Led Telephone Intervention Study
JMIR Res Protoc 2025;14:e63498
URL: https://www.researchprotocols.org/2025/1/e63498
doi:10.2196/63498
PMID:

Protocol

Centering Birthing Experiences of Women of Color: Protocol for a Qualitative Maternal Near Miss Study

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Abstract

Background: In the United States, Black women are 3-4 times more likely to experience maternal near miss (MNM) or severe maternal morbidity (SMM) than non-Hispanic White women. However, there is a limited narrative-based investigation into Black and other marginalized women's MNM experiences. Additionally, limited extant research on the impact of MNM and SMM on birthing women's families or support persons and health care providers precludes the development of multilevel, patient-centered methods to eliminate these racial or ethnic disparities.

Objective: This paper presents the protocol for a study that aims to draw insights from the experiences of racially and socioeconomically diverse mothers with MNM and SMM, their family or support persons (eg, partners), and health care providers to inform legislation, clinical practice, and infrastructure for optimal social support using PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) guidelines. Using a storytelling approach to assess participants' risk factors, document underlying causes, and research clinical causes of MNM, researchers hypothesize these data will inform policies to improve maternal conditions and provide safe and effective prevention and treatment options for birthing persons.

Methods: Morehouse School of Medicine (MSM) will partner with health services and community-based organizations to promote inclusive participant recruitment for this multiphase study. In phase 1, qualitative interviews were conducted with birthing women (n≤87) who have experienced MNM and SMM. In phase 2, we will conduct qualitative interviews with the following groups: birthing women's partners or support persons (n≤50), health care providers serving birthing women (n≤50), and adults who lost their mothers to pregnancy-related complications (n≤50). In each phase, the total number of participants interviewed will be based on theoretical saturation, that is, the point in iterative data collection and analysis when all important insights have been exhausted from the data already available.

Results: Recruitment for phase 1 started in July 2021. As of March 2024, we have recruited 87 racially and socioeconomically diverse birthing women. Of those, 74% (64/87) self-identified as Black or African American, 20% (17/87) as Hispanic or Latina, and 9% (8/87) as Native American or Alaska Native. Severe preeclampsia accounted for 46% (40/87) of participants' pregnancy-related adverse experiences. Qualitative interviews grounded in narrative-based medicine are ongoing. Recruitment for phase 2 will occur between July 2023 and December 2024. Study results will be published in peer-reviewed scientific journals.

Conclusions: The findings from this research will deepen the understanding of how severe obstetric complications (1) are experienced by birthing women; (2) are perceived by their partners, support persons, and health providers; and (3) impact the lives of bereaved family and community members.

(JMIR Res Protoc 2025;14:e58410) doi:10.2196/58410

KEYWORDS

maternal health disparities; maternal near miss; minority health; mental health; narrative-based medicine; experiences; birthing experience; women; Black women; United States; maternal morbidity; patient-centered; racial; ethnic; disparities; socioeconomically; pregnancy; childbirth; postpartum; antenatal

Introduction

Maternal health encompasses the well-being of both mothers and their newborns during pregnancy, childbirth, and the postpartum period. Despite advancements in medical technology and health care systems, there remain persistent challenges with maternal mortality (MM) and morbidity. The Centers for Disease Control and Prevention reports that the MM rate for the United States in 2021 was 32.9 deaths per 100,000 live births, compared to a rate of 23.8 in 2020 and 20.1 in 2019—statistics that suggest MM is increasing [1]. Likewise, severe maternal morbidity (SMM) is also on the rise in the United States [2]. SMM involves unforeseen birth outcomes that cause short-term and long-term health effects for birthing persons, including hemorrhage, cardiac arrest, organ failure, major surgery, and other life-threatening complications that require interventions [3]. Sadly, disparities in adverse pregnancy-related outcomes are widening. Research shows women of color experience disproportionate rates of MM and SMM in comparison to their non-Hispanic White counterparts [4,5]. This issue is perpetuated by racism embedded within the maternal health care infrastructure to the extent of which social determinants, such as higher income and education, no longer serve as protective factors for health [5-9].

The World Health Organization (WHO) contends that maternal near miss (MNM), defined as "a woman who nearly died but survived a complication that occurred during pregnancy, childbirth or within 42 days of termination of pregnancy," is a more useful indicator for studying the evaluation and improvement of obstetric health care than MM [10]. To date, little is understood about the contributors to MNM, especially for women and birthing people of color. Public health's tendency to rely on medical records and statistics often renders those most affected by health disparities unseen, unheard, and unnoticed in the discourse [11]. As Silverio et al [12] wrote, "it is not uncommon for quantitative approaches to be unable to detect the nuances of the experiences we seek to understand." Social context is needed to conceptualize the intricacies of health inequity as a means for developing effective and sustainable solutions [13]. Therefore, using a narrative-based medicine (NBM) model [14], this study centers on women of color's lived experiences [15] with surviving life-threatening pregnancy complications. Additionally, we are collecting a multistakeholder perspective by interviewing health care providers and partners or support persons who have witnessed an MNM experience and gathering narratives from adults and caretakers of adults, who lost their birth mother due to maternal causes. Using this approach, we hope to obtain an understanding of these stakeholders' perceptions and the impact of their experiences. Our goal is to uplift participants' stories as data points for influencing maternal health legislation, clinical practice, and health care strategy.

Methods

Study Design and Conceptual Framework

This study explores the burden of MNM and SMM using a narrative or storytelling approach recognizing birthing persons' experiences as legitimate sources of data. We used the Three Delays Model [16] to inform data collection and analysis. This model posits that MNM and SMM are largely the result of three critical delays, that are, first, delayed decision to seek care—barriers to making this critical decision include underestimation of the severity of the problem and its potential complications, poor understanding of danger signs and the potential scope of complications, cultural beliefs, customs, and attitudes (eg, distrust) regarding seeking care, and lack of social supports, among others. Second, delayed action or delay in reaching an appropriate site of care—getting to care, by definition, requires adequate transportation. A notorious problem in the developing world, transportation is also a challenge in many US states. Many states lack a sufficient number of perinatal providers; for example, half of Georgia's 159 counties lack a maternity provider [17]. Barriers like health care insurance enrollment and coverage, provider network limitations, as well as financial constraints can also be difficult to navigate. Further, lack of social support and lack of personal agency may hinder a woman's ability to act. Third, delayed diagnoses and appropriate treatment once a facility is reached—lack of facility resources (ie, equipment, blood, and drugs), a deficit of appropriately trained personnel, and systems that are poorly organized to manage obstetrical and medical emergencies are among the factors which can contribute to this delay.

Eligibility and Recruitment

In phase 1, to be eligible for the study, participants had to meet the criteria of (1) self-identity as Black or African American, Indigenous, or Latinx; (2) older than 18 years of age; (3) meet WHO near miss criteria, that is, experience with severe postpartum hemorrhage, severe preeclampsia, eclampsia, sepsis or severe systemic infection, and ruptured uterus during pregnancy; and (4) can speak and read English. Additionally, the screener survey was modified to include specific questions about medical interventions participants may have experienced to differentiate between MNM and SMM experiences. Recruitment occurred from July 2021 through April 2022. States originally chosen for recruitment included Georgia, Louisiana, New Jersey, and the DMV area (Washington, DC; Maryland; and Virginia) due to their high rates of MM. In September 2021, New York, Connecticut, South Carolina, and Mississippi were added to increase recruitment, followed by the addition of Alabama, Texas, and Oklahoma in December 2021. After numerous inquiries from birthing persons outside the previously included states, the study was expanded to include the entire United States in March 2022.

In phase 2, health care providers must meet the criteria of (1) self-identify as a physician, nurse practitioner, physician assistant, midwife, pediatrician, psychologist, or doula; (2) over 50% of their patient population identifies as a racial or ethnic minority; and (3) had a patient that experienced an MNM or witnessed an MNM. Support persons or partners will be considered eligible if they meet the criteria of (1) self-identify as a support person for a birthing person who experienced an MNM; (2) self-identify as Black or African American, Indigenous, or Latinx; (3) older than 18 years of age; and (4) can read and speak English. For adults whose mothers died due to maternal causes and caretakers of adults whose mothers died due to maternal causes, participants are considered eligible if they meet the criteria of (1) the death of the mother must have occurred within 1 year of the adult's birth; (2) self-identify as Black or African American, Indigenous, or Latinx; (3) older than 18 years of age; and (4) can read and speak English. An eligibility screener survey was created via REDCap (Vanderbilt University) for both phases of the study to identify participants.

Data Collection

All internal and external team members were required to complete the basic Collaborative Institutional Training Initiative course. Team members were also trained in research interviewing techniques, including how to ask additional questions that may be relevant to each specific interview.

Before the interviews, each participant completed the screening survey to verify their eligibility. Participants also completed a voluntary survey collecting sociodemographic data in addition to data surrounding the structural determinants that may have contributed to their MNM experience. These factors include age, parity, marital status, place of residence, education level, income, neighborhood characteristics, food insecurity, and so forth. Scheduling for interviews took place over email or messages via the technology platforms provided by Optum. Interviews were conducted virtually over the Zoom platform (Zoom Video Communications), included both audio and video, and typically lasted between 1 and 2 hours.

Birthing persons were identified through contacts with Morehouse School of Medicine (MSM) partner organizations, including our national community partner Reaching Our Sisters Everywhere (ROSE). ROSE was founded to address breastfeeding disparities in Black communities and works to normalize breastfeeding by providing resources and networking opportunities for individuals and communities. As a national expert, and in partnership with communities, ROSE builds equity in maternal and child health and fatherhood initiatives through culturally appropriate training, education, advocacy, and support. This partnership served as an opportunity to combine our advocacy and support of the community. ROSE used its network to recruit participants and assisted in conducting interviews. MSM and ROSE team members closely supported one another in debriefing some of the challenging and emotionally charged conversations held with participants about their MNM experiences [12]. This study was supported by Optum, the health services business of United Health Group, through grant support and research participant recruitment. Screening criteria were the same across all tools, and participants were cross-referenced against past and scheduled participants to avoid duplication of data.

Consent for interview facilitation and recording and transcription of interviews in addition to the demographic information were all collected via REDCap. A detailed informed consent form was developed by the research team and approved by the MSM institutional review board (IRB). The consent form was completed during the Zoom session with a team member present to answer any questions prior to beginning the interview. After determining that mental health effects were a common theme during several interviews, the consent form was modified in the event that emergency professionals needed to be contacted. The adjusted language stated, "This certificate does not stop Morehouse School of Medicine from giving out information to prevent harm to you or others." Any participants who mentioned suicidal ideation were also sent a Patient Safety Plan Template. This template, completed by individuals in their own time, collects warning signs, coping strategies, crisis contacts, and other material for participants to reference as needed [18]. Acknowledging that reliving traumatic experiences may have an effect, all participants received a detailed list of mental health resources located in their indicated state of residence.

Folders containing information about interviews and data analysis, including recruitment tracking, team interviewer availability, interview scheduling, and progress, were securely stored in an encrypted drive. Access was restricted to certified team members via password. Regular biweekly meetings were set up for the internal team to discuss updates and recruitment strategies. Additionally, separate biweekly working sessions were held with the funder.

As aforementioned, this study uses the power of storytelling, particularly NBM, which applies the narratives of patients or participants to medical practice [14]. We sought to understand participants' interactions with health providers, perceptions of quality of care, the circumstances of their "near miss," social support received, and their lived experiences prior to becoming pregnant. The interview guide was developed using the Three Delays Model and the International Consortium for Health Outcomes Measurement Set of Patient-Centered Outcome Measures for Pregnancy and Childbirth. These measures, including survival, morbidity, patient-reported health and well-being, and patient satisfaction with care were developed for providers to assess to improve patients' health outcomes and well-being [19]. The interview guide was submitted to and approved by the MSM IRB. In total, the interview guide contained 12 main questions and 13 probing questions.

For example, 1 key question of the interview guide used the Three Delays Model:

> *How was the process when you arrived at the hospital and how was your complication resolved? Take me through this part. What was said to you? Did you know what was going on? What was communication like? How did you feel at that moment?*

- Who/what were obstacles or facilitators to timely care?
- What was the wait time for care?
- Reasons for any delays

- Perceptions of quality of care

Furthermore, most of the interviews were spent answering the "near-miss" question:

> *Tell me about your birth experience. Tell me the story, all the way from beginning to end, describe the setting, who was involved, do you have any pictures you would like to share, please address important timelines...*

After the completion of the interviews, each participant received an email with a US $100 gift card as compensation. Also included in the email was the list of mental health resources and a link to the screener if any participants wanted to share the study with others.

Ethical Considerations

All Collaborative Institutional Training Initiative certificates were submitted and approved by the MSM IRB (ID number 1754465-15). Informed consent and the ability to opt out were provided to every participant. Participant data were deidentified. All participants who completed an interview were compensated with a US $100 gift card.

Data Analysis

After interviews were transcribed using a transcription service, transcripts were uploaded into Dedoose, a web-based qualitative data analysis program developed by SocioCultural Research Consultants, LLC [20]. A qualitative analysis training session was conducted and recorded for all Optum and MSM team members involved in the process. Our team used an open coding approach in which the codes identified emerged from the data itself, also known as inductive coding [21,22]. Once codes were found, they were classified under larger themes to establish a codebook. Research team members met periodically to refine and collate codes. Each coded transcript was reviewed by another team member to ensure the consistency of the code application. If there were any disagreements regarding codes, team members were informed to bring it to the attention of the principal investigator, and a final code would be decided via a team discussion. Additionally, any suggestions for new codes were brought to the attention of the principal investigator. Data analysis began in May 2022 and was completed in March 2023. Coding included about 12-15 team members per round.

Our research question is qualitatively focused, though we will collect and analyze quantitative data in a few ways. We will use demographic and quantitative data first to comprehensively describe the study population. Second, we will use these data to explore whether qualitative themes vary across participant characteristics such as race, age, income, education, and the presence or absence of social support. As we iteratively review the interview data throughout the analysis process, we will also examine thematic differences across other relevant factors that may emerge. Finally, given there are adequate data to support these analyses, we will assess whether factors including demographic (eg, race, age, income, and education); psychosocial; and clinical (eg, receipt and timing of prenatal care) factors are associated type of pregnancy-related complications experienced. We will perform qualitative analyses with SAS (version 9.4; SAS Institute) and SPSS Statistics (version 29; IBM Corp) [23,24].

Results

This study was funded in 2021 and recruitment for phase 1 started in July 2021. As of March 2024, we have recruited 87 racially and socioeconomically diverse birthing persons for phase 1. Of those, 74% (64/87) have self-identified as Black or African American, 20% (17/87) as Hispanic or Latina, and 9% (8/87) as Native American or Alaska Native (Table 1). Given the relatively low representation of some racial or ethnic groups, we will tailor ongoing recruitment efforts for phase 2 to improve inclusivity.

Table 1. Demographics of participants who completed an interview about the maternal near miss or severe maternal morbidity experience (N=87).

Variable	Values, n (%)
Race and ethnicity	
Black or African American	64 (74)
Hispanic or Latino or Latina	17 (20)
Native American, Alaska Native	8 (9)
Asian	4 (5)
Middle Eastern	1 (1)
Indian	1 (1)
Hawaiian or Other Pacific Islander	0 (0)
White	0 (0)
Other	4 (5)

Severe preeclampsia accounted for 46% (n=40) of participants' pregnancy-related adverse experiences (Table 2). Qualitative interviews grounded in NBM are ongoing.

Recruitment for phase 2 is scheduled to occur between July 2023 and December 2024. Findings from each phase will be published in peer-reviewed scientific journals.

Table 2. Pregnancy-related complications that participants indicated experiencing (n=86).

Variable	Values, n (%)
Severe preeclampsia	40 (46)
Severe postpartum hemorrhage	22 (26)
Eclampsia	3 (4)
Ruptured uterus	2 (2)
Sepsis or severe systemic infection	1 (1)
Other	18 (21)

Discussion

Principal Findings

Collecting stories from our participants' unique birthing experiences, as they relate to severe pregnancy-related complications, has allowed us to investigate the contributors to MNM and SMM and seek opportunities for improvement. Additionally, the majority of this study's participants completed college or a graduate or professional degree and reported an annual household income of $50,000 or more. Therefore, gathering demographic data from participants provides insight into whether socioeconomic "protective" factors, including income and education, have a significant impact on a birthing person's likelihood of experiencing MNM and SMM.

Sharing narratives from women of color who have experienced an MNM and SMM not only provides an opportunity to amplify the voices of those who have been historically silenced; but also, the evidence needed to advance maternal health justice. These perspectives are imperative in guiding the development of health priorities, policies, and strategies that drive optimal experiences for all birthing people. Some of our recommendations include equitable and respectful health care training, workforce diversification promotion, and health system disparity dashboards. Gathering stories from additional stakeholders will allow us to use their perspectives to refine our recommendations.

Strengths and Limitations

Initially, the interviews conducted were determined to be experiences of SMM and MNM. Using the WHO near-miss approach, the screener survey was edited to include questions regarding critical interventions [10]. Participants were asked which critical interventions were performed to save their lives, including cesarean section, blood transfusion, and intensive care unit admission. After implementing these changes, the following interviews were determined to be the experiences of MNM. All SMM interviews were noted as such, and they were organized separately from the MNM interviews. Additionally, we noted many completed screener surveys were fraudulent. There was an influx of emails, in both the internal email account and our funder's email account, that were spam and fraudulent. Screeners and emails were determined to be fraudulent if there were multiple screeners completed with different answers under the same email, the email addresses provided were invalid, and the open-ended answers or email communication did not grammatically make sense. To combat this issue, we incorporated a reCAPTCHA (Google) into our survey. Campbell et al [25] explain that humans and advanced bots can successfully avoid these mechanisms; this was consistent with our findings, given that reCAPTCHA did not seem to reduce the number of fraudulent screeners completed.

Future Directions

At this time, the study has expanded to include partners and support persons of those who have experienced an MNM, health care providers who have witnessed an MNM, and adult children and their caretakers who lost their mothers due to maternal causes. Garnering a multistakeholder perspective about MNM, SMM, and maternal deaths will allow us to examine the impact that severe obstetric complications may have on family members, survivors, and health care providers.

Acknowledgments

The authors would like to thank Reaching Our Sisters Everywhere (ROSE) for recruiting participants and conducting interviews. The authors would also like to thank all the birthing persons who shared their stories for this project. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health and the Department of Health and Human Services.

Funding

This study is supported by the Eunice Kennedy Shriver National Institute of Child Health and Human Development of the National Institutes of Health under award number U54HD113292. This project was also funded in part by the Health Resources and Services Administration (HRSA), U.S. Department of Health and Human Services, under grant number UR6MC50349. This study was supported in part by Optum through grant support and assistance in developing this protocol (as of publication of this study protocol, the grant mechanism is no longer active).

Data Availability

The datasets generated during and/or analyzed during this study are available from the corresponding author on reasonable request.

Authors' Contributions

NHG was the principal investigator and performed the conceptualization, project administration, supervision, and writing (review and editing). KHS coordinated the submission and performed writing (review and editing). OF contributed to the supervision and writing (review and editing). LC performed supervision and writing (review and editing). TL performed the writing (review and editing). AS contributed to writing (review and editing). KB contributed to writing (review and editing). KS contributed to writing (review and editing). AM performed writing (review and editing). SM contributed to writing (review and editing).

Conflicts of Interest

None declared.

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Abbreviations

IRB: institutional review board
MM: maternal mortality
MNM: maternal near miss
MSM: Morehouse School of Medicine
NBM: narrative-based medicine
PRISMA-P: Preferred Reporting Items for Systematic review and Meta-Analysis Protocols
ROSE: Reaching Our Sisters Everywhere
SMM: severe maternal morbidity
WHO: World Health Organization

Edited by A Mavragani; submitted 15.03.24; peer-reviewed by A Hakkim, S Sanders, S Dubare, M Das; comments to author 04.07.24; revised version received 25.07.24; accepted 30.08.24; published 27.03.25.

Please cite as:
Hernandez-Spalding K, Farinu O, Clarke L, Lewis T, Suarez A, Bugg K, Strickland K, Molleti A, Maxy S, Hernandez-Green N
Centering Birthing Experiences of Women of Color: Protocol for a Qualitative Maternal Near Miss Study
JMIR Res Protoc 2025;14:e58410
URL: https://www.researchprotocols.org/2025/1/e58410
doi:10.2196/58410
PMID:

Protocol

Effects of a Monophasic Hormonal Contraceptive With Norgestimate+Ethinyl Estradiol on Menstrual Bleeding: Protocol and Design of a Multicenter, Prospective, Open-Label, Noncomparative Study in Italy

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Abstract

Background: Norgestimate (NGM) is a progestin with negligible androgenic activity that is available in combination with ethinyl estradiol (EE) as a monophasic combined oral contraceptive (COC). It has been more than 30 years since a clinical study evaluated the effects of monophasic NGM/EE on menstrual cycle characteristics in healthy women, and in the interim, there has been growing recognition that clinical trials of contraceptives should evaluate a wide range of potential positive and negative impacts for users.

Objective: The aim of this study is to investigate menstrual cycle control during the use of a monophasic COC formulation containing NGM 0.25 mg and EE 0.035 mg (Effimia; Italfarmaco SpA), using established methodologies as well as patient-reported outcomes.

Methods: This is a prospective observational study being undertaken in a target population of 228 healthy Italian women aged 18-35 years who are starting oral contraception for the first time or switching from another COC. The participants are asked to complete a diary for 6 cycles recording information about their menstrual cycles (frequency, duration, regularity, estimated flow volume, and breakthrough bleeding), any unscheduled bleeding, and an evaluation of dysmenorrhea, using a 100-mm visual analog scale from 0=no pain to 100=very severe pain, and any adverse events. Compliance is assessed after 3 and 6 months via returned medication. The primary end point is the change from baseline in the rate of intermenstrual bleeding during the sixth cycle. At baseline, 3 months, and 6 months, acne will also be assessed using the Global Acne Grading Scale, and participants will complete a Profile of Mood State to assess premenstrual syndrome and the Female Sexual Function Index to evaluate the quality of their sex life. A subgroup of 28 participants at 1 site (Genoa) is also providing a blood sample for the assessment of metabolic, endocrine, and coagulation parameters.

Results: Study enrollment began in July 2023 and is expected to be complete by December 2024. Data analysis is expected to be complete by October 2025.

Conclusions: This study into the effects of monophasic NGM/EE 0.25/0.035 mg on menstrual characteristics in healthy Italian women will provide up-to-date data on these effects and includes assessments of a range of other parameters, such as acne severity and patient-reported outcomes, in line with recent international consensus recommendations.

Trial Registration: ClinicalTrials.gov NCT06067256; https://clinicaltrials.gov/study/NCT06067256 and EudraCT 2021-003027-15; https://www.clinicaltrialsregister.eu/ctr-search/trial/2021-003027-15/IT

International Registered Report Identifier (IRRID): DERR1-10.2196/63683

(JMIR Res Protoc 2025;14:e63683) doi:10.2196/63683

KEYWORDS

combined oral contraceptive; ethinyl estradiol; menstrual cycle; monophasic; norgestimate; hormonal contraceptive; menstrual health; Italy; women's health; patient-reported outcomes; methodology; observational study; reproductive health; data analysis; assessment

Introduction

Combined oral contraceptives (COCs) are the most commonly prescribed form of hormonal contraception in Italy and in other European countries [1]. These contraceptive pills contain a combination of estrogen and progestin to suppress ovulation (the primary contraceptive effect) and to change endometrial and cervical secretions, hindering the passage of sperm [2]. COCs may be monophasic or multiphasic. Monophasic COCs contain the same dose of estrogen and progestin in each pill, whereas the ratio of these hormones varies over the course of a cycle in multiphasic COCs.

Since the first development of COCs in the 1960s, formulations have been modified to reduce the risk of undesirable adverse events (AEs) and cardiovascular health risks [3]. The early progestins used in first- and second-generation COCs were chemically related to testosterone and caused androgenic AEs such as acne, hirsutism, and oily skin, which could undermine adherence as well as negative effects on high-density lipoprotein cholesterol [4]. Newer progestins have been structurally modified to be less androgenic or are structurally related to spironolactone [5,6]. In addition, estrogen doses have been progressively lowered, and most COCs in use today contain ≤0.035 mg of ethinyl estradiol (EE) [3]. COCs containing the first- and second-generation progestins were associated with a markedly higher risk of venous thromboembolism (VTE) compared with COCs containing the newer-generation progestins [7].

One such newer-generation progestin is norgestimate (NGM). NGM is a third-generation progestin derived from 19-nortestosterone [8]. It is rapidly hydrolyzed in vivo to norelgestromin, the primary active metabolite (75% to 80%), and levonorgestrel (20% to 25%) [9]. Both NGM and its metabolites have activity similar to endogenous progesterone but have a very poor affinity for androgen receptors and are therefore less androgenic than earlier progestins such as norgestrel, gestodene, or levonorgestrel [9,10]. In addition, unlike levonorgestrel, NGM increases levels of sex hormone–binding globulin in plasma, but does not bind to sex hormone–binding globulin, and is associated with reduced levels of free testosterone [11]. Data show that COCs containing NGM carry a lower risk of VTE than COCs containing cyproterone acetate, desogestrel, dienogest, drospirenone, or gestodene [12,13]. On the other hand, contraceptive patches containing norelgestromin are associated with a slightly higher incidence of VTE compared with levonorgestrel-containing COCs, presumably because of the high cumulative dose of EE that accompanies the transdermal route of administration [9].

Women want their contraceptives to be effective in preventing pregnancy, convenient, safe, and well tolerated, and with excellent cycle control [14]. Unscheduled bleeding has a number of negative impacts on a woman's life, in addition to the inconvenience, including the potential for a negative effect on their sexual life and confusion about the status of their cycle [14]. Some women may interpret unscheduled bleeding as an indication that the COC is not working or interrupt use because of it [14]. Monophasic COCs containing 0.030-0.035 mg of EE offer women the greatest likelihood of a regular bleeding pattern with a low risk of estrogen-associated risks as well as the option of fewer periods by reducing or eliminating the placebo period altogether [15]. As well as preventing pregnancy and potentially providing better cycle control (increased regularity and reduced intermenstrual bleeding), COCs may also offer improvements in acne and premenstrual or menstrual symptoms, such as mood changes, headaches, and pelvic pain [16]. However, effects on these parameters vary between COCs [16].

A large German study (N=59,701) demonstrated that the use of a monophasic COC containing 0.25 mg of NGM and 0.035 mg of EE reduced the rate of breakthrough bleeding in healthy women compared with the rate before they started taking NGM/EE [17]. Similar results were seen in an Italian study among 92 women receiving NGM/EE [18]. However, both of these trials were conducted more than 30 years ago, and there has been no recent research in Italy to confirm the effects of monophasic NGM/EE in healthy women. Moreover, since then, there has been growing recognition that clinical trials of contraceptives should evaluate a wide range of potential positive and negative impacts for users [19].

Thus, this study is being undertaken to investigate menstrual cycle control during the use of a monophasic COC formulation containing NGM/EE 0.25/0.035 mg (Effimia; Italfarmaco SpA), using established methodologies as well as patient-reported outcomes (PROs).

Methods

Recruitment

This prospective, open-label study is being conducted at 6 centers in Italy in healthy women aged 18 to 35 years who are starting oral contraception for the first time or planning to switch to a new COC for the purpose of contraception and not for therapeutic reasons. No specific tests are performed before enrollment, consistent with Italian guidelines that such tests are not indicated in women without individual or family risk factors [20]. Patients who are switching need to undergo a 1-month washout phase prior to entry by discontinuing their previous COC 1 month prior to starting NGM/EE 0.25/0.035 mg. The participants must be residents of Italy and be sufficiently proficient in Italian to understand the informed consent form and the instructions for COC use. The key exclusion criteria are contraindications to the COC according to the current summary of product characteristics, concomitant conditions that place users at risk of AEs, or the use of COC for indications other than contraception, such as polycystic ovarian syndrome, endometriosis, or recurrent menometrorrhagia. Complete inclusion and exclusion criteria are shown in Textbox 1. Certain concomitant medications are not permitted for the duration of the study to minimize the potential for drug interactions or confounding of end-point assessment (Textbox 1).

Textbox 1. Complete inclusion and exclusion criteria.

Inclusion criteria (all must be met)

- Healthy women aged between 18 and 35 years (inclusive) in need of contraception.
- Residing in Italy and having a good knowledge of the Italian language, such as to correctly understand the informed consent form and the instructions for use and to ensure potential adherence to the study.
- Willing and able to understand and complete the written informed consent form.
- Willing to comply with the study protocol.

Exclusion criteria (any 1 of these disqualifies an individual from participating)

- Any contraindications to the use of combined oral contraceptives (COCs) according to the current summary of product characteristics of Effimia, that is, women presenting (or having ever presented) with myocardial infarction, transient ischemic attack, stroke, angina pectoris, deep vein thrombosis, pulmonary embolism (or presence of blood clots in organs other than legs and lungs), any blood clotting disorder (such as protein C deficiency, protein S deficiency, and antithrombin-III deficiency), or who need to undergo surgery or lie down for a long period of time (including the risk of previous deep vein thrombosis, arterial thromboembolism, hypertension in the course of treatment, and diabetes). If any of the listed conditions should appear during the use of the tested COC, the product must be stopped immediately, and the participant withdrawn from the study.
- Severe diabetes with blood vessel damage, heart valve disease with complications, severe hypertension, severe hypercholesterolemia or hypertriglyceridemia, hyperhomocysteinemia, migraine with aura, hepatitis C (and taking medications for this condition), endometrial hyperplasia, or unexplained vaginal bleeding.
- Women who are breastfeeding or pregnant or suspect they are pregnant.
- Current or history of any liver disease not yet recovered (liver function not yet normalized), any benign or malignant tumor of the liver, any breast or genital organs cancer (even suspected), or jaundice during pregnancy or while using hormonal contraceptives.
- Galactose intolerance, total lactase deficiency, or glucose-galactose malabsorption syndrome.
- Hypersensitivity to the active substances or to any excipients of the tested COC (eg, norgestimate, ethinyl estradiol, or lactose).
- Use of any of the following during the study period (according to the summary of product characteristics of Effimia): treatments for tuberculosis (eg, rifampicin), epilepsy (eg, primidone, phenytoin, barbiturates, carbamazepine, or oxcarbazepine), HIV and hepatitis C virus infection (protease inhibitor drugs and nonnucleoside reverse transcriptase inhibitors such as ritonavir, nevirapine, efavirenz, and also ombitasvir, paritaprevir, or dasabuvir), fungal infections (eg, griseofulvin), arthritis, osteoarthritis (etoricoxib), or pulmonary arterial hypertension (bosentan), and St John's wort used as an antidepressant. Medicines containing cyclosporine, antiepileptic lamotrigine, tranexamic acid, theophylline (used to treat respiratory problems), and tizanidine (used to treat muscle pain or cramps) should not be taken as well.
- Use of hormonal contraceptives in the previous month.
- BMI ≥30 kg/m^2 (class I obesity).
- Smoking >15 cigarettes per day.
- Off-label use of COC (eg, for polycystic ovarian syndrome, endometriosis, or recurrent menometrorrhagia).
- Currently taking part or who took part in clinical studies with experimental products in the previous month.
- Incapacity or inability to comply with the study protocol (unreliability in the intake of the product or in the completion of the diary) according to the investigator's opinion.

Ethics Approval

The study protocol and amendments were approved by the ethics committee at the coordinating center (Territorial Ethics Committee—Liguria; application 202100302715-003), with the latest version approved on June 17, 2024. The study is being conducted in accordance with the Declaration of Helsinki (seventh revision, 2013), the Convention of Oviedo in April 1997 and the additional protocol in January 1998, and the national laws, regulations, and applicable guidelines of Italy. In addition, the study is consistent with the International Conference on Harmonization Tripartite Guidelines for Good Clinical Practice requirements. Prior to any procedures, participants are given information about the study and asked to sign an informed consent form. Their personal data are deidentified before being stored and protected according to the current European General Data Protection Regulations. The women do not receive any financial compensation for participating in the study.

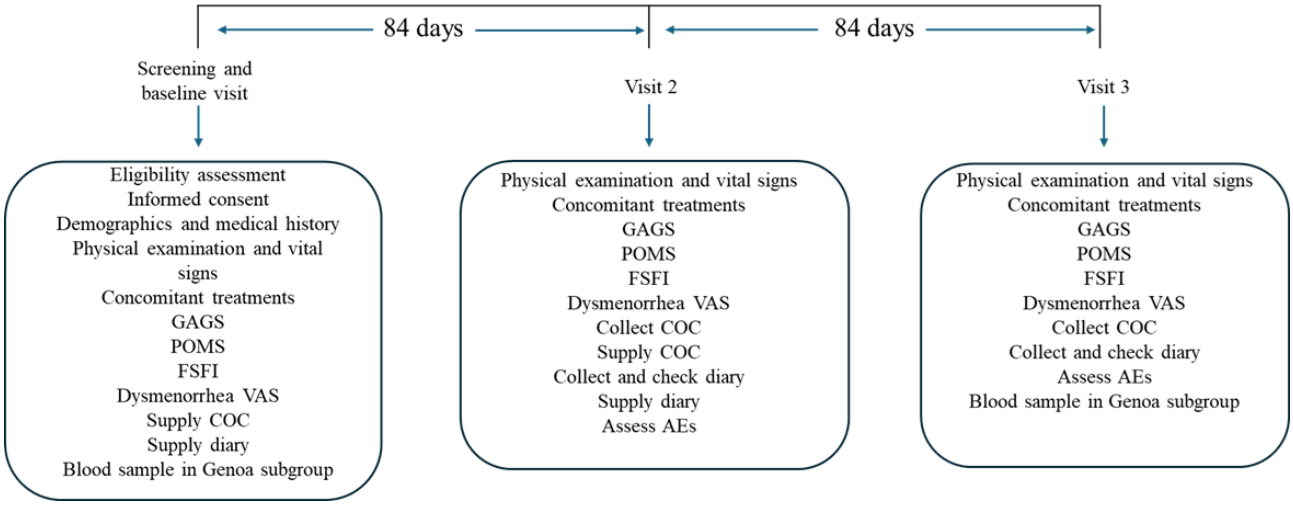
Procedures

During the baseline visit, participants have a physical examination, including an assessment of acne severity (using the Global Acne Grading Scale [GAGS] [21]), and provide a complete medical and menstrual history (Figure 1). They are asked about the characteristics of their menstrual cycle (frequency, duration, regularity, estimated flow volume, and breakthrough bleeding), any unscheduled bleeding, and an evaluation of dysmenorrhea, using a 100-mm visual analog scale (VAS) from 0=no pain to 100=very severe pain. Participants are also being asked to complete a Profile of Mood State (POMS) to assess premenstrual syndrome and the Female Sexual Function Index (FSFI) to evaluate the quality of their sex life, using the validated Italian language versions of these questionnaires [22-24]. At 1 site (Genoa), 28 participants are also providing a blood sample for the assessment of metabolic, endocrine, and coagulation parameters (Textbox 2).

At the baseline visit, participants are provided with NGM/EE 0.25/0.035 mg for the first 3 cycles and a diary, in which they are asked to record cycle evaluation parameters (Table 1), their medication-taking behavior, concomitant medications including over-the-counter medications (start and stop dates and dose), and any AEs.

Study participants are asked to return to the study site for 2 further visits, at day 84 and day 168 (Figure 1), and to bring their diaries and medication with them (whether used, partially used, or not used). At visit 2, researchers check the diaries to verify that participants are completing them correctly and provide them with new diaries and another 3 cycles of NGM/EE 0.25/0.035 mg. At both visits 2 and 3, the same assessments are conducted as at the baseline visit (physical examination, GAGS, POMS, FSFI, and dysmenorrhea VAS), and participants are asked about concomitant treatments, adherence, and AEs. At visit 3, the diaries are collected for final verification, and the subgroup of participants from Genoa provides another blood sample. In the case of an early withdrawal before the end of the sixth cycle, the investigator asks the participant to return for a final visit and records the reasons for the participant's decision to discontinue the study.

Figure 1. Study design. AE: adverse event; COC: combined oral contraceptive; FSFI: Female Sexual Function Index; GAGS: Global Acne Grading Scale; POMS: Profile of Mood State; VAS: visual analog scale.



Textbox 2. Parameters evaluated in blood samples in the subgroup of participants from Genoa.

Metabolic

- Glucose
- Insulin
- Total cholesterol
- High-density lipoprotein cholesterol
- Low-density lipoprotein cholesterol
- Triglycerides

Endocrine

- Total testosterone
- Dehydroepiandrosterone
- Androstenedione
- Sex hormone–binding globulin
- Free androgen index

Related to coagulation

- Fibrinogen
- Factor VII
- Antithrombin III
- Factor VIII
- Protein C
- Thrombin time
- Anticoagulant functional protein C
- Total protein S
- Activated protein C resistance

Table 1. Cycle evaluation parameters.

Parameter	Normal	Abnormal
Frequency	• ≥24 and ≤38 days	• Absent (no bleeding): amenorrhea • Infrequent (>38 days)
Duration	• ≤8 days	• Prolonged (>8 days)
Regularity	• Regular (shortest to longest cycle variation: ≤7 to 9 days[a])	• Irregular (shortest to longest cycle variation: ≥10 days)
Flow volume (participant determined)	• Participant considers normal	• Participant considers light • Participant considers heavy

Breakthrough bleeding (bleeding or spotting between the cyclically regular onset of menses)	• None	• Random
		• Cyclical (predictable):
		  • Early cycle
		  • Mid cycle
		  • Late cycle

Unscheduled bleeding on progestin±estrogen gonadal steroids (contraceptive pills, rings, patches, intrauterine contraceptive devices, or injections)	• None (for a participant on gonadal steroid medication) • Not applicable for participants not on gonadal steroid medication	• Present

[a]Normal variation depends on age; these data are calculated excluding short and long outliers.

Data Management

Investigators collect the information in a validated electronic data system managed by a contract research organization (Advice Pharma Group Srl). The contract research organization is responsible for checking the completeness of the data, monitoring the quality of the data, identifying any extreme values (outliers), and storing the information securely according to legal requirements. Access to the data is strictly limited to authorized personnel only, and individual patient information is deidentified prior to analysis.

End Points

The primary objective of the study is to investigate menstrual cycle control by evaluating breakthrough bleeding (ie, bleeding or spotting between the cyclically regular onset of menses) during the use of the monophasic NGM/EE 0.25/0.035 mg COC. This is measured by calculating the intermenstrual bleeding or spotting occurrence rate at the sixth cycle and comparing this with the rate at baseline.

Secondary outcomes include the change from baseline at visits 2 and 3 in other parameters of cycle control (frequency, duration, regularity, participant-determined flow volume, and unscheduled bleeding), GAGS score, POMS, FSFI, and dysmenorrhea severity based on the VAS rating. Adherence and contraceptive failure rate over the 6-month study period are also secondary outcomes, as are changes from baseline in the metabolic, hormonal, or coagulation parameters in the subgroup of participants from Genoa. Adherence is being evaluated as a percentage of tablets taken, based on the medication returned by participants at each visit. Contraception failure is defined as the proportion of women who become pregnant during the 6-month study period. The reasons for any contraception failure will be identified and listed (eg, discontinuation or poor adherence).

Safety Outcomes

AEs, including any serious adverse events (SAEs), are the key safety outcome. An AE can be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of NGM/EE 0.25/0.035 mg, whether considered related or not. This may include exacerbation of existing conditions, suspected drug-drug interactions, or clinically significant abnormal laboratory findings, although an abnormal laboratory finding may not be considered as an AE if there is no change compared to baseline values. Abnormal laboratory values or test results represent an AE only if they induce clinical signs or symptoms, are clinically significant, or require therapy. An SAE is any AE that results in death, is life-threatening, requires inpatient hospitalization or prolongation of an existing hospital stay, results in persistent or significant disability or incapacity, or results in a congenital anomaly or birth defect. Other medical events that may jeopardize the participant or may require a medical or surgical intervention to prevent an SAE are also considered to be serious.

Investigators will record any AEs or SAEs in a case report form, with a description of the event, date of occurrence, an assessment of its severity and potential relationship to NGM/EE 0.25/0.035 mg, and the outcome (including date of resolution). If there is at least a reasonable possibility that NGM/EE 0.25/0.035 mg is the cause of the AE (ie, that causality cannot be ruled out), the AE will be considered as an adverse drug reaction. The severity of the AE will be rated as mild (transient and generally not interfering with usual activities), moderate (sufficiently discomforting to interfere with usual activities), or severe (inability to perform usual activities). AEs of special interest in this study are hypertension, arterial thromboembolism,

myocardial infarction, stroke, transient ischemic attacks, venous thrombosis and pulmonary embolism, liver and breast tumors, cancer of the cervix, and disturbances in liver function (such as increased hepatic enzyme levels).

Statistical Analysis

Based on the previous large-scale study with NGM/EE 0.25/0.035 mg, the rate of breakthrough bleeding is expected to decrease from 4.5% before use to 3% after 6 cycles, and the rate of intermenstrual spotting to decrease from 9% to 4% [17]. Therefore, a sample size of 175 participants would have 80% power to detect a treatment effect on breakthrough bleeding at a 1-sided α level of 5%. To account for a potential dropout rate of 30%, we plan to screen 240 women for eligibility and enroll 228 participants, an average of 38 participants at each of the 6 centers.

Two datasets have been defined for analysis: the per-protocol set, which includes all participants with full treatment adherence and no major protocol deviations, and the intention-to-treat set, which includes all enrolled participants who received at least 1 dose of NGM/EE 0.25/0.035 mg. The primary outcome will be evaluated only in the per-protocol population to avoid any effects of noncompliance on the interpretation of this outcome. However, secondary efficacy outcomes and safety will be assessed in the intention-to-treat population using robust statistical methods against missing data, like linear mixed models.

Continuous variables will be described using the mean and standard deviation if they are normally distributed or using the median and interquartile range if nonnormally distributed. The distribution of these variables will be assessed using the 2-tailed Student *t* test for paired data or the Wilcoxon signed rank test. Categorical variables will be described using frequencies and percentages and compared using the chi-square test or Fisher exact test [25]. There will be no imputation for missing data, and data from unscheduled visits will not be included in the analysis. No adjustment for multiplicity will be made to adjust for a type I error in secondary end points. A *P* value of .05 is considered to be statistically significant.

All statistical analyses will be performed using the R statistical software (version 3.5 or later; R Foundation for Statistical Computing). The final analysis will be completed after all participants have completed the study, any queries have been resolved, and the database has been locked.

Results

Study enrollment began in July 2023 and is expected to be complete by December 2025. The last participant's last visit is anticipated to be in June 2026, and data analysis will be complete by October 2026.

Discussion

Overview

We anticipate that our study will confirm previous research [17,18], showing that monophasic COC with NGM/EE 0.25/0.035 mg reduces breakthrough bleeding in healthy women. However, our study will also investigate other effects of this COC on menstrual characteristics (regularity, flow volume, and dysmenorrhea). Moreover, the study will assess the impact of NGM/EE 0.25/0.035 mg on the other factors women want from their oral contraceptives in terms of pregnancy prevention, safety, and tolerability [14].

The absolute risk of VTE is 6.29 per 10,000 woman-years in women taking COCs, which while being twice the rate in women not taking COCs is still low [26]. Although the risk is low, it is still present; therefore, physicians should be vigilant to the potential for this AE among their patients taking COCs. The risk of VTE appears to be lower with NGM than with many other types of progestin [12,13], so we do not anticipate the development of VTE among women participating in this study, which is probably too small and of too short a duration to estimate the incidence of VTE associated with NGM/EE 0.25/0.035 mg. Nevertheless, thromboembolism of any type is an AE of special interest in the study, and any occurrence will be thoroughly investigated and reported.

Our study includes an evaluation of the effects of NGM/EE 0.25/0.035 mg on acne using the GAGS. It is expected that acne will improve during the use of monophasic NGM/EE 0.25/0.035 mg since the exacerbation of acne is usually related to the androgenic potency of the COC [27].

Comparison to Prior Work

The previous large-scale study conducted in Germany among 59,701 women evaluated 342,348 menstrual cycles and showed a reduction in breakthrough bleeding from 4.5% at baseline to 3% during cycle 6 of the COC and in intermenstrual spotting from 9% to 4% during cycle 6 [16]. In the Italian study by Affinito et al [18], in which 92 women received monophasic NGM/EE, the incidence of breakthrough bleeding decreased from 3.3% to 0% at cycle 6, and the rate of spotting from 14.3% to 3.7%. Our study will include at least twice the number of women as in the earlier Italian study and therefore a more robust assessment of the effects of NGM/EE on these menstrual characteristics.

The large German study highlighted the extremely high contraceptive efficacy of NGM/EE, showing a use-efficacy Pearl index of 0.25 (95% CI 0.19-0.31) pregnancies per 100 woman-years [17], and no pregnancies were reported in the earlier Italian study [18]. There was a low incidence of AEs and a high rate of compliance in both these analyses [17,18]. Our study will provide updated information on the contraceptive efficacy, adherence rate, and safety or tolerability profile of NGM/EE 0.25/0.035 mg. The substudy is investigating the effect of NGM/EE 0.25/0.035 mg on lipid and metabolic parameters, expected to be negligible based on previous research [17,18].

Strengths and Limitations

A key difference between our study and the earlier ones is the incorporation of PROs to gather subjective information about the impact of monophasic NGM/EE on the women who take it, specifically the impact on sexuality, mood, and menstrual pain. The inclusion of PROs in our study predated, but is nevertheless consistent with, international consensus recommendations on

research into contraceptive-induced menstrual changes, which recommend investigating the physical and psychosocial impact of these changes on the lives of the women who take them, including their sexual well-being and anxiety or stress [19].

Sexual side effects are a leading reason for women to discontinue or switch contraceptives [28], so it is important to ask women about the effect of COCs on their sexual function. The reported impact of COCs on sexual function is highly variable and encompasses negative, positive, and no effects [29,30]. Female sexuality is complex, and the association between hormone levels and sexuality is nonlinear and multidimensional since a number of different hormones regulate sexual response [29]. Data suggest that the androgenicity of the progestin and the dosage of EE in COCs have a negligible impact on sexual function [31]. Based on the available literature, we do not anticipate a significant effect of NGM/EE 0.25/0.035 mg on sexual function, but to our knowledge, this is one of the first studies to investigate the effects of this COC on sexuality using a validated instrument, the FSFI.

We are also investigating any changes in mood after 6 cycles of NGM/EE 0.25/0.035 mg using the POMS. This instrument has been used previously to investigate changes in mood during oral contraceptive use [32,33], but to our knowledge, this is the first study to use POMS to evaluate mood in women taking NGM-containing COCs.

Finally, our study includes an assessment of the severity of pain associated with menstruation in accordance with international consensus recommendations [19]. Previous studies have evaluated the incidence of pain in women taking monophasic NGM/EE but not the severity of pain [17,18]. This is an important distinction because pain is a continuum rather than a binary outcome. Data indicate that at least 90% of women experience some kind of discomfort during menstruation [34], although their experiences vary across time [35]. Dysmenorrhea is often underreported for many reasons, including that symptoms are considered normal or that women find the symptoms tolerable [36]. Therefore, pain was likely underreported in clinical trials because participants may only report pain that is new, worse, or acute [34]. Using a tool like VAS will provide nuanced information about both the incidence and severity of menstrual pain in women taking NGM/EE 0.25/0.035 mg. Limitations of our study are the absence of a control group and the relatively short duration of follow-up.

Conclusions

This study into the effects of monophasic NGM/EE 0.25/0.035 mg on menstrual characteristics in healthy Italian women will provide up-to-date data on these effects, since there has been no similar study for more than 30 years, and includes the assessment of NGM/EE 0.25/0.035 mg on PROs, in line with recent international consensus recommendations.

Acknowledgments

The authors would like to thank Catherine Rees who developed the first draft of this manuscript. This medical writing assistance was funded by Italfarmaco SpA. This study, development of the manuscript, and open-access publishing fee were supported by Italfarmaco SpA.

Conflicts of Interest

GG received honoraria for sponsored lectures and participation in advisory boards from Bayer AG, Teva/Theramex, Exeltis, Italfarmaco, Opocrin, Organon, and Gedeon Richter outside of the scope of this manuscript. AC, GC, AMF, GM, and VB declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper. EP and MM are employees of Italfarmaco SpA. EC is a medical consultant for Italfarmaco SpA.

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Abbreviations

AE: adverse event
COC: combined oral contraceptive
EE: ethinyl estradiol
FSFI: Female Sexual Function Index
GAGS: Global Acne Grading Scale
NGM: norgestimate
POMS: Profile of Mood State
PRO: patient-reported outcome
SAE: serious adverse event
VAS: visual analog scale
VTE: venous thromboembolism

Edited by A Schwartz; submitted 26.06.24; peer-reviewed by ES Ferreira-Filho; comments to author 31.10.24; revised version received 12.11.24; accepted 20.01.25; published 31.03.25.

Please cite as:
Cagnacci A, Grandi G, Capobianco G, Fulghesu AM, Morgante G, Biondelli V, Piccolo E, Casolati E, Mangrella M
Effects of a Monophasic Hormonal Contraceptive With Norgestimate+Ethinyl Estradiol on Menstrual Bleeding: Protocol and Design of a Multicenter, Prospective, Open-Label, Noncomparative Study in Italy
JMIR Res Protoc 2025;14:e63683
URL: https://www.researchprotocols.org/2025/1/e63683
doi:10.2196/63683
PMID:

Protocol

Assessing Pulmonary Function in Children and Adolescents After Cancer Treatment: Protocol for a Multicenter Cohort Study (Swiss Childhood Cancer Survivor Study FollowUp–Pulmo)

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Abstract

Background: Childhood cancer survivors (CCS) are at risk of pulmonary dysfunction due to cancer treatments, but evidence on prevalence and risk factors remains limited. Most previous studies had small sample sizes or retrospective study designs, little information about treatments, or a lack of standardization of pulmonary function tests (PFTs) or limited their investigation to certain PFTs. Since spirometry mainly assesses the large airways but cancer therapy also affects peripheral airways, additional functional tests are needed. The nitrogen multiple breath washout test (N_2MBW) is sensitive to peripheral airway damage in other patient populations, but its benefit in CCS is unknown. Therefore, comprehensive and standardized evaluation of pulmonary function after cancer treatment in childhood, using different PFTs that include N_2MBW, is needed to address these knowledge gaps and provide insights into possible early stages of pulmonary dysfunction.

Objective: In the Swiss Childhood Cancer Survivor Study (SCCSS) FollowUp–Pulmo, we will comprehensively assess lung function in children and adolescents after treatment for cancer to identify risk factors for pulmonary dysfunction, assess the ability of N_2MBW to detect pulmonary dysfunction compared to other PFTs, and investigate the association of functional outcomes from PFTs with self-reported respiratory symptoms.

Methods: SCCSS FollowUp–Pulmo is a prospective multicenter longitudinal cohort study embedded in routine clinical care that enrolls CCS aged 6-20 years for whom at least 1 year has passed since a childhood cancer diagnosis, who have completed

treatment, and who attend regular pediatric oncological follow-up care. Inclusion criteria comprise any of the following: systemic anticancer treatment (chemotherapy, immunotherapy, or targeted agents), thoracic surgery, thoracic radiotherapy, or hematopoietic stem cell transplantation (HSCT). CCS undergo a standardized pulmonary assessment, including spirometry, body plethysmography, diffusing capacity of the lung for carbon monoxide (DLCO), and N_2MBW, and complete a questionnaire on respiratory symptoms and lifestyle. Data from previous and subsequent routine care PFTs will be included in this study.

Results: Recruitment started in June 2022 at the University Children's Hospital Bern, Switzerland. Subsequently, patient recruitment expanded to the University Children's Hospitals in Basel and Geneva, Switzerland. By October 2024, we had invited 220 patients, of which 201 have already participated in this study, resulting in a response rate of 91%. Their median age at the time of the study was 14 years (IQR 10-17), and the median time since diagnosis was 7 years (IQR 4-10). The study will continuously enroll new CCS.

Conclusions: This study will contribute to a comprehensive understanding of pulmonary function in CCS and assess related risk factors, as well as the utility of N_2MBW compared to other PFTs. The results will assist in the development of more targeted screening and risk-stratified follow-up care.

Trial Registration: ClinicalTrials.gov NCT04732273; https://clinicaltrials.gov/study/NCT04732273

International Registered Report Identifier (IRRID): DERR1-10.2196/69743

(JMIR Res Protoc 2025;14:e69743) doi:10.2196/69743

KEYWORDS

childhood cancer survivors; respiratory function tests; late effects; pulmonary toxicity; multiple breath washout test; cohort study

Introduction

Survival Rates and Long-Term Complications

Advances in childhood cancer treatment and supportive care have resulted in survival rates that now exceed 80% in high-income countries [1]. Yet, even as cancer treatments are curative in targeting cancer cells, they can harm healthy tissue and potentially cause late complications, such as second neoplasms and chronic diseases [2,3]. The cumulative incidence of such late effects among childhood cancer survivors (CCS) thus predisposes them to increased morbidity and premature mortality [4]. Among late effects, pulmonary complications are the third-leading cause of excess mortality after second neoplasms and cardiovascular diseases [5].

Pulmotoxic Treatments

Several cancer treatment modalities can be pulmotoxic. These include the chemotherapeutic agents busulfan, bleomycin, carmustine, and lomustine; thoracic radiotherapy; thoracic surgery; and hematopoietic stem cell transplantation (HSCT) [6,7]. The underlying mechanisms of pulmonary toxicity involve alveolar, vascular, and parenchymal damage resulting from chemotherapy and radiotherapy, which may progress to lung fibrosis [6-8]. HSCT-related lung damage can result from intensive conditioning regimens, infections, or graft-versus-host disease (GvHD), while surgery of the chest or lungs may reduce lung volumes and impair chest wall compliance [7,9]. However, recently published recommendations for surveillance of pulmonary function among CCS from the International Late Effects of Childhood Cancer Guideline Harmonization Group (IGHG) could not consistently confirm the pulmonary toxicity of all these treatments, particularly certain chemotherapeutics, due to limited and low-quality evidence [10]. Other chemotherapeutics, such as methotrexate and cyclophosphamide, have also been suspected of causing lung damage [8,11], but findings across studies remain inconsistent [12,13]. Considering that these treatments may harm developing lungs and potentially lead to progressive pulmonary damage [14], it is important to study their effects on lung function.

Prevalence and Detection of Pulmonary Dysfunction

Pulmonary dysfunction in CCS exposed to pulmotoxic treatments has been reported in varying proportions of CCS (44%-77%), depending on study populations and criteria used to define obstructive, restrictive, and diffusion impairments [12,13,15,16]. The lung has a large functional reserve, and early disease may often remain asymptomatic, particularly when it affects the lung periphery [17]. Most studies have used conventional pulmonary function tests (PFTs), such as spirometry, body plethysmography, and diffusing capacity of the lung for carbon monoxide (DLCO), to assess lung function in CCS. However, spirometry and body plethysmography lack the sensitivity to detect changes in small airways [18], which may be damaged first [6]. The nitrogen multiple breath washout test (N_2MBW), which measures ventilation inhomogeneity of the ventilated lung, detecting small airway disease, has been increasingly used in other patient populations, including those treated with allogeneic HSCT [19-21]. In a small prospective study of adult CCS, N_2MBW identified more cases of pulmonary dysfunction than spirometry, even among those who had not been exposed to previously defined pulmotoxic treatments [22]. Though larger prospective studies with standardized assessments are still needed, these findings suggest that N_2MBW could be a valuable complementary test in screening CCS for early pulmonary damage.

Current Knowledge Gaps

The recently published IGHG recommendations not only summarized existing evidence but also highlighted large knowledge gaps and methodological weaknesses in previous research [10]. These gaps emphasize the need for prospective, longitudinal studies with larger sample sizes and a broader range of treatment exposures to characterize the onset and progression

of treatment-related pulmonary dysfunction. The long-term effects of newer chemotherapeutic and immunotherapeutic agents on lung function are understudied [23]. Evidence on how treatment-related complications, comorbidities, and genetic variants influence lung damage risk is limited as well. Similarly, standardization is lacking in PFTs and in the use of appropriate age- and sex-specific reference values. For example, results should be reported as z-scores rather than just proportions of patients with reduced lung function. Additionally, few studies have assessed diagnostic tests specific to the location and type of potential dysfunction, such as N_2MBW for peripheral inhomogeneity in ventilation. More data are also needed on the association between PFT outcomes and clinical symptoms. To address these gaps, we designed the Swiss Childhood Cancer Survivor Study (SCCSS) FollowUp–Pulmo.

Study Objectives

The primary objective of SCCSS FollowUp–Pulmo is to longitudinally investigate lung function in children and adolescents after cancer treatment using a comprehensive set of PFTs that also assess small-airway disease. Second, the study will investigate possible effects of treatment-related risk factors (systemic anticancer agents, thoracic radiotherapy, thoracic surgery, and HSCT), treatment-related complications (pulmonary infections, GvHD), and existing comorbidities (eg, pulmonary or cardiac disease) on lung function. Third, the study will examine the ability of N_2MBW to detect pulmonary dysfunction in comparison with other PFTs. Fourth, it will investigate the association between lung function and self-reported respiratory symptoms.

Methods

Study Design and Inclusion Criteria

SCCSS FollowUp–Pulmo is a multicenter prospective longitudinal cohort study integrated into the routine clinical care of several children's hospitals in Switzerland. The study is an interdisciplinary collaboration between the pediatric hematology/oncology and pediatric pulmonology departments of respective centers, the Institute of Social and Preventive Medicine (ISPM) at the University of Bern, and the Swiss Childhood Cancer Registry (ChCR). The ChCR is a nationwide, population-based cancer registry that includes Swiss residents diagnosed up to the age of 20 years with leukemia, lymphoma, central nervous system (CNS) tumors, malignant solid tumors, or Langerhans cell histiocytosis, classified according to the *International Classification of Childhood Cancer, Third Edition* (ICCC-3) [24]. Although the ChCR captures over 95% of children diagnosed in Switzerland [25], SCCSS FollowUp–Pulmo will also include a few patients treated and followed up in Swiss clinics who may not be registered in the ChCR due either to registration delays or residency outside of Switzerland.

All CCS aged 6-20 years for whom 1 year or more has elapsed since cancer diagnosis, who have completed treatment, and who are in regular pediatric hemato-oncological follow-up care are eligible for SCCSS FollowUp–Pulmo. The following treatment modalities possibly affecting lung function are included in SCCSS FollowUp–Pulmo: any systemic anticancer treatment (chemotherapy, immunotherapy, or targeted therapy) [26]; thoracic surgery involving the chest or lungs (excluding central line placement) [27]; radiation of the lungs, the chest (axilla, mantle, mediastinal), or scattered radiation from other radiation fields, including the whole abdomen or any upper abdominal field, spinal doses of 30 Gray or higher, and total body irradiation [27]; and HSCT [28]. Excluded are CCS who were treated only with surgery or radiation outside the thorax due to their low risk for pulmonary dysfunction [29] and patients with relapse or in palliative care at the time of recruitment.

Ethical Considerations

Ethical approval was granted by the Ethics Committee of the Canton of Bern, Switzerland (KEK-BE: 2019-00739), and the study is registered on ClinicalTrials.gov (NCT04732273). All participants provide a signed informed consent form. If any patient declines to participate, their data are not collected. Data are entered into the Research Electronic Data Capture (REDCap) database version 14.0.10 (Vanderbilt University), which complies with legal requirements for data security and data protection.

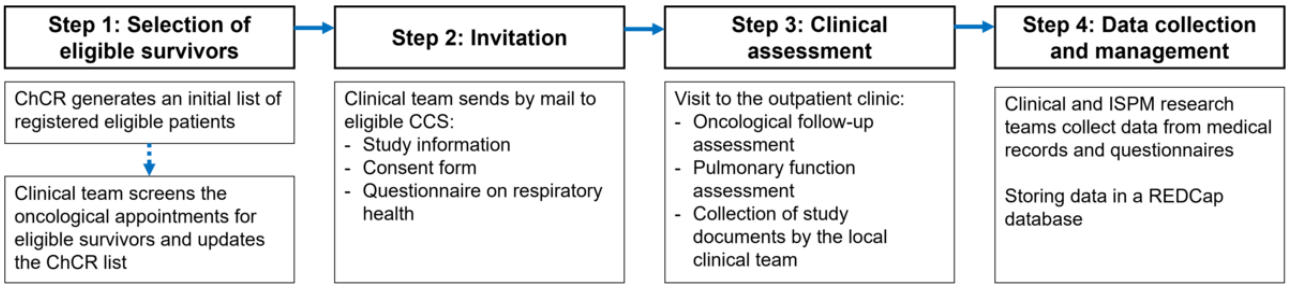
Study Procedures

The study is coordinated by the ISPM research team, which is responsible for overall study management, monitoring recruitment progress, and handling administrative and financial aspects. Clinical teams at each participating center include pediatric oncologists, pulmonologists, data managers, and study nurses.

Step 1: Selection of Eligible CCS

Eligible CCS are identified in 2 ways: (1) the ChCR provides an initial list of eligible patients to participating hospitals, and (2) a member of the clinical team regularly screens upcoming follow-up appointments, cross-referencing with the ChCR and identifying any additional eligible patients (Figure 1). This process ensures the inclusion of all eligible patients. The treating physician organizes pulmonary function assessments for the upcoming oncological follow-up appointment. Detailed recruitment procedures are developed at each center to consider clinical workflows.

Figure 1. Flowchart of SCCSS FollowUp–Pulmo procedures. CCS: childhood cancer survivors; ChCR: Swiss Childhood Cancer Registry; ISPM: Institute of Social and Preventive Medicine; REDCap: Research Electronic Data Capture.



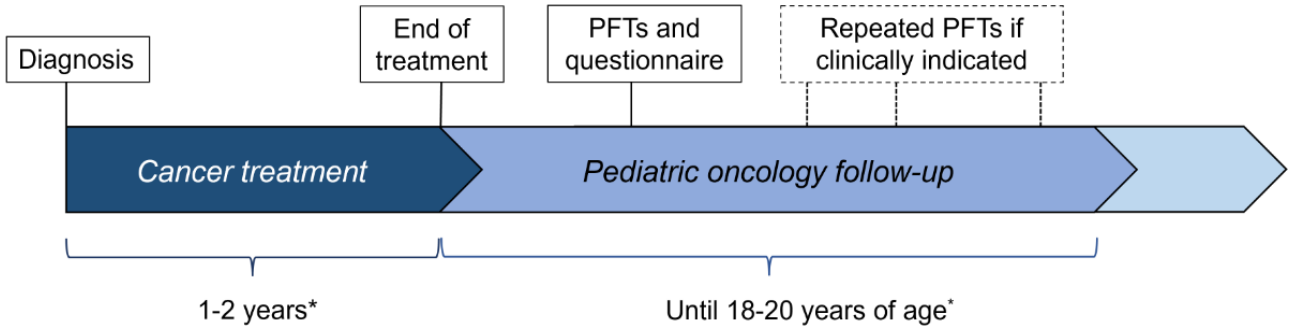
Step 2: Invitation

The clinical team sends the study information, consent form, and a questionnaire on respiratory health to eligible survivors prior to their next oncological follow-up appointment that will include PFTs. CCS who consent to participate send the documents back or bring them to the consultation.

Step 3: Clinical Assessment

At the oncological follow-up assessment, patients first meet their pediatric oncologist, who obtains a history, performs a physical examination, and refers them to pediatric pulmonology for PFTs. Since the PFTs are scheduled within the follow-up care, they are conducted irrespective of study consent. Patients with pathological results will undergo repeated PFTs, as clinically indicated (Figure 2). The clinical team collects the signed consent form and questionnaire. If patients do not complete the consent form and questionnaire prior to or during the clinical visit, they can still return the documents later. If a patient declines to participate, no data are collected for study purposes.

Figure 2. Timeline of pulmonary function assessments during SCCSS FollowUp–Pulmo. *The duration of cancer treatment varies based on the specific cancer diagnosis and the corresponding treatment protocol, while the age at which a patient transitions out of pediatric oncology follow-up may vary individually, depending on the cancer treatment protocol and the practices of the respective center. PFT: pulmonary function test; SCCSS: Swiss Childhood Cancer Survivor Study.



Step 4: Data Collection and Management

The clinical team at the respective study centers and the research team at the ISPM extract the data of each consenting participant from medical records, PFTs, and questionnaires. All data are stored in the REDCap database. In the database, each patient has a unique REDCap ID.

Exposures and Outcomes of Interest

Pulmonary Function Tests

CCS undergo a set of PFTs, including spirometry, body plethysmography, DLCO, and N_2MBW, according to the American Thoracic Society/European Respiratory Society (ATS/ERS) recommendations [30,31]. PFTs are conducted in pediatric lung function laboratories by trained technicians. Standard operating procedures for PFTs are harmonized among centers to ensure comparability, with quality control performed by lung function technicians. Because N_2MBW is not yet widely used in clinical settings, centralized quality control is additionally performed to ensure that only high-quality tests and the latest algorithms are included. Specialized software developed by experts at the University Hospital in Bern detects evidence of leaks, insufficient waiting time between tests, early termination of tests, synchronization issues, and abnormal breathing patterns or volumes in accordance with consensus guidelines [32,33]. Experienced pulmonologists interpret and review the results of PFTs.

Since asthma and allergic conditions are common differential diagnoses in young patients, including CCS, most clinics also measure fractional exhaled nitric oxide (FeNO) in those with obstructive patterns on spirometry or asthma-like symptoms [34]. High FeNO levels suggest an asthmatic or allergic etiology, while low levels may indicate noninflammatory causes related to cancer treatment effects.

Table 1 shows the main outcome measures from PFTs, their interpretation, anatomical correlates, and studies for reference values used for respective PFTs. SCCSS FollowUp–Pulmo also collects all prestudy PFT data from patients who previously underwent these assessments and subsequent PFTs conducted as part of ongoing clinical care.

Table 1. PFTs[a] performed in CCS[b], their interpretation, and anatomical correlates.

Test	Main outcomes	Meaning of abnormal results	Anatomical correlates	Reference values
Spirometry	FVC[c], FEV_1[d], FEV_1/FVC, $FEF_{25\%-75\%}$[e]	Airway obstruction, reduced dynamic lung volume	Fibrotic destruction of lung tissue and large airways, reduced lung compliance	Quanjer et al [35]
Body plethysmography	FRC[f], SR_{eff}[g], SR_{tot}[h], RV[i], TLC[j], VC[k]	Reduced static lung volume, hyperinflation	Fibrotic destruction of lung tissue and large airways, reduced lung compliance	Hall et al [36]
DLCO[l]	DLCO	Reduced alveolar-capillary gas transfer, reflected by diffusion deficits	Alveolar-capillary membrane damage	Stanojevic et al [37,38]
N_2MBW[m]	LCI[n], S_{ACIN}[o], S_{COND}[p]	Increased ventilation inhomogeneity of airways with reduced global, alveolar, and conducting ventilation	Fibrotic damage of small airways	Ramsey et al [39]
FeNO[q]	FeNO	Eosinophilic airway inflammation as a key component of allergic asthma	Allergic inflammation as an alternative cause of pulmonary obstruction	Jacinto et al [34]

[a]PFT: pulmonary function test.

[b]CCS: childhood cancer survivors.

[c]FVC, forced vital capacity.

[d]FEV_1, forced expiratory volume in 1 second.

[e]$FEF_{25\%-75\%}$, forced expiratory flow at 25%-75% of the FVC.

[f]FRC, functional residual capacity.

[g]SR_{eff}: specific effective resistance.

[h]SR_{tot}: specific total resistance.

[i]RV: residual volume.

[j]TLC: total lung capacity.

[k]VC: vital capacity.

[l]DLCO: diffusion capacity of the lung for carbon monoxide.

[m]N_2MBW: nitrogen multiple breath washout test.

[n]LCI: lung clearance index.

[o]S_{COND}: conductive ventilation inhomogeneity index.

[p]S_{ACIN}: acinar ventilation inhomogeneity index.

[q]FeNO: fractional exhaled nitric oxide (measured in CCS with symptoms suggestive of asthma, eg, wheeze, dyspnea, cough, or signs of obstruction in spirometry).

Medical and Questionnaire Data

Information obtained from medical records includes anthropometric measures, respiratory disease history, physical evaluation, PFTs, cancer diagnosis and treatment, and additional data from the medical history, including comorbidities and significant treatment-related complications (GvHD, pulmonary infections) (Table 2). CCS complete a detailed questionnaire on respiratory health that includes sections on respiratory symptoms, infectious diseases, exercise-induced problems, allergic and pulmonary diseases, family history of respiratory conditions, lifestyle and environmental factors, and sociodemographic information.

Table 2. Description of medical and questionnaire data collected as part of SCCSS[a] FollowUp–Pulmo.

Data source and data items	Description
Medical records	
Personal information and anthropometric measures	• Date of birth • Sex • Height • Weight • BMI
Respiratory history and physical evaluation	• Recent history of airway infections • Lung auscultation • Thoracic inspection • Signs of dyspnea • Oxygen saturation
PFTs[b,c]	• Spirometry • Body plethysmography • DLCO[d] • N_2MBW[e] • FeNO[f]
Cancer diagnosis	• Date of diagnosis • Type of cancer and location • Metastases • Relapse • Second malignant neoplasm
Cancer treatment	• Treatment protocol and arm • Start and end dates • Cumulative doses of all individual chemotherapy drugs, targeted agents, and immunotherapies • Radiotherapy (cumulative dose, location, duration) • Surgery (location, type) • HSCT[g] (autologous or allogeneic, donor type and source, conditioning regimens, complications)
Additional data from medical history	• GvHD[h] (acute or chronic, affected organs, grade, treatment) • Significant pulmonary infections during or after cancer treatment (diagnosis, causing pathogen, duration of hospitalization) • Comorbidities
Questionnaire	
Respiratory symptoms	• Cough (type, duration, with or without a cold) • Wheeze (frequency, duration, triggers) • Dyspnea(frequency, duration, triggers)
Infectious diseases[i]	• Otitis • Sinusitis • Pneumonia
Exercise-induced problems	• Frequency • Types • Triggering situations
Allergic diseases	• Allergic rhinitis • Hay fever • Atopic dermatitis
Pulmonary diseases[j]	• Asthma • Bronchitis • Lung fibrosis • Emphysema

Data source and data items	Description
Lifestyle and environment	• Physical activity (compulsory school sport, recreational sport) • Active and passive smoking (amount and type of tobacco products)
Sociodemographic data and family history	• Citizenship • Parental education and profession • Family history of asthma, chronic bronchitis, hay fever, and atopic dermatitis

[a]SCCSS: Swiss Childhood Cancer Survivor Study.

[b]PFT: pulmonary function test.

[c]For each pulmonary function test, the date, test quality, and multiple outcomes (as listed in Table 1) are recorded.

[d]DLCO: diffusing capacity of the lungs for carbon monoxide.

[e]N_2MBW: nitrogen multiple breath washout test.

[f]FeNO: fractional exhaled nitric oxide.

[g]HSCT: hematopoietic stem cell transplantation.

[h]GvHD: graft-versus-host disease.

[i]Data includes the recurrence and treatment of each disease.

[j]Data includes the treatment of each disease.

Sample Size Calculation

To determine the sample size needed for our study, we based calculations on the study by Schindera et al [22], who assessed lung function in long-term CCS using spirometry and N_2MBW. This single-center study was conducted on Swiss CCS and applied the same inclusion criteria for treatment exposures, making it a suitable reference. The main outcome from N_2MBW was the lung clearance index (LCI). The mean LCI z-score was 1.37 (SD 2.69). We calculated the number of participants necessary to achieve a statistical significance level of 0.05 and a power of 0.80, while accounting for a 15% dropout rate. This calculation indicated that a minimum of 146 participants would be required to detect a similar deviation in LCI with sufficient statistical power. We plan to include a larger sample size to increase precision, improve our ability to detect smaller deviations, and ensure adequate power to analyze other lung function outcomes and investigate specific subgroups of patients defined by tumor type and treatments received.

Statistical Analysis

To compare PFT outcomes with normal values, we will calculate z-scores and percent-predicted values using external Global Lung Initiative (GLI) reference data [35-37,39]. We will define pulmonary dysfunction as z-scores below –1.64 or above +1.64 for respective PFT indices since these thresholds represent deviations from the reference population mean and indicate abnormalities in pulmonary function. To characterize pulmonary function among CCS, we will analyze z-scores for predefined outcomes and assess differences based on characteristics such as treatment exposure, age at treatment, and time since cancer diagnosis. We will assess group differences using appropriate statistical tests based on the type of variable, such as the *t*-test or the Mann-Whitney test for continuous variables and the χ^2 test or the Fisher exact test for categorical variables. For analyses of associations between outcomes and covariates, we will apply regression models adjusted for potential confounders. For longitudinal data, we will use mixed effects models to account for repeated measures over time. We will use Stata (Stata Corp LLC) and R (Foundation for Statistical Computing) for statistical analyses.

Results

Recruitment started in June 2022 at the University Children's Hospital in Bern, in March 2023 at the University Children's Hospital in Basel, and in March 2024 at the University Children's Hospital in Geneva. The number of new participants per month varies across the centers, depends on clinical capacity, and is steadily growing (Figure 3). As of October 2024, a total of 220 patients had been invited to participate in the study. Of those, 201 patients consented to and underwent PFTs, resulting in a response rate of 91%. Bern registered 125 (62%) participants, Basel 70 (35%), and Geneva 6 (3%). The time required to perform all PFTs and complete the questionnaire was 45-60 minutes per participant.

More than half of the 201 participants (n=119, 59%) were male, the median age at the time of the study was 14 years (IQR 10-17), and the median time since diagnosis was 7 years (IQR 4-10), as shown in Tables 3 and 4. The most common diagnoses were leukemia (n=105, 52%), lymphoma (n=22, 11%), and neuroblastoma (n=18, 9%). All but 2 (1%) participants had been treated with chemotherapy, 25 (13%) had received thoracic radiotherapy, and 15 (8%) had undergone thoracic surgery. In total, 20 (10%) participants had undergone HSCT, with 11 (6%) having been treated with autologous and 9 (4%) with allogeneic HSCT.

Figure 3. Number of participants in SCCSS FollowUp–Pulmo since the start of the study. SCCSS: Swiss Childhood Cancer Survivor Study.

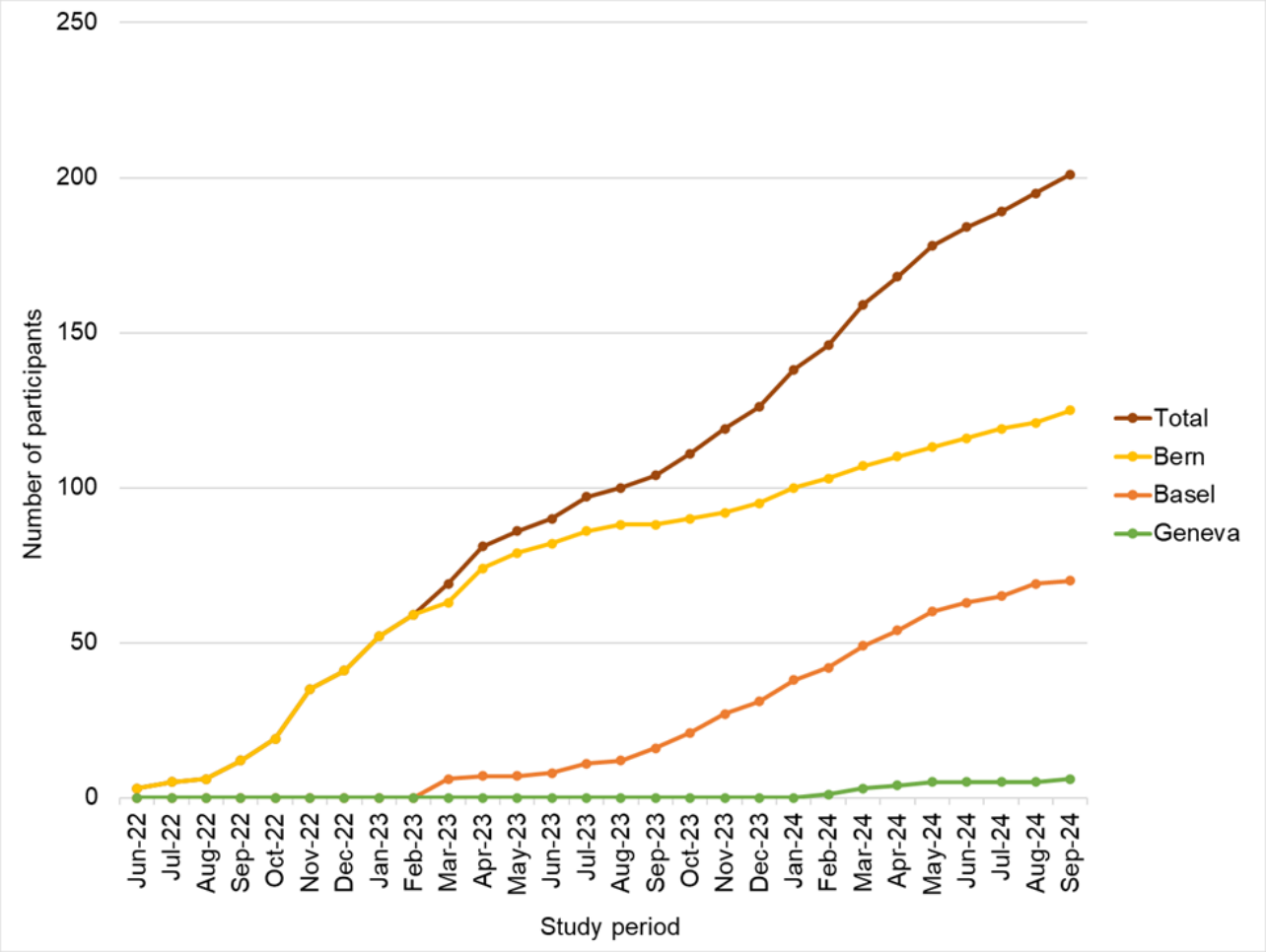


Table 3. Demographic characteristics of CCS[a] participating in SCCSS[b] FollowUp–Pulmo up to October 2024.

Characteristics	Participants (N=201)
Sex, n (%)	
Male	119 (59)
Female	82 (41)
Age at the time of study (years), median (IQR)	14 (10-17)
Age group (years), n (%)	
6-10	47 (23)
11-14	73 (36)
15-18	66 (33)
≥19	15 (8)

[a]CCS: childhood cancer survivors.

[b]SCCSS: Swiss Childhood Cancer Survivor Study.

Table 4. Clinical characteristics of CCS[a] participating in SCCSS[b] FollowUp–Pulmo up to October 2024.

Characteristics	Participants (N=201)
Age at diagnosis (years), median (IQR); range	5 (3-9); 0.1-17
Time since diagnosis (years), median (IQR); range	7 (4-10); 1-17
Time since diagnosis (years), n (%)	
<5	68 (34)
5-10	83 (41)
11-15	41 (20)
>15	9 (5)
Diagnosis (ICCC-3[c]), n (%)	
Leukemia	105 (52)
Lymphoma	22 (11)
CNS[d] tumor	11 (6)
Neuroblastoma	18 (9)
Retinoblastoma	0
Renal tumor	15 (8)
Hepatic tumor	2 (1)
Bone tumor	6 (3)
Soft tissue sarcoma	14 (7)
Germ cell tumor	2 (1)
Other tumor[e]	2 (1)
Langerhans cell histiocytosis	4 (2)
Chemotherapy[f] (n=199, 99%), n (%)	
Pulmotoxic chemotherapy	16 (8)
Other treatments, n (%)	
Thoracic radiotherapy[g]	25 (13)
Thoracic surgery[h]	15 (8)
HSCT[i] (n=20, 10%), n (%)	
Autologous	11 (6)
Allogeneic	9 (5)
Relapse, n (%)	15 (8)

[a]CCS: childhood cancer survivors.

[b]SCCSS: Swiss Childhood Cancer Survivor Study.

[c]*ICCC-3*: *International Classification of Childhood Cancer, Third Edition*.

[d]CNS: central nervous system.

[e]Other malignant epithelial neoplasms, malignant melanomas, and other/unspecified malignant neoplasms.

[f]Any chemotherapy alone or combined with other treatments.

[g]Radiotherapy involving chest, abdomen, spine, or total body irradiation alone or combined with other treatments.

[h]Surgery involving the thorax or lungs alone or combined with other treatments.

[i]HSCT: hematopoietic stem cell transplantation alone or combined with other treatments.

Discussion

Summary

This prospective, multicenter cohort study of lung function in children and adolescents after cancer treatment investigates risk factors, compares the detection of pulmonary dysfunction using N_2MBW and conventional PFTs, and examines the association of functional outcomes from PFTs with respiratory symptoms.

Comparison With Previous Research

Previous studies of pulmonary dysfunction after treatment for childhood cancer have mostly been retrospective, based on chart reviews [14,40-42]. This has entailed methodological weaknesses, particularly a risk of selection bias because CCS for whom PFT results were obtained might overrepresent symptomatic CCS or those treated more intensively. We identified several prospective studies on pediatric CCS, but like the retrospective ones, they mostly recruited specific groups of patients treated with previously defined pulmotoxic treatments, such as HSCT [42-44] or thoracic radiation [14,45], or specific tumor types like leukemia [46] or lymphoma [47,48]. Data on the pulmotoxic effects of individual agents, such as busulfan [49], melphalan [50], cyclophosphamide [46,50], and methotrexate [51], remain limited. By including CCS exposed to systemic therapies, including any chemotherapy, targeted agents, or immunotherapy, our study will provide a better understanding of treatment-related pulmonary dysfunction in a broadly representative population of CCS. Continuous recruitment will allow us to collect data on the pulmonary effects of newer treatments used in contemporary protocols, whose impacts remain largely unknown [52]. Detailed information from medical records will allow the investigation of effects of comorbidities and treatment-related complications on PFT outcomes.

Previous studies have rarely included sensitive tests, such as N_2MBW, that can detect early changes in the lung periphery. Most have used spirometry, body plethysmography, and DLCO [12,14,15,49]. A study investigating 57 pediatric CCS with a median follow-up time of 6.2 years from end of treatment did not find differences in ventilation inhomogeneity measured using N_2MBW compared to healthy controls [53]. In contrast, several studies on patients after allogeneic HSCT have reported the LCI to be a sensitive measure for early pulmonary complications [20,21,54]. This study will obtain N_2MBW data for CCS exposed to a wide range of treatment modalities and investigate whether N_2MBW is more sensitive than other PFTs in detecting early pulmonary dysfunction.

Another drawback of many existing studies is that they report PFT data using binary cut-offs and describe results as either normal or abnormal [12,15,49]. This reduces statistical power and introduces interpretations based on predefined threshold values. Reporting PFT results as raw data and z-scores based on internationally agreed-upon, age-adjusted reference values will allow better comparison and pooling across studies. Limited data exist on how lung function correlates with clinical symptoms [10]. Questionnaire data collected in this study will help investigate symptoms and other patient-reported outcomes, as well as their correlation with PFT results.

Collaboration With Other Ongoing Studies

The SWISS-Pearl Study (ClinicalTrials.gov ID: NCT05427136), currently conducted in multiple centers in Switzerland, investigates lung function in patients with pediatric cancer. The study includes spirometry, body plethysmography, N_2MBW, magnetic resonance imaging of the lungs, and questionnaires at different points during cancer treatment. We plan to combine that study with ours to create a comprehensive database, enabling us to analyze lung function trajectories in patients and survivors of pediatric cancer.

The GECCOS (Genetic Risks for Childhood Cancer Complications Switzerland) study is a nationwide cohort study collecting germline genetic data from patients and survivors of childhood cancer in Switzerland [55]. In consenting patients, we will link clinical and PFT data with the genetic data from GECCOS, allowing us to investigate the effects of genetic predisposition on pulmonary toxicity. This will assist the development of personalized treatment strategies and risk-adapted long-term care for survivors.

Study Limitations

A current limitation of this study is the limited number of participants and the heterogeneity of the study population, which can limit the statistical power for conducting subgroup analyses. For instance, exploring rare tumors or assessing specific effects of individual chemotherapeutic agents may at present be challenging. However, we plan to expand the study to more centers and pool data with international collaborations. Another limitation is the lack of systematic baseline PFT assessments before cancer treatment, making it difficult to distinguish treatment-related pulmonary dysfunction from preexisting conditions. Future studies should include pretreatment PFTs to better track changes in z-scores over time and improve the assessment of therapy-related effects. Finally, there is a small risk of selection bias because CCS with a longer time since the end of treatment, who do not experience respiratory symptoms or were not exposed to pulmotoxic treatments, may be less likely to participate in the study, potentially leading to underrepresentation of healthy CCS. Yet, because the study is embedded in regular follow-up care and supported by oncologists, with initial results showing a high participation rate, exceeding 90%, this bias should be minimal.

Conclusion

This multicenter cohort study prospectively investigates pulmonary dysfunction in young CCS. By assessing lung function as an intermediate outcome, rather than established disease or mortality, this study will provide a resource for evaluating pulmonary dysfunction at an earlier stage in the disease trajectory, particularly within the early years posttreatment. The initial response shows that integrating standardized pulmonary evaluations into routine follow-up care in Switzerland is feasible and widely accepted by both survivors and health care providers. The findings of this study will provide new insights to inform the development of guidelines and recommendations for pulmonary follow-up care.

Acknowledgments

We would like to acknowledge all childhood cancer survivors for their participation in the study. We thank the clinical teams from participating centers and the quality control team at the University Hospital in Bern. We thank the study team of the Childhood Cancer Research Group, Institute of Social and Preventive Medicine, University of Bern, and the team of the Swiss Childhood Cancer Registry. We also appreciate the editorial assistance provided by Christopher Ritter.

This work was supported by the Swiss Cancer Research and Swiss Cancer League (grant nos: KFS-5027-02-2020, KFS-5302-02-2021, KLS/KFS-4825-01-2019), Childhood Cancer Switzerland, Kinderkrebshilfe Schweiz, Stiftung für krebskranke Kinder-Regio Basiliensis, the CANSEARCH Foundation, and the Association Jurassienne d'Aide aux Familles d'Enfants atteints de Cancer (AJAFEC).

Data Availability

Researchers interested in collaborative work can contact the corresponding author (CK) to discuss planned projects.

Authors' Contributions

All authors contributed to the study's conception and design. MŽ, CS, GS, and CK wrote the initial draft of the manuscript, and all authors provided feedback on earlier versions. All authors have read and approved the final manuscript.

Conflicts of Interest

PL reports relationships with Vertex, OM Pharma, Vifor, Polyphor, Santhera, Allecra, and Sanofi Aventis. These include grants, consulting fees, payments for lectures, advisory board memberships, and travel reimbursement. None of these relationships are associated with this study.

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Abbreviations

CCS: childhood cancer survivors
ChCR: Swiss Childhood Cancer Registry
CNS: central nervous system
DLCO: dffusing capacity of the lung for carbon monoxide
FeNO: fractional exhaled nitric oxide
GECCOS: Genetic Risks for Childhood Cancer Complications Switzerland
GvHD: graft-versus-host disease
HSCT: hematopoietic stem cell transplantation
ICCC-3: International Classification of Childhood Cancer, Third Edition
IGHG: International Late Effects of Childhood Cancer Guideline Harmonization Group
ISPM: Institute of Social and Preventive Medicine
LCI: lung clearance index
N_2MBW: nitrogen multiple breath washout test
PFT: pulmonary function test
REDCap: Research Electronic Data Capture
SCCSS: Swiss Childhood Cancer Survivor Study

Edited by A Schwartz, S Basha; submitted 06.12.24; peer-reviewed by VF Edem, SL Coven; comments to author 08.02.25; revised version received 18.02.25; accepted 21.02.25; published 08.04.25.

Please cite as:
Žarković M, Schindera C, Sommer G, Schneider C, Usemann J, Otth M, Lüer S, Ansari M, Latzin P, Kuehni CE
Assessing Pulmonary Function in Children and Adolescents After Cancer Treatment: Protocol for a Multicenter Cohort Study (Swiss Childhood Cancer Survivor Study FollowUp–Pulmo)
JMIR Res Protoc 2025;14:e69743
URL: https://www.researchprotocols.org/2025/1/e69743
doi:10.2196/69743
PMID:

Protocol

Real-World Effectiveness of COVID-19 Vaccines (ChAdOx-1s, CoronaVac, BBIBP-CorV, mRNA-1273, and BNT162b2) in Jakarta: Protocol for Test-Negative Design of Health Care Data

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Abstract

Background: ChAdOx-1s, CoronaVac, BBIBP-CorV, mRNA-1273, and BNT162b2 are the five common COVID-19 vaccines used in Jakarta. Randomized controlled trials have provided robust evidence of the safety and efficacy profile of these vaccines, but their real-world vaccine effectiveness against symptomatic COVID-19 and deaths in communities with social inequalities and health care constraints remains unclear.

Objective: This study aims to evaluate the real-world effectiveness of these COVID-19 vaccines during the waves associated with the Delta and Omicron variants by analyzing existing electronic health care sources.

Methods: A population-based study with a test-negative case-control design will be used to evaluate COVID-19 vaccine effectiveness in Jakarta, focusing on the Delta and Omicron waves. It includes adults 18 years and older who underwent reverse transcription polymerase chain reaction testing for symptomatic COVID-19, classifying them as cases or controls based on their test results. The analysis will consider multiple COVID-19 vaccines introduced during these periods, with participants categorized by vaccination status. Several potential confounders will be assessed, including demographic factors and comorbidities. Data will be linked from various health datasets, and statistical analyses will be performed to determine vaccine effectiveness and potential waning immunity over time. After data linkage, patients' identities will be encrypted.

Results: The research, funded from 2022 to 2024, involved proposal preparation and ethical review in 2023 and enrollment from early 2024 to July 2024, resulting in about 4 million linked data points. Data analysis is ongoing, with initial results expected for publication in early 2025.

Conclusions: This study will be the first to evaluate the effectiveness of different types of COVID-19 vaccines (inactivated, viral-vector, and mRNA) used in Jakarta during the pandemic, providing valuable scientific evidence to inform future vaccination strategies in the country.

International Registered Report Identifier (IRRID): DERR1-10.2196/56519

(JMIR Res Protoc 2025;14:e56519) doi:10.2196/56519

KEYWORDS

COVID-19; protocol; vaccine; vaccine effectiveness; Delta; Omicron

Introduction

Background

Since its emergence in December 2019, SARS-CoV-2, which is the virus that causes COVID-19, has been continuously spreading worldwide [1]. As of November 12, 2021, this pandemic has caused more than 250 million cases and more than 5 million deaths over the previous 2 years [2]. Vaccination programs are one of the most successful public health interventions that primarily aim to develop herd immunity and protection against pathogens. To date, the World Health Organization has approved 8 COVID-19 vaccines that are efficacious in preventing infection, reducing the level of severity and the number of deaths due to SARS-CoV-2 infection [3]. However, most data were generated from clinical trial studies that were different from a real-world setting due to their well-controlled nature [4]. Furthermore, real-world vaccine effectiveness (VE) studies were mostly conducted in high-income nations, and few studies came from low- and middle-income countries, even though these countries might have unique social and economic characteristics that not only affect vaccination acceptance but also disease outcomes [5]. A previous study has reported the association of living in an impoverished neighborhood with an increased risk for mortality even after COVID-19 vaccination [6]. Therefore, studies investigating how these COVID-19 vaccines might perform in real-world settings where social inequalities exist are still essential for informing policies and strategies to improve disease outcomes in future pandemics, especially in societies with health care system constraints [7]. This study aims to evaluate COVID-19 VE against symptomatic and fatal SARS-CoV-2 infection during the Delta and Omicron waves in Jakarta, where income inequality and socioeconomic segregation have become a common phenomenon [8].

Study Objectives

The primary objective is to study real-world VE against symptomatic COVID-19 (mild, moderate, and severe).

The following secondary objectives were also explored:

- Real-world VE against mortality 30 days after the first positive COVID-19 result
- Real-world VE based on vaccination status at the time of the reverse transcription polymerase chain reaction (RT-PCR) test
- Real-world VE based on the time since receipt of the last vaccine dosage

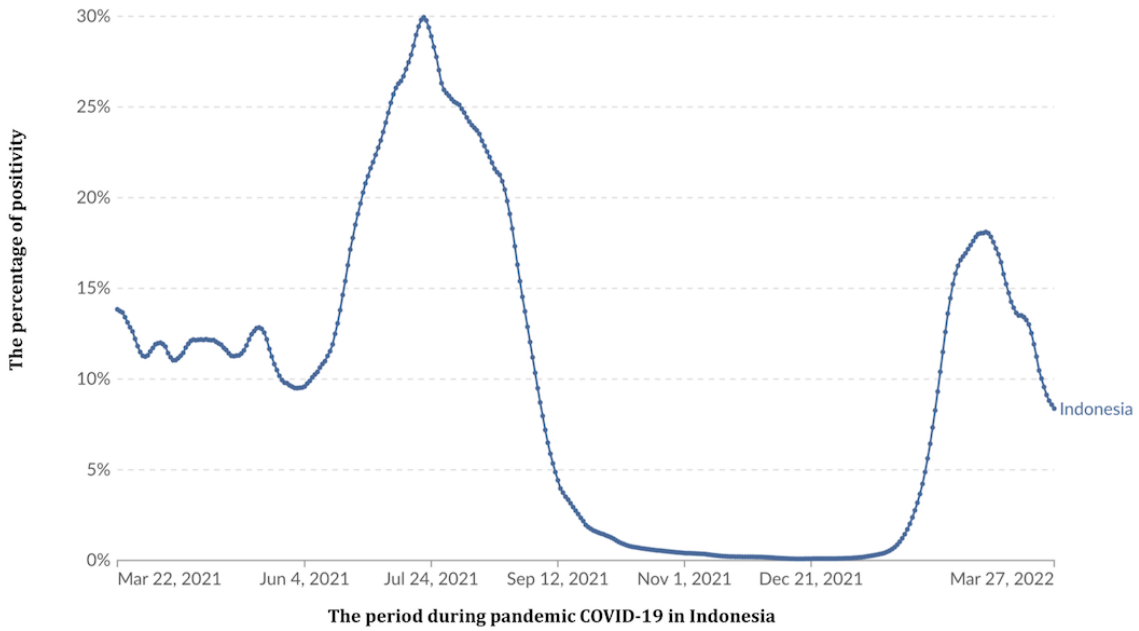
Methods

Study Design and Setting

This population-based study adopts a test-negative case-control design to analyze COVID-19 VE against symptomatic and fatal SARS-CoV-2 infection from available health care datasets in the Special Capital Region of Jakarta, one of the provinces with the highest population density (15,900 people per km^2 in 2020) and case rate per population relative to other regions in Indonesia [9]. Despite its robust development and economic growth, the contrast between rich and poor neighborhoods was highly prevalent in many parts of Jakarta's districts [8,10].

This study will estimate VE against COVID-19 during the period of interest, which were the COVID-19 waves associated with the Delta and Omicron variants, from June 1 to August 31, 2021, and January 1 to April 2, 2022, respectively. Within each of these periods, a cycle of sustained upward and downward trends of the test positivity rate was observed [11-15] (Figure 1). Furthermore, the Delta and Omicron variants were estimated to be responsible for around 90% of SARS-CoV-2 infections in Jakarta during these two periods [14,16].

Figure 1. Trend of the national COVID-19 positivity rate in Indonesia from 2021 to 2022. This modified image is cited from Our World in Data.



During the Delta and Omicron periods, several brands of COVID-19 vaccines were introduced in Jakarta for vaccine rollout, such as AstraZeneca, SinoVac-CoronaVac Biofarma, Covovax-Novovax, Indovax, Johnson & Johnson, Moderna, Sinopharm BBIBP, and Pfizer (Table S1 in Multimedia Appendix 1) [17]. Among these COVID-19 vaccines, Coronavac-Sinovac was the earliest COVID-19 vaccine to be introduced in January 2021 and used for mass vaccinations of doses 1 and 2, followed by AstraZeneca, Sinopharm, Pfizer, and Moderna in August 2021 [18,19]. Booster vaccinations 6 months after the 2-dose primary vaccination with Moderna and Pfizer vaccines were initially introduced to health care workers in July 2021, followed by the approval of the AstraZeneca vaccine as a booster in the national vaccination program in January 2022 [20,21]. To expedite the booster vaccination coverage, the timeline for booster administration was shortened to 3 months after the 2-dose primary vaccination, and additional inactivated COVID-19 vaccines, such as SinoVac and Sinopharm, were included in the national booster program [22]. Different from Pfizer, Moderna, and AstraZeneca, these inactivated COVID-19 vaccines were only approved as boosters for patients who received similar vaccine platform for their primary vaccination regimen [23]. Until the end of the Omicron period, all of the distributed COVID-19 vaccines in Jakarta were developed from the ancestral strain of SARS-CoV-2.

Study Participants

The study will include people 18 years or older who domiciled in Jakarta and underwent an RT-PCR test for SARS-CoV-2 infection due to symptoms of influenza-like illnesses within 10 days of the test date. Although people may have more than one RT-PCR result during the period of interest, this study will only account for the first positive or negative result per person as the index test date for each of the COVID-19 waves. People who had at least one sample with a positive SARS-CoV-2 RT-PCR result during the period of interest will be classified as cases, while people with a negative SARS-CoV-2 RT-PCR without any positive results over the period of interest will be classified as controls.

People with a positive RT-PCR test result within 90 days of the preceding index test date, with inconclusive RT-PCR results, who received different vaccines for dose 1 and dose 2 or a heterologous primary vaccine series, or who had a time interval between dose 1 and dose 2 that was less than the government recommendation (<21 days for Pfizer and Sinopharm, <28 days for CoronaVac and Moderna, and <12 weeks AstraZeneca) will be excluded from the analysis. We will also exclude people with incomplete vaccination records, such as people who declared receiving 2 vaccine doses without being able to verify the previous dose.

Study Variables

The primary outcome in this study is symptomatic SARS-CoV-2 infection, defined as a positive RT-PCR test within 10 days from the onset of influenza-like illness. The secondary outcome in this study is fatal SARS-CoV-2 infection, defined as death within 30 days after a positive RT-PCR test result [24]. Meanwhile, the primary exposure in this study was vaccination status, which can be classified as unvaccinated, dose 1 or partial vaccination, dose 2 or primary vaccination, and booster dose. People without any vaccination entries after data linkage with the PCARE Vaksin dataset at the end of each period of interest will be classified as unvaccinated persons. For vaccinated people, we will only consider the last vaccination data entry that happened before the patients' index RT-PCR test date.

Several covariates should be assessed as potential confounders in the study, such as age in years at the index test date, gender, calendar week of the RT-PCR collection during the period of interest, living in impoverished neighborhoods, presence of any

comorbidities, occupation, and reinfection status. The calendar week of the RT-PCR collection during the period of interest will be presented as a whole number starting from week 1 as the start of the period of interest. Living in an impoverished neighborhood will be presented as a dichotomous variable. People will be classified as living in an impoverished neighborhood if their neighborhood number at the subdistrict level is listed as one of the impoverished neighborhoods in the 2018 Jakarta Governor's regulation concerning improving the quality of settlements in residential areas. Occupation will be presented as categorical variables that consist of health care worker, public or government official, and civilian. Reinfection or people with previous SARS-CoV-2 infections will be presented as a dichotomous variable. People with a previous positive RT-PCR SARS-CoV-2 result that occurred more than 90 days after the current case will be classified as people with a previous SARS-CoV-2 infection [25].

To control for unmeasured confounders [26], such as societal preventive measures or the changing dynamic of the viral transmission within the community, this study will match each case with a control using a ratio of 1:2 by matching for age within 10 years of the case's age, gender, and the calendar week of the RT-PCR collection during the period of interest. The matching procedure will be assessed with standardized mean differences, with values less than 0.1 indicating sufficient matching [27,28].

Data Sources

This study will analyze the final datasets derived from the integration of several datasets provided by the Jakarta Provincial Health Office, Ministry of Health, and Social Security Agency on Health after April 2022 (Table 1). Variables such as ID number and date of birth will be used for the dataset linkage (Figure 2). From the New All Records (NAR) and Suspect and Probable (SUSPROB) datasets, symptomatic people with a positive or negative first RT-PCR test result within each of the periods of interest will be identified as cases or controls. Furthermore, people identified as cases will be linked to the entries in the REV POS dataset to extract the outcome of their disease course (Figure 2). People with incomplete data for ID number, date of birth, gender, swab collection date, PCR test result, domicile address, outcome, and date of death (if the case ends in death) will be excluded from further data linkage.

Table 1. List source for merged datasets.

Name	Developer	Description	Variable identified
NAR[a]	Ministry of Health Republic of Indonesia	Record of all RT-PCR[b] SARS-CoV-2 tests carried out by affiliated laboratories	• Name • ID number • Date of birth • Sex (male, female) • Comorbidity • Domicile address • Laboratory name • Reason for testing • Swab collection date • RT-PCR result confirmation date • RT-PCR testing result
SUSPROB[c]	Jakarta Provincial Health Office	Record and follow-ups of all people with influenza-like illness or probable COVID-19	• Name • ID number • Date of birth • Sex (male, female) • Comorbidity • Domicile address • Presence of influenza-like illness (fever, chill, cough, etc) • Date of symptom onset • Travel history • Plan swab testing date • Swab collection date • RT-PCR testing result
REV POS	Jakarta Provincial Health Office	Records and follow-ups on all positive cases in Jakarta	• Name • ID number • Date of birth • Sex (male, female) • Comorbidity • Domicile address • Date of swab collection • Case severity (asymptomatic, mild, moderate, severe) • Outcome (survived or death) • Date of death
PCARE[d] Vaksin	Social Security Agency on Health Indonesia (BPJS Kesehatan)	Record of all administered COVID-19 vaccines and their recipients	• Name • ID number • Date of birth • Sex (male, female) • Domicile address • Occupation or vaccination batch group (health workers, government officials, elderly, children, civilians) • Name of health care facility/vaccination center • Vaccination date • Vaccination ticket number • Vaccination dose • Vaccine name • Vaccine batch/lot number
Variant dataset	Jakarta Provincial Health Office	Sequencing and genotyping results of the randomly picked positive SARS-CoV-2 samples in the Jakarta area	• Sample registry number • Date of sample collection • Name of the sender laboratory • Date of the sample arrival at sequencing lab • Name of the sequencing lab • Date of the sequencing test • Date of result confirmation • Variant of SARS-CoV-2

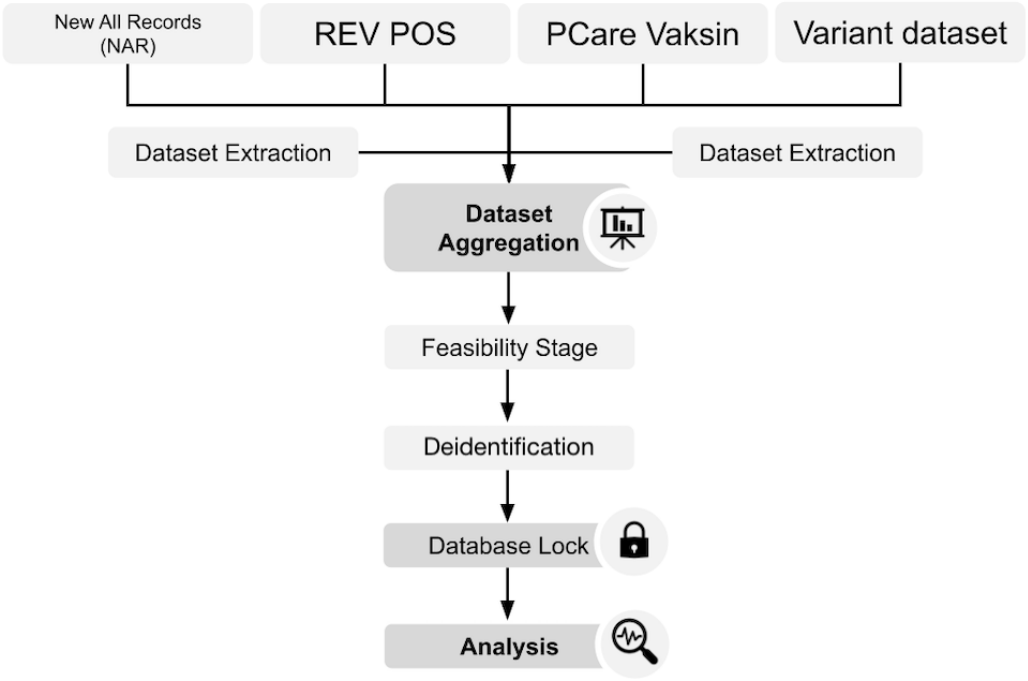
[a]NAR: New All Records.

[b]RT-PCR: reverse transcription polymerase chain reaction.

[c]SUSPROB: Suspect and Probable.

[d]PCARE: Primary Care.

Figure 2. Study workflow. PCare: Primary Care.



People with data linked to the entries within the Primary Care (PCARE) Vaksin dataset will be classified as vaccinated people (Figure 2). To avoid misclassification of foreigners as unvaccinated people, the study will only use entries with national identity card numbers as ID numbers from each of the study datasets. Vaccinated people with incomplete data on vaccination date and vaccine name will be excluded from the final dataset (Table S2 in Multimedia Appendix 1). From the final dataset, a subset of data containing the matched cases and controls will be created (Table S3 in Multimedia Appendix 1).

As genomic testing was not routinely performed in Indonesia, no data linkage will be performed on the variant dataset. In contrast, the variant dataset, which consisted of the genomic test result of the randomly sampled specimen from the population, will be used to confirm the dominant SARS-CoV-2 variant in Jakarta during each period of interest.

Sample Size

The calculation formula for the sample size used in this study will follow the methodology described by O'Neill [29]. Assuming vaccination coverage between 20%-90%, a precision of ±5%, a type 1 error rate of 0.05, and an anticipated VE of 50%-90%, the minimum sample size needed for each specific COVID-19 vaccine brand and dose VE analysis is roughly around 15,000, with 5000 cases and 10,000 controls [24,29] (Table S4 in Multimedia Appendix 1).

We expect to analyze 400,000-900,000 people after the aggregation of all datasets. Therefore, we should have enough data to conduct the VE analyses for each specific COVID-19 brand and regimen in our final dataset. We will compare the proportion of COVID-19 vaccines received by eligible people in our dataset during each period of interest to those reported by the Ministry of Health [17] (Table S1 in Multimedia Appendix 1). Furthermore, we will exclude people who received COVID-19 vaccine brands with vaccination coverage of less than 20%, as these vaccines are usually distributed briefly in the population or only available to specific subgroups within the community. Moreover, we might consider combining different COVID-19 vaccine brands with the same platform into one group to decrease the required sample size, especially for the subgroup VE analysis [24].

Statistical Analysis

We adopted our VE analysis from the Interim Guidance of Evaluation of COVID-19 Vaccine Effectiveness by the World Health Organization, where the final estimate of absolute VE (aVE) will be determined by calculating the adjusted odds ratio (aOR) for vaccination using the formula aVE = (1 – aOR) × 100% [24]. Unconditional multivariable logistic regression will be used to analyze the aOR of having symptomatic and fatal SARS-CoV-2 infection between the unvaccinated and vaccinated participants. We will perform separate analyses for the Delta- and Omicron-dominant periods. Furthermore, within each period, we will also analyze each vaccinated person separately by their vaccine brand or platform and vaccination doses, such as dose 1, dose 2, or booster. For the main aVE analyses, we will include only vaccinated people with the last dose 1 or dose 2 vaccination date within 14-90 days or with the last booster dose within 7-90 days before their index test date and compare them to the unvaccinated people.

One main logistic model will be assembled by forward inclusion, and only covariates with less than 20% missing data will be considered to be included in the model building. Assessment for confounders and effect modifiers will be performed with the Wald test and by observing the change in the primary exposure coefficient SE. Covariates that act as confounders will be included in the model. If effect modification is present, it is essential to report VE and CIs for each subgroup individually.

The linearity between continuous variables and the log odds of having symptomatic SARS-CoV-2 infection will be assessed, and the continuous variables will be modified into categorical variables if necessary. The overall fit of the final multivariate logistic regression model will be assessed with Hosmer and Lemeshow goodness-of-fit test [30], as matching might incur matching-related bias from the cases and controls having similar exposure, thus underestimating the aVE. We will also perform conditional logistic regression as a sensitivity analysis for measuring the aVE estimation against symptomatic SARS-CoV-2 infection or our primary objectives [31,32]. Furthermore, for the analysis of the Omicron period, we will perform an additional analysis of relative VE (rVE) by comparing recipients of one booster dose to recipients of the 2 doses who were eligible to receive the booster dose. The rVE will be calculated using the formula rVE = [(aVE from booster dose – aVE from 2 doses and eligible for booster)/(1 – aVE from 2 doses and eligible for booster)] × 100%. For the rVE analyses, we will include only people whose last booster dose was within 7 to 90 days before their index test date and compare them to people whose last 2-dose vaccination date was ≥90 days before their index test date [24].

This study will also conduct subgroup analyses based on the time between the last vaccination date and test index date to assess for waning of immunity (Table 2). These subgroup analyses will be conducted separately for each wave and vaccine brands or regimens. Similar to the main analysis, each vaccinated subgroup will be compared to unvaccinated people.

Table 2. Subgroup analysis based on time since last vaccination.

Subgroup	Description
1	7-14 days between the last vaccination dose and index test date
2	14-28 days between the last vaccination dose and index test date
3	28-56 days between the last vaccination dose and index test date
4	56-90 days between the last vaccination dose and index test date
5	90-180 days between the last vaccination dose and index test date
6	>180 days between the last vaccination dose and index test date

A 2-sided *P* value derived from the multivariable logistic regression analysis will be used to assess VE. Data linkage and data cleaning will be performed in Google Collaboratory with the Python programming language. Furthermore, the Statsmodel library package will be used for statistical analysis [33].

Ethical Considerations

The research protocol received ethics approval from the Ethical Committee of Persahabatan Hospital Jakarta (40.A.1/KEPK-RSUPP/11/2022). The research conducted in accordance with this protocol will not collect consent from people as it involves the use of secondary data. A consent waiver statement has been issued by the Ethical Committee of Persahabatan Hospital Jakarta (DP.04.03/D.XX.10.4/0001/2024).

Results

This research received funding from 2022 to 2024. The proposal preparation, protocol development, and ethical review processes began in 2023, alongside efforts to gather access to datasets from various stakeholders. Enrollment commenced at the beginning of 2024 and was completed in July 2024 after the data-cleaning process. A total of approximately 4 million data points were available from the linked datasets. Data analysis is currently underway, with the first results expected to be submitted for publication at the start of 2025.

Discussion

The general objective of this research is to estimate the real-world effectiveness of COVID-19 vaccines during the Delta and Omicron waves. Since the study covers two different periods, the results may also reveal changes in VE across these two variant phases. The study follows World Health Organization guidelines for conducting real-world COVID-19 vaccine research and incorporates linkage across multiple research datasets to enhance its validity. The use of the Google Collaboratory online platform for data integration demonstrates adaptability to modern technologies. As of mid-2024, there are over 4 million combined records from RT-PCR test results and vaccination data.

Vaccine effectiveness refers to the average response to the vaccine under real-world conditions, assessed through observational studies, and is generally lower than the efficacy observed in controlled settings [34]. When a vaccine is administered to the general population, various factors such as individuals' medications and overall health status, and vaccine storage and administration conditions, among others, can diminish its effect and increase variability in responses among recipients. This phenomenon is anticipated for all vaccines, underscoring the importance of continuous monitoring for emerging data as vaccination programs progress. The collection, analysis, and communication of these experiences are crucial for gaining authoritative knowledge on effectiveness, including potential rare or delayed side effects. Assessments of COVID-19 VE also contribute to understanding the overall community immunity required to safeguard the population [35].

The study's inclusion of a wide variety of vaccine platform, including mRNA, adenovirus-based, and inactivated vaccines, is one of its main strengths. For low- and middle-income countries, which may depend on several types of vaccine due to availability constraints, this variety enables a more nuanced knowledge of vaccination performance across various methods.

In contrast to many previous studies, this study additionally considers important factors that could affect the chance of vaccination and the risk of contracting or dying from COVID-19 in various communities. The study provides a more complete picture of VE in the real world by taking these factors into account, particularly in different urban environments like Jakarta.

Nevertheless, certain limitations still exist despite the test-negative design study design's attempts to lessen biases. If those who test negative for COVID-19 were exposed but did not exhibit symptoms, misclassification bias may occur, as indicated in Table 3 on potential biases related to test-negative design. Furthermore, since those who choose to get tested might not be representative of the whole community, health care–seeking behavior may introduce additional bias. Collider bias is still a worry and has not yet been completely mitigated, even though sampling has been used to reduce problems like selection bias. This is especially important because the study looks at communities with different socioeconomic and health characteristics, which could affect the results. Addressing collider bias in future research could significantly improve the reliability and validity of the findings, offering a clearer understanding of the true VE in different contexts.

Table 3. Potential biases of COVID-19 vaccine effectiveness studies using test-negative design.

Potential bias	Explanation	Magnitude	Direction on VE[a] estimate	Outcome/subgroups affected	Method to control	Comments
Health care–seeking behavior bias (access to health care)	Individuals who are more likely to get vaccinated tend to seek medical care more frequently, which increases their chances of being identified as cases	Large	Underestimate VE	Nonsevere outcome	Using TND[b]	By using TND, we only include individuals who seek care for similar symptoms or indications thus reducing differences in health care–seeking behavior, but TND can create collider bias
Health care–seeking behavior bias (vaccine status)	Vaccinated individuals less likely to seek testing for COVID-19–like illness due to perception of protection	Small to moderate	Underestimate VE	Nonsevere outcome	Using TND	TND partially controls this bias
Collider bias	This arises when we restrict analysis on a collider variable (eg, testing). TND only analyzes individuals who were tested.	Unknown	Depends on how health care–seeking behavior and infection affects testing	Nonsevere outcome	Limit to severe individuals or older adults	We could not control this bias because the information on the collider variable (testing) is not available.
Misclassification of the exposure	During high levels of transmissibility, infection may occur soon after vaccination. Meanwhile, vaccines need time to confer an acceptable protective immune response.	High	Underestimate VE	All	Limit analysis only after vaccine performance has acceptable time to confer acceptable protection (eg, 14 days after the first or second dose, 7 days after third dose)	This study excludes infection that occurs <14 days after vaccination in the analysis of primary vaccine (first and second dose) and excludes events (eg, infection) that occur <7 days after vaccination in the analysis of booster vaccines. This measure will prevent underestimation of VE in the time when infection occurs during suboptimal immune response after vaccination.
Misclassification of the outcome	False positive and false negative	Small	Underestimate VE	All	Use only highly sensitive test (eg, RT-PCR[c])	This study only includes RT-PCR SARS-CoV-2 results (see eligibility criteria) to control this bias
Spurious waning bias	This refers to an apparent VE reduction over time that does not reflect the decay of immunity over time but rather results from biases or confounding factors in the study design or analysis (eg, different variants, differences in exposure risk).	Small to large	Underestimate VE	All	Perform analysis for specific variant/period. Control difference in viral dynamic transmissibility over time. Perform stratification analysis by time since vaccination.	To prevent bias due to variants, this study conducts two sets of analyses (Delta and Omicron). To prevent bias due to differences in exposure risk over the periods of interest, we conducted matching case and control by calendar week of sample collection. To show VE waning, we perform stratification analysis by time since vaccination.

[a]VE: vaccine effectiveness.

[b]TND: test-negative design.

[c]RT-PCR: reverse transcription polymerase chain reaction.

The response to the COVID-19 pandemic has highlighted new challenges in Indonesia's healthcare system, particularly data fragmentation from numerous health applications and insufficient standardization [36]. Disparities in recording and storing health data in Indonesia also present challenges during the pandemic [37]. Both of these obstacles hinder large-scale health research in the country. To address this, dataset integration is necessary to obtain comprehensive and complete data. Upon completion of our study, it is hoped to demonstrate the capability of health researchers in Indonesia to conduct research using big data, serving as an initiation for the digital transformation of health care.

Acknowledgments

This study will receive an AstraZeneca research funding grant (ESR-21-21574 – D8111L00006.) as an external sponsor, and the sponsor will not be involved in conducting the study.

Data Availability

The data that supports the findings of this study will be available upon request from EB and FA. The data, which contain personal information, are not publicly available due to the strategic health policy of the province of Jakarta.

Authors' Contributions

Conceptualization: EB, FA, FM
Methodology: FA, FAGS, ATR, RAR, HA
Project administration: FM, MIDR, IA
Supervision: EB, FA
Validation: EB
Visualization: FA, FAGS, MIDR
Writing – original draft preparation: FA, FAGS, MIDR, IA
Writing – review and editing: EB, FA, FAGS, MIDR, IA
All authors mentioned critically reviewed the manuscript for significant intellectual content and approved the final version for publication.

Conflicts of Interest

None declared.

Multimedia Appendix 1
List source datasets.
[DOCX File , 16 KB - resprot_v14i1e56519_app1.docx]

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Abbreviations

aOR: adjusted odds ratio
aVE: absolute vaccine effectiveness
NAR: New All Records
PCARE: Primary Care
RT-PCR: reverse transcription polymerase chain reaction
rVE: relative vaccine effectiveness
SUSPROB: Suspect and Probable
VE: vaccine effectiveness

Edited by A Schwartz; submitted 18.01.24; peer-reviewed by JL Suah, P Kumwichar; comments to author 24.06.24; revised version received 14.10.24; accepted 24.01.25; published 10.04.25.

Please cite as:
Burhan E, Azzumar F, Sinuraya FAG, Rakasiwi MID, Akbar I, Mubarak F, Rengganis AT, Rachmadi RA, Afidjati H
Real-World Effectiveness of COVID-19 Vaccines (ChAdOx-1s, CoronaVac, BBIBP-CorV, mRNA-1273, and BNT162b2) in Jakarta: Protocol for Test-Negative Design of Health Care Data
JMIR Res Protoc 2025;14:e56519
URL: https://www.researchprotocols.org/2025/1/e56519
doi:10.2196/56519
PMID:39902869

Protocol

Maternal Metabolic Health and Mother and Baby Health Outcomes (MAMBO): Protocol of a Prospective Observational Study

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Abstract

Background: Metabolic disease is increasingly impacting women of reproductive age. In pregnancy, uncontrolled metabolic disease can result in offspring with major congenital anomalies, preterm birth, and abnormal fetal growth. Pregnancy also accelerates the complications of metabolic diseases in mothers resulting in an increased risk of premature cardiovascular events. Despite the convincing evidence that preconception care can largely mitigate the risks of metabolic disease in pregnancy, there are few data about how to identify the highest-risk women so that they can be connected with appropriate preconception care services.

Objective: The aim of the study is to determine the maternal phenotype that represents the highest risk of having adverse neonatal and maternal pregnancy outcomes.

Methods: This will be a prospective cohort study of 500 women recruited in early pregnancy. The primary outcome is a composite of offspring born small for gestational age (SGA) or large for gestational age (LGA) (customized birthweight ≤10th and ≥90th centile for gestational age). Secondary outcomes are (1) composite of adverse neonatal birth outcomes (SGA, LGA, major congenital abnormalities, preterm birth [<37 weeks' gestation]) and (2) composite of new maternal metabolic outcomes (gestational diabetes, diabetes in pregnancy, type 2 diabetes [T2D] or prediabetes; gestational hypertension, preeclampsia, eclampsia or new essential hypertension after pregnancy; and gestational weight gain ≥20kg or new overweight/obesity at the 12-18 months postpartum visit). A multivariable logistic regression analysis will be conducted to identify candidate predictors of poor pregnancy outcomes due to metabolic disease. From this model, model coefficients and the associated 95% CIs will be extracted to derive the risk score for predicting the delivery of LGA/SGA offspring (primary outcome) and composites of adverse neonatal outcomes and maternal outcomes (secondary outcomes).

Results: Seed funding for the project was acquired in November 2022 and subsequent funding was acquired in May 2024. The first participant was recruited on March 23, 2023. At the time of manuscript submission, 402 participants have been recruited. Data analysis has not yet been performed. Results are expected to be published in the first half of 2027.

Conclusions: This is a prospective observational cohort study that intends to identify the metabolic disease risk factors, or combination of factors, that are most likely to cause adverse maternal and fetal health outcomes. These characteristics will be used to develop a risk calculator which will assist in identifying the highest risk women and in triaging them to appropriate services. The study has been approved by the institutional Human Research Ethics Committee (HREC/90080/MH-2022).

Trial Registration: Australian New Zealand Clinical Trials Registry ACTRN12623000037606; https://tinyurl.com/yeytsxtp

International Registered Report Identifier (IRRID): DERR1-10.2196/72542

(JMIR Res Protoc 2025;14:e72542) doi:10.2196/72542

KEYWORDS

preconception; large for gestational age; small for gestational age; pregnancy outcomes; metabolic disease; diabetes; obesity; hypertension

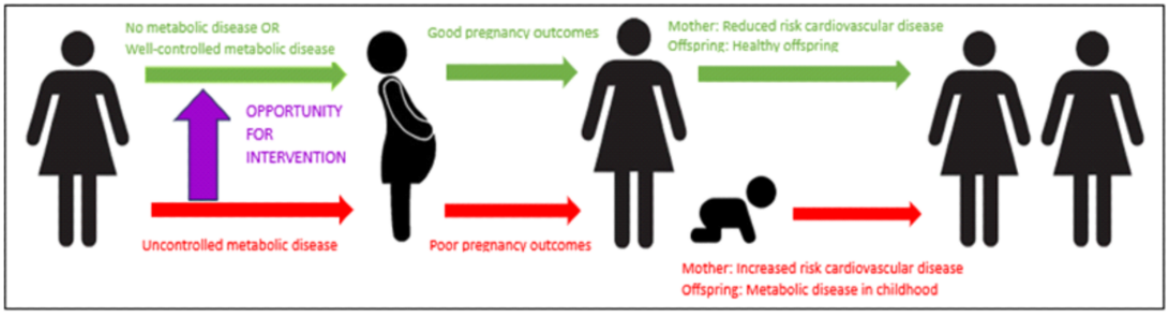
Introduction

The offspring of mothers with pre-existing metabolic diseases—obesity, diabetes, and hypertension—have an increased risk of significant congenital anomalies and premature birth compared with the offspring of mothers without metabolic disease [1]. These offspring are also twice as likely to develop obesity, diabetes, and hypertension in childhood [2]. For the mothers, pregnancy accelerates the complications of metabolic diseases, resulting in an increased risk of premature cardiovascular events including ischemic heart disease, stroke, and death [3]. Although the consequences of uncontrolled metabolic disease in pregnancy are entirely preventable, our current clinical services are not effective. This is because the highest-risk women are often not identified prior to pregnancy and because high-risk women frequently have poor access to appropriate care.

The women who are most at risk of adverse consequences of metabolic disease in pregnancy are women of low socioeconomic status, women who have experienced trauma, and women living in rural and remote areas [4]. Major barriers for these women accessing and using preconception services include (1) failure to be identified as "high risk" by a health care provider prior to pregnancy; (2) accessing a suitable referral pathway; (3) attending clinic appointments especially if limited by remoteness or finances; and (4) accepting care for metabolic diseases which are often stigmatized diseases and may have implications for the women's place in her family or wider cultural group. Ironically, there are well-developed services for preconception care of women with severe metabolic disease. However, these services are generally based in tertiary maternity hospitals in metropolitan cities. Due to geographical factors and because referral pathways and clinic entry criteria are often unclear, these services are often used by high socioeconomic status women with a relatively low risk of adverse pregnancy outcomes.

We hypothesize that the mothers and offspring at the highest risk of the adverse consequences of metabolic disease are predictable based on the phenotype of the mother prior to pregnancy. Despite the high fetal morbidity that can be associated with metabolic syndrome, little has been done to identify and capture at-risk individuals at a preconception or early antenatal stage. The aim of this study is to develop risk calculators that best predict (1) a mother's risk of having a neonate with abnormal fetal growth (large for gestational age [LGA] or small for gestational age [SGA]); (2) a mother's risk of having a serious adverse neonatal outcome; and (3) a mother's risk of developing new metabolic disease after pregnancy (Figure 1). We will translate this to a user-friendly mobile app that will allow any health care worker to access and triage women to appropriate preconception care.

Figure 1. Schematic of the rationale for research study.



Methods

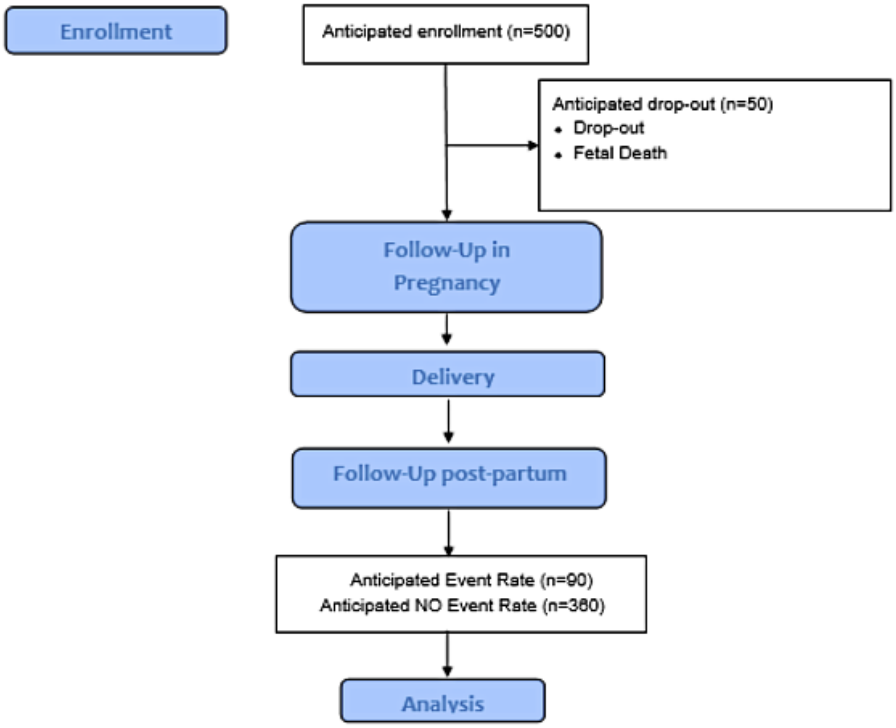
Study Design and Setting

Study phase I is a multicenter prospective observational cohort study. Study phase II involves the development of risk calculators from the observational cohort established in phase I. The study was prospectively registered with the Australian New Zealand Clinical Trials Registry (ACTRN12623000037606).

The observational cohort study will recruit 500 women who have been referred to either a public or a private tertiary maternity hospital (Figure 2). Both hospitals are tertiary referral centers based in metropolitan Melbourne Australia, and collectively manage >8000 births per year. The recruiting maternity hospitals accept referrals from the entire state of Victoria, such that the hospital populations comprise of metropolitan women and a smaller group of women living in regional and rural areas.

The first participant was recruited on March 23, 2023. The projected timeline for recruitment is that the last participant will be recruited in June 2025. It is anticipated that the last participant will have completed all study visits by June 2026.

Figure 2. Flowchart of the anticipated study cohort.



Eligibility and Recruitment

Inclusion Criteria

Eligibility for the study will be women aged 18 years and older with pregnancies of 20±4 completed weeks of gestation who provide written consent and are attending a prespecified study site for maternity care. The study will include those with multifetal pregnancies, chronic disease, and those using medications of any type. Women from non–English speaking backgrounds will be included and telephone interpreting services and cultural liaison officers will be used as required.

Exclusion Criteria

Women will be excluded from the study if they do not have maternity care at one of the prespecified study sites before 20±4 completed weeks of gestation. Women will also be excluded if they do not wish to provide informed consent or are unable to provide informed consent. This may be due to the inability to read and write, intellectual disability, or a severe active mental illness. It is anticipated that fewer than 1 out of 1000 women screened at maternity hospitals would fulfill this criterion.

Withdrawal Criteria

Participants are free to withdraw from the study at any time through revocation of consent (patient preference) or via ceased communication with the recruitment site (lost to follow-up). All data collected prior to the withdrawal of consent will be included in the analysis. Participants who start with maternity care at the recruiting hospitals and then move to seek maternity care elsewhere may continue to take part via telephone/telehealth study visits. Participants who have a pregnancy or neonatal loss will not continue in the study, but information collected until this point will be included in the analysis.

Recruitment Procedure

Women will be recruited when they attend maternity care visits between 16 and 24 weeks' gestation. Initial contact will be made by the maternity care provider. Subsequent contact will be made by a dedicated study nurse/doctor at the time of the standard maternity care visit. All participants will receive standard individualized antenatal care based on their clinical needs.

No study activities will be performed before eligibility has been assessed and informed consent has been formally documented. To encourage attendance at clinical visits, parking and meal vouchers will be provided. At the final visit, women will be provided with a comprehensive summary of their metabolic health and a plan for appropriate long-term follow-up.

Expected Outcomes

Primary Outcomes

Metabolically prone offspring defined as a composite of offspring with birthweight ≥90th centile (LGA) and offspring with birthweight ≤10th centile (SGA) based on population-based charts [5,6].

Secondary Outcomes

A composite of adverse neonatal outcomes includes the following:

- Offspring with birthweight ≥90th centile on population-based charts (LGA).
- Offspring with birthweight ≤10th centile on population-based charts (SGA).
- Offspring with major congenital abnormalities.
- Offspring born preterm (<37 completed weeks' gestation).

A composite of new maternal metabolic disease that develops during pregnancy or <18 months postpartum is defined below:

- Gestational diabetes (GDM) as per the International Association of the Diabetes and Pregnancy Study Group (IADPSG)/World Health Organization (WHO) definition (reference); or diabetes in pregnancy as per WHO/IADPSG definition; or previously undiagnosed type 2 diabetes as per American Diabetes Association/WHO definition; or prediabetes as per American Diabetes Association definition (Table S1 in Multimedia Appendix 1).
- Gestational hypertension; or pre-eclampsia; or eclampsia; or new essential hypertension after pregnancy (Table S2 in Multimedia Appendix 1).
- Gestational weight gain ≥20 kg or new overweight/obesity after pregnancy (BMI ≥25 kg/m^2 and body weight increase of ≥5 kg compared with prepregnancy weight) at the 12-18 months postpartum visit.

Clinical Assessments

A schedule of assessments and measurements is presented in Table 1.

Table 1. Summary of study activities.

	Visit 1 (20, SD 4 weeks gestation)	Visit 2 (36, SD 4 weeks gestation)	Visit 3 (Peripartum)	Visit 4 (12-18 months postpartum)
Informed consent and eligibility	✓	✓		
Collect basic demographic details including postcode	✓			
Collect past medical, surgical, obstetric, and gynecological	✓			
Collect new medical, surgical, obstetric, and gynecological		✓	✓	✓
Adverse events		✓	✓	✓
Medication	✓	✓	✓	✓
Allergies	✓	✓	✓	✓
Smoking, drug, and alcohol use history	✓			
Maternal Anthropometry				
Height	✓			
Weight	✓	✓		✓
Waist circumference	✓	✓		✓
Bioimpedance	✓	✓		✓
Blood tests				
Glucose, insulin, and c-peptide	✓	✓		✓
HbA_{1c}[a]	✓	✓		✓
CRP[b]	✓	✓		✓
Leptin	✓	✓		✓
Provide maternal and neonatal mouth swabs to participants		✓		
Collect 75g OGTT[c] result		✓		✓
Collect obstetric ultrasound results		✓		
Collect maternal and neonatal mouth swabs for epigenetic analysis		✓	✓	
Collect obstetric medical records including the birth summary		✓	✓	
Collect height and weight data from the childhood development book (“Baby book”)		✓		✓

[a]HbA_{1c}: hemoglobin A_{1c}.

[b]CRP: C-reactive protein.

[c]OGTT: oral glucose tolerance test.

Medical History and Medications

At the first visit, a full medical history will be taken by a trained clinician including past medical history and surgical history. Outcomes of previous pregnancies will be recorded including outcome of the pregnancy, gestation, pregnancy complications, and (if relevant) birthweight and neonatal complications. Current medications including dose, and dosing schedule will be

recorded. Smoking, alcohol, and recreational drug use will be recorded.

Blood Pressure

Blood pressure will be measured after 5 minutes of rest in a seated position using an appropriately sized cuff on the bared left upper arm supported at heart level. Auscultatory readings with an aneroid sphygmomanometer and stethoscope or automated oscillometric readings with a single read per activation device will be collected by trained operators**.**

Weight, Height, and Waist Circumference

Weight will be measured by a trained technician on calibrated digital scales with an accuracy of ±0.01 kg. Participants will be asked to wear light clothing but no shoes. Height will be measured by a trained technician using a standing stadiometer with an accuracy of ±0.5 cm. Waist circumference will be measured with an accuracy of ±0.5 cm using a standard tape measure according to the WHO guidelines (at the end of a normal expiration, at the midpoint between the lower margin of the last palpable rib and the top of the iliac crest, as the average of 2 measurements). BMI will be calculated by dividing weight in kg by height in meters squared.

Bioimpedance Analysis

Bioimpedance will be performed using the DC-430MAS Tanita Dual Frequency Body Composition Analyser. Data obtained from bioimpedance analysis will include fat mass (%), fat mass (kg), free fat mass (kg), muscle mass (kg), and bone mass (kg).

Laboratory Assays

Phlebotomy is a low-risk procedure. At each visit, the required blood samples will be taken for glucose, insulin, C-peptide, high-sensitivity C-reactive protein, and leptin using an aseptic technique. Samples will be mixed by inversion and centrifuged at 4 °C. Plasma from the tubes will be aliquoted into 5 microtubes with 2 spare microtube samples. Plasma samples will be batched for analysis to minimize interassay error. The sample will be stored at –80 °C before analysis. Spare tubes will only be used in the event of a processing error.

Samples will be tested by commercial laboratories accredited by the National Association of Testing Authorities (Australia) and The Royal College of Pathologists of Australia for compliance with National Pathology Accreditation Advisory Council (Australia) standards and ISO (International Organization for Standardization) 15189. Test results were interpreted in accordance with normative reference values. The study database allows the management of the samples.

Calculated Insulin Resistance

Homeostasis model assessment of insulin resistance (HOMA-IR) values will be calculated by the equation (fasting insulin [µU/mL] × fasting glucose [mM])/22.5. Insulin resistance is defined by a HOMA value >4 (reference).

Oral Glucose Tolerance Test Results and Other Forms of Testing for Gestational Diabetes

The 75-g oral glucose tolerance test (OGTT) is a standard of care to screen for GDM at 24-28 weeks' gestation in Australia. A 75-g OGTT may also be performed at 10-20 weeks of gestation if there are risk factors for GDM. A diagnosis of GDM may also be made using other methods such as HbA_{1c} (hemoglobin A_{1c}), glucose readings from a period of fingerstick monitoring, or by evaluating continuous glucose monitoring CGM) metrics. If the woman is considered to have GDM by the treating clinical team, she will also be given this diagnosis for the purpose of the study. All medications used to treat GDM will be recorded.

For all such women, a 75-g OGTT or some other form of testing for diabetes should be repeated >6 weeks' post partum and these results will also be collected.

Obstetric Ultrasound

Obstetric ultrasounds are routinely performed in Australia to assess fetal morphology at 20-22 weeks' gestation. The fetal morphology scan report will be collected from all participants. Fetal growth scans may be performed at 28, 32, or 36 weeks for obstetric indications. If growth scans are performed, the estimated fetal weight and abdominal circumference will be collected from ultrasounds that have been formally reported. The reported customized growth centiles are based on GROW customized charts which are customized for known constitutional variables (maternal height, weight, ethnic origin, and parity) but not pathological factors such as smoking and diabetes. This method of customization has been demonstrated to classify the greatest number of offspring at risk of perinatal mortality [7-9]. Any congenital anomalies reported on ultrasound will also be recorded.

Obstetric Discharge Summary

All neonates born at recruiting maternity hospitals have a standard obstetric discharge summary on discharge from the hospital. Neonatal information collected will include date of birth, gestation at delivery, birthweight, birthweight centile, sex, Apgar's score, neonatal complications (hypoglycemia, jaundice, congenital anomalies [major/minor], and others). Maternal information will include mode of delivery, and maternal pregnancy complications (GDM, gestational hypertension/preeclampsia, and others).

Cheek Swab (for Epigenetic Analysis)

Swabs will be taken from mother and baby using a sterile regular flocked dry swab using a kit supplied at 36 (SD 4) weeks of gestation. These samples will be self-collected by rubbing the swab against the inside of the cheek 10 times and reinserting the swab into the plastic applicator. Samples will be given to nursing staff before discharge. The swabs will be sent to pathology for long-term storage until all samples are collected.

Sample Size

We estimate recruitment of 500 participants over 24 months, with an estimated dropout of 5% inclusive of dropouts due to fetal/neonatal death. The primary outcome variable of interest is LGA/SGA offspring (yes/no) due to the known association with short- and long-term metabolic consequences and the fact that most babies with congenital anomalies and prematurity will have abnormal fetal growth. By definition, LGA (<90th centile for gestational age) and small for gestational age (>10th centile

for gestational age) occurs in 20% of the population. With 475 participants (500 minus 25 dropouts), we would expect 95 offspring of interest compared with 380 normal-weight offspring.

Sample size calculation for the multivariable prediction modeling was conducted using the pmsampsize package in Stata (version 17.0; StataCorp) according to the 3 criteria (shrinkage, overfitting, and precision). From prior data, it is anticipated that the primary outcome of interest (presence of LGA/SGA offspring) will occur in 20% of the population. Åmark et al [10] reported an area under the receiver operating characteristics curve (AUC) of 0.8 from a logistic regression-based prediction model. Therefore, a minimum sample size of 440 is required with at least 88 events to ensure the expected shrinkage required is 10% or less (to minimize the potential overfitting), and a small absolute difference of 0.05 in the model's apparent and adjusted Nagelkerke R^2 value.

We anticipate that ≈20% of women will develop a maternal metabolic disease of interest including ≈15% who develop diabetes, ≈5% who gain excessive weight (>20 kg), and ≈15% who develop a hypertensive disease of pregnancy. Given the anticipated overlap of these conditions, ≈20% (n=90) of women will have at least one maternal metabolic disease of interest (secondary outcome).

Methodology

Data Collection

Study data are collected using paper case report forms. These paper documents will be kept in a locked cupboard accessible only to local research staff. Patient information is collected and stored by the investigators in a confidential REDCap (Research Electronic Data Capture system; Vanderbilt University), with password protection and restricted access. This will include patient information transcribed from the hospital's electronic medical record. REDCap is a secure, web-based app designed for research studies, providing a validated data entry interface, audit trails for data tracking, automated export procedures, and secure procedures for data import [11]. Internet access to the REDCap database will use a secure server located at the University of Melbourne, Australia (REDCap consortium host). Access will be limited to local research staff, approved data administrators, and project statisticians.

All biological samples will be labeled with a reidentifiable study number. The electronic study information will be stored in a dedicated, limited-access clinical database. Only study investigators and key study staff will have access to the database. Biological samples will be stored at –80 °C until all samples are collected. They will then be processed in batches by the local pathology network according to standard protocols.

Epigenetic samples (buccal swabs) will be stored at –80 °C until all samples are collected. DNA will then be extracted using standard processes for DNA extraction, and samples will be prepared for shipping. Methylation analysis will occur at an external genomics facility [12,13]. Once processed, data will be interpreted with the assistance of appropriate clinicians at Murdoch Research Institute. These samples are hypothesis-generating only and will not be included in the prediction modeling.

Data Management

Management of comprehensive and valid records will be the responsibility of each site. To ensure a systematic approach to data collection, the same team of study nurses will work between the sites using the same protocol and standard operating procedures. Data integrity will be maintained through a review of the collected data prior to, during, and after each study visit. Medication and adverse event data will be reviewed during each study visit. In addition, every 3 months the study coordinator will review the data collected to ensure completeness and consistency of data. Any data discrepancies will be queried with the participant by email or telephone within 4 weeks of being noted. All data, including the attendance of study visits, will be captured on a REDCap database. This will ensure that the study can meet regular deadlines required for process reporting as required by the Human Research Ethics Committee.

Data and Safety Monitoring

We anticipate very few study-related adverse events or serious adverse events. The only anticipated adverse events are phlebotomy-related side effects (ie, bruising, bleeding, vasovagal syncope) and a negative psychological response to clinical visits (ie, having weight measured). These events will be circumvented by having provided participants with a full and comprehensive review of study visits at the time of enrolment and prior to each study visit.

Reports of measurements taken at the time of clinical visits including weight and bioimpedance data, and the results of laboratory tests that are clinically relevant, will be made available to participants. Results that are not clinically relevant will not be disclosed to participants as they will not impact clinical care and may be difficult to interpret (ie, lack of reference ranges in pregnant women). Any concerning results will immediately be relayed to the treating maternity team. All other results will be reviewed within 1 week. The outcomes of participants will be discussed with the chief investigator each month. Any systematic problems with data management and adverse event monitoring or reporting will be rectified. REDCap queries will be addressed monthly by the study coordinator and reviewed quarterly by the study statistician.

Ethical Considerations

This is a prospective observational cohort study that intends to identify the metabolic disease risk factors, or combination of factors, that are most likely to cause adverse maternal and fetal health outcomes. No study-related adverse events are anticipated. The study has been granted ethics approval from the Royal Melbourne Hospital Human Research and Ethics Committee (HREC/90080/MH-2022) and recruitment is ongoing. Each participant will provide written informed consent before any study activities are undertaken and participants are free to withdraw consent at any time. Confidentiality will be maintained and only group data will be presented. Dissemination will be through peer-reviewed publications at national and international conferences, national and international obstetric medicine societies, and specialist colleges.

Statistical Methods

This study will follow the Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis reporting guidelines for prognostic studies [14]. Summary characteristics of the study cohort will be described using means (with SD) or medians (with IQRs) for continuous variables, depending on the shape of the distribution, and numbers and percentages for categorical variables.

A risk calculator will be developed to determine the risk of an abnormally grown fetus (ie, the primary outcome of the study). Participant data will be split randomly into either training (70%) or validation (30%) datasets according to standard prediction model methods. Multivariable logistic regression analysis will be conducted to identify candidate predictors of poor pregnancy outcomes due to metabolic disease. After starting with the most comprehensive model that includes all potential risk factors for an LGA or SGA offspring (ie, the primary outcome). These include categorical variables including maternal SES (based on postcode), maternal parity, maternal smoking status, maternal obesity class, maternal preexisting diabetes, maternal preexisting renal disease, essential hypertension, use of antihypertensive medication, use of metformin, gestational hypertension, preeclampsia/eclampsia, previous LGA/SGA offspring, major congenital anomaly, and continuous variables including maternal age, maternal gestational weight gain, maternal glycemic control (HbA_{1c}), total daily dose insulin, maternal systolic blood pressure, maternal diastolic blood pressure, birthweight of previous offspring, fasting glucose, plasma insulin, plasma C-peptide, plasma leptin, HOMA-IR.

A backward selection method will be performed to determine which combination of risk factors generates the most parsimonious predictive model. The number of candidate variables will be limited to data collected in the dataset. From this parsimonious model, model coefficients and the associated 95% CIs will be extracted to derive the risk score for predicting the delivery of LGA/SGA offspring. Internal validation of the model will be performed using 5-fold cross-validation and bootstrap validation. The performance of the model will be assessed using the AUC and calibration slope.

A similar approach will be taken for the secondary outcomes, and these models will be used to develop risk calculators for a composite of neonatal adverse outcomes and a composite of maternal adverse outcomes. Ongoing statistical input will be provided by the University of Melbourne.

Results

This project was funded by a National Health and Medical Research Council Investigator Grant awarded in November 2021 (CIA Price 2022-2026; 2007957), and by a Translational Challenge Grant from the Ramsay Hospital Research Foundation awarded in April 2024 (CIA Price 2024-2027; 2023/TCG/0038). The first participant was recruited on March 23, 2023. At the time of manuscript submission, 402 participants have been recruited. The projected timeline for recruitment is that the last participant will be recruited in June 2025. Therefore, it is anticipated that the last participant will have completed all study visits by June 2026. Data analysis has not yet been performed. Results are expected to be published in the first half of 2027.

Discussion

Why Predict Adverse Pregnancy Outcomes?

Uncontrolled maternal metabolic disease can profoundly impact both maternal and neonatal outcomes. Major congenital anomalies due to maternal metabolic disease are a common cause of neonatal death and long-term disability. For example, the risk of a major congenital anomaly such as congenital heart defect or spina bifida is 25% with suboptimally controlled diabetes (HbA_{1c} >10%) compared with 3% with well-controlled diabetes (HbA_{1c} <7%) [15,16]. Similarly, preterm birth can result in long-term neurodevelopmental issues and poor academic outcomes [17].

Even in children born at term, abnormal fetal growth can result in a long-term predisposition to metabolic disease. Around half of children born LGA (>90th centile for gestational age) or SGA (<10th centile for gestational age) [16] go on to develop metabolic syndrome (obesity, dysglycemia, and hypertension) by school age [2] with subsequent deterioration of metabolic disease in early adolescence [18]. This occurs due to a combination of factors including altered body composition at birth, altered appetite at birth, and atypical organ development including a lower endowment of cardiac myocytes, pancreatic beta cells, and nephrons [19].

For women, metabolic disease during pregnancy is an independent risk factor for later cardiovascular disease [20]. In the decade after preeclampsia, a meta-analysis including 200,000 women demonstrated a 4-fold increase in the relative risk of developing chronic hypertension and a 2-fold increase in the relative risk of ischemic heart disease and stroke [21]. For women who develop GDM, the lifetime risk of T2D is increased by 7-fold [22]. Lee et al [23] found that all-cause mortality was increased in women who were obese during pregnancy (BMI>30 kg/m^2) versus normal BMI after adjustment for confounding factors (hazard Ratio 1.35, 95% CI 1.02-1.77). Pregnancy loss due to late first-trimester miscarriage or stillbirth is also associated with increased cardiovascular disease in the mother, likely because pregnancy unmasks an underlying endothelial dysfunction [15].

Why Existing Prediction Models Are Inadequate

There are very few studies that have aimed to predict adverse pregnancy outcomes based on the maternal phenotype, and most of these have used maternal characteristics in combination with obstetric tests such as biomarkers in blood or ultrasound [24-27]. To the investigator's knowledge, there has only been one study that has used maternal prepregnancy characteristics to predict the risk of poor pregnancy outcomes [28].

The Generation R study group used easily obtainable maternal preconception characteristics including age, ethnicity, parity, BMI, and smoking status to model the risk of offspring born LGA/SGA. Basic models demonstrated an AUC of 0.63 (95% CI 0.61 to 0.65) and 0.64 (95% CI 0.62 to 0.66) for preterm birth/SGA and LGA, respectively. Interestingly, more complex

models involving sociodemographic and dietary details only led to small improvements in the model [28].

However, the Generation R study was a population-based prospective cohort study that aimed to identify early and genetic causes and casual pathways leading to abnormal growth and development of the offspring [29]. Risk prediction modeling in this study focused on all potential causes of LGA and SGA in a whole population cohort. This study did not specifically focus on LGA/SGA in the context of metabolic disease, nor did it consider the metabolic outcomes of the mother. Women with metabolic disease are known to be at higher risk of adverse pregnancy outcomes than the general population [30]. This cohort requires information about the risk of poor pregnancy outcomes both for themselves and their offspring.

Within an established pregnancy, Frick et al [31] found that LGA offspring (>95th centile) could be predicted based on increasing maternal BMI, diabetes status, and the presence of chronic hypertension. However, this prediction was less accurate in non-Caucasian women, in smokers, and in nulliparous women. In parous women, LGA offspring were predicted based on the birth-weight Z-score of previous offspring, a prior history of GDM, and a decrease with interpregnancy interval. This study then refined the prediction model using early fetal ultrasonography [31].

A population-based study from Ontario Canada (n=634,290) found that it was possible to predict and prevent severe maternal morbidity with moderate discrimination. Those women who had poor short-term pregnancy outcomes were older, had more medical comorbidities, and conceived using assisted reproductive technologies [32]. Similarly, Akinci et al [33] reported that in a small cohort (n=164), prepregnancy obesity, greater gestational weight gain, and a fasting glucose level (>5.5 mmol/L) on the 75-g OGTT predicted the development of metabolic syndrome in postpartum women with moderate to high discrimination.

What the Metabolic Health and Mother and Baby Health Outcomes Study Will Contribute

There are very few studies that use maternal characteristics to predict both maternal and fetal/neonatal pregnancy outcomes, even though they are inextricably linked. There are also few studies that consider the impact of metabolic disease as a whole rather than focusing on individual components of metabolic disease- hypertension, obesity, or dysglycemia.

We anticipate the Metabolic Health and Mother and Baby Health Outcomes (MAMBO) project will be able to fill this gap by developing a risk prediction tool that (1) considers how multiple maternal metabolic risk factors interact to result in adverse pregnancy outcomes, and (2) considers both maternal and neonatal pregnancy outcomes.

A risk calculator that can be used as a mobile app would provide health care workers with a simple effective tool to objectively calculate pregnancy risk and to triage women to appropriate services based on a standard dataset. Health care providers would require very little background knowledge to use the risk calculator. However, the tool would produce personalized data about the risks of an adverse pregnancy outcome. This would assist health care workers in effectively communication with the woman, her family, and with other health care providers.

Limitations

Ideally, the MAMBO cohort would have been recruited prior to conception. However, this would have required a very large sample size to allow for women who did not conceive in a specified timeframe and for additional dropouts due to the lag time between recruitment and conception. Therefore, the pragmatic decision was made to recruit women at 20±4 weeks' gestation. Existing data demonstrates a strong correlation between maternal anthropometric data and biomarkers in early pregnancy and the prepregnancy period [34].

The MAMBO cohort consists entirely of women attending major metropolitan maternity hospitals. Although these hospitals accept referrals from primary care and smaller hospitals that provide maternity care for women living in rural and remote locations, nonmetropolitan women are likely to be underrepresented in this cohort. Women from minority culture groups and women from non–English speaking backgrounds may also be less likely to participate in a prospective cohort study. To address these issues, translators and cultural liaison officers will be made available. We will aim to pair study visits with usual maternity care appointments. The final clinical study visit can be performed by phone if necessary.

Outcomes and Significance

Growing numbers of women are impacted by metabolic disease when they pursue pregnancy. However, women of low socioeconomic status, non-English speaking backgrounds, and women living in rural and remote areas are less likely to access preconception care services. Therefore, these women are at a greater risk of short-term adverse pregnancy outcomes, and long-term due to metabolic programming in the infant and unmasking of endothelial dysfunction in mothers.

The development of a risk calculator that predicts the women most likely to have poor pregnancy outcomes may assist in preventing these adverse pregnancy outcomes. It would allow women to be triaged by any health care professional and would ensure that the highest risk women are identified and have the opportunity to be referred to high-quality preconception care services and to receive information on how to prevent adverse health outcomes for themselves and their offspring. The risk calculator also has the potential to act as a platform that assists health care professionals in providing lower-risk women with basic preconception care information.

Conclusions

Currently, the women at the highest risk of adverse pregnancy outcomes due to metabolic disease are the least likely to access preconception health interventions. The MAMBO project intends to bridge this gap by developing a risk prediction tool that allows any health care practitioner to accurately assess risk, and to triage women to appropriate preconception care services. In this way, we aim to prevent adverse maternal and fetal health outcomes.

Acknowledgments

We gratefully acknowledge the women and their families who agreed to participate in the MAMBO study. SP is supported by a National Health and Medical Research Foundation (NHMRC) investigator grant (2007957). This study is supported by a Translational Challenge Research grant from Ramsay Hospital Research Foundation (2023/TCG/0038). Funders had no role in study design, data collection, analysis, or manuscript preparation.

Data Availability

The datasets generated during this study are available from the corresponding author on reasonable request.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Additional tables.
[DOCX File , 18 KB - resprot_v14i1e72542_app1.docx]

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Abbreviations

AUC: area under the receiver operating characteristics curve
GDM: gestational diabetes

HbA_{1c}: hemoglobin A_{1c}
HOMA-IR: homeostasis model assessment of insulin resistance
IADPSG: International Association of the Diabetes and Pregnancy Study Group
LGA: large for gestational age
MAMBO: Metabolic Health and Mother and Baby Health Outcomes
OGTT: oral glucose tolerance test
REDCap: Research Electronic Data Capture
SGA: small for gestational age
T2D: type 2 diabetes
WHO: World Health Organization

Edited by J Sarvestan; submitted 11.02.25; peer-reviewed by P Dasari, M Dekker Nitert; comments to author 20.02.25; revised version received 24.02.25; accepted 02.03.25; published 11.04.25.

Please cite as:
Price SAL, Koye DN, Lewin A, Nankervis A, Kane SC
Maternal Metabolic Health and Mother and Baby Health Outcomes (MAMBO): Protocol of a Prospective Observational Study
JMIR Res Protoc 2025;14:e72542
URL: https://www.researchprotocols.org/2025/1/e72542
doi:10.2196/72542
PMID:40215105

Protocol

Development and Validation of the "Basic Oral Health Assessment Tool" (BOHAT) for Nondental Health Care Professionals to Use With the Indian Adult Population: Protocol for a Mixed Methods Study

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Abstract

Background: Oral health is a significant indicator of general health, well-being, and quality of life. The prevention of oral health problems requires periodic inspection of the oral cavity. Routine oral health examinations at the individual level appears to be one way to deliver quality oral health care but are too often missed as an opportunity for improved oral health in the nondental health care setting in India. This is because of limited training and inaccessible or lack of specialized oral health assessment tools.

Objective: This study will focus on the development, validation, and implementation of the Basic Oral Health Assessment Tool (BOHAT) to improve the oral health assessment capabilities of nondental health care professionals and thus contribute to improved overall health outcomes of the Indian adult population.

Methods: This study will be a mixed methods, multistage study conducted in 3 stages. The study will be conducted with 708 nondental health care professionals in 33 Primary Health Centers (PHCs) of Mangalore Taluk, Karnataka. Ethical approval was sought from the institutional ethics committee of Manipal College of Dental Sciences Mangalore. Informed consent will be obtained from every participant prior to the study. A literature review and qualitative interviews will be used for item and domain generation with respect to BOHAT, and an expert panel review and pilot testing will be used to refine the items and domains. Finally, statistical analyses will be conducted to validate the reliability and consistency. The second phase will involve capacity building and user experience exploration through comprehensive training for nondental health professionals using audio and visual aids, with hands-on learning methodologies including relevant feedback processes in the form of focus group discussions. The third stage will check the effectiveness of BOHAT regarding the changes in knowledge, attitudes, and practices through pre- and posttraining questionnaires, which will then be followed by a retention analysis 3 months later.

Results: As of January 20, 2025, the study is in its preliminary phase: "Substage A: Item and Domain Development." We have received institutional ethics committee and Institutional Protocol Approval Committee approval for the study. Data collection procedures have not started yet. The study is progressing as per the planned timeline.

Conclusions: The BOHAT study holds considerable potential to promote oral health care through collaborative and interdisciplinary approaches. It will facilitate early diagnosis, timely referrals, and comprehensive care by integrating assessment actions for oral health into routine practices of nondental primary health care professionals.

International Registered Report Identifier (IRRID): PRR1-10.2196/63480

(JMIR Res Protoc 2025;14:e63480) doi:10.2196/63480

KEYWORDS

oral health assessment tool; oral health; screening; nondental health care professionals; primary health centers; India; tool validation; health care training; mixed methods research

Introduction

Oral health is a significant indicator of general health, well-being, and quality of life [1]. The functioning of the oral cavity, teeth, and orofacial structures, which enables people to perform fundamental bodily activities like eating, respiration, and speaking, is commonly referred to as oral health, and it undergoes changes throughout the various stages of life, from early childhood to advanced age [2,3]. Oral health problems can have a significant effect on people's quality of life, interpersonal connections, general well-being, and self-esteem [4]. Therefore, emphasizing the importance of preventive measures and early detection of oral diseases becomes crucial in mitigating the likelihood of developing subsequent challenges impacting both oral and overall health.

Oral health assessments serve as a good indicator of disease risk, the proper management of existing disease, and even the improvement of health outcomes because of appropriate oral health care [5]. Prevention of oral health problems requires periodic inspection of the oral cavity. Routine oral health examinations at the individual level appear to be one way to deliver quality oral health care but are too often missed as an opportunity for improved oral health in the nondental health care setting [6]. Health care professionals, from the allopathic doctor (physician and surgeon) to Ayurveda, yoga, naturopathy, Unani, Siddha, and homeopathy (AYUSH) practitioners; nurses; auxiliary nurse midwives; and community health workers (CHWs) [7], are very essential for the delivery of holistic health care but have limited capacity to comprehensively assess oral health issues and subsequently intervene because of significantly limited training on its own as well as inaccessible or lack of specialized supportive tools adapted to suit the population. This might ultimately delay the diagnosis and institution of appropriate interventions for oral health conditions in such patients and increase the possibility of further disease progression, which will then compromise overall health outcomes.

The separation between oral health and general health care practices may contribute to the insufficient integration of oral health assessments into routine health care protocols, limiting the overall effectiveness of health care delivery. Screening of oral health, early detection and triage of oral health issues, and immediate referral to dental specialists ultimately require the integration of frontline health care professionals [8]. Several instruments for health care providers to evaluate oral health have been developed over time. A few of these tools are the Holistic Reliable Oral Assessment Tool (THROAT) [6], Revised Oral Assessment Guide [9], Oral Health Assessment Tool (OHAT) [10], and Oral Assessment Guide [11]. However, the tools in current use lack reference pictures, challenging the completeness, relevance, and clarity of wording [12]. The Federation Dentaire Internationale and International Consortium for Health Outcomes Measurement collaboration developed a preliminary standard core set of oral health outcome measures for adults with a primary focus on periodontal disease and caries. The subsequent action is to conduct a validation and feasibility study in different clinics seeking to fine-tune the Adult Oral Health Standard Set more, and studies to do that are ongoing [13].

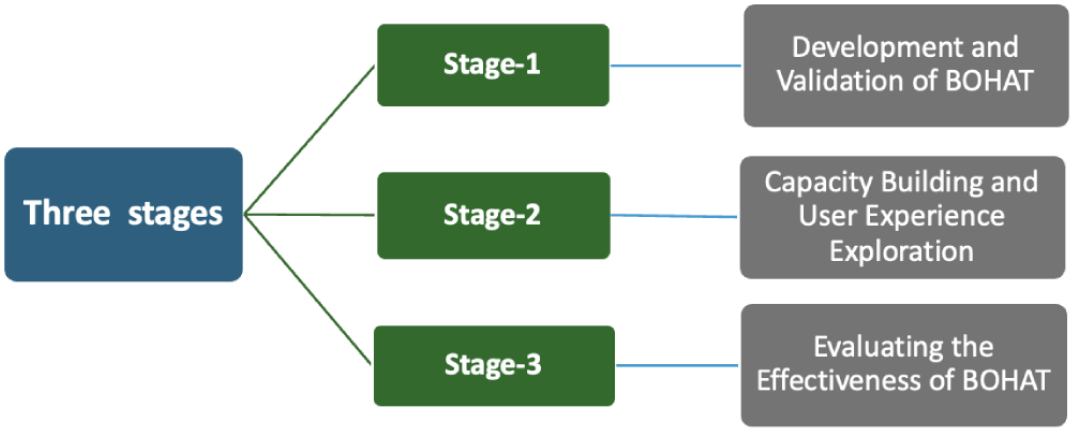
To bridge this gap, this research aims to develop, validate, and implement a Basic Oral Health Assessment Tool (BOHAT) that is tailored for use by nondental health professionals working with populations aged 18 years and older in India. BOHAT will be a screening tool for health professionals who are not dentists, to enable rapid identification of the need to refer patients for dental consultation. This tool will further empower nondental health care professionals to perform effective oral health assessments, thereby addressing an emerging critical need for holistic health care approaches at large. This study will focus on the development, validation, and implementation of BOHAT to improve the oral health assessment capabilities of nondental health care professionals and thus contribute to improved overall health outcomes of the Indian adult population.

Methods

Stages

This study will be a mixed methods, multistage study conducted in 3 stages. Stage 1 focuses on the development and validation of the tool. Stage 2 involves capacity building and user experience exploration, and stage 3 aims to check the effectiveness of BOHAT using a pre-post intervention study (Figure 1).

Figure 1. Multiple stages of the study. BOHAT: Basic Oral Health Assessment Tool.



Study Setting

The study will be carried out in Primary Health Centers (PHCs) located within Mangaluru Taluk of Dakshina Kannada District. This selected study setting will enable insights into the applicability and effectiveness of the developed tool, BOHAT, under Mangaluru Taluk's health care infrastructure. In this approach, oral health assessment practices will be examined more precisely and contextually in relevance to the geographic area selected. PHCs in this region will be the primary sites for data generation, data collection, pilot testing, validation studies, and execution of training programs for nondental health professionals. Approval to conduct the studies in PHCs will be obtained from the District Health Officer, Dakshina Kannada, Karnataka.

Sampling Technique and Sample Size

The sampling technique used in this study is census sampling or complete enumeration, which includes all 708 nondental health care professionals working in the 33 PHCs of Mangalore Taluk. This covers professionals from both urban (10 PHCs) and rural (23 PHCs) areas, ensuring that this target population is widely and appropriately represented.

Nondental health care professionals, including allopathic doctors (physicians and surgeons), AYUSH practitioners, nurses, auxiliary nurses, midwives, and CHWs [7]. Within the urban PHCs, there are 216 nondental health care and allied health care professionals, while the rural PHCs have a workforce of 488 nondental health care and allied health care professionals. The inclusive nature of this study aims to involve all 708 nondental health professionals across all 33 PHCs in Mangalore Taluk who provide their consent for participation.

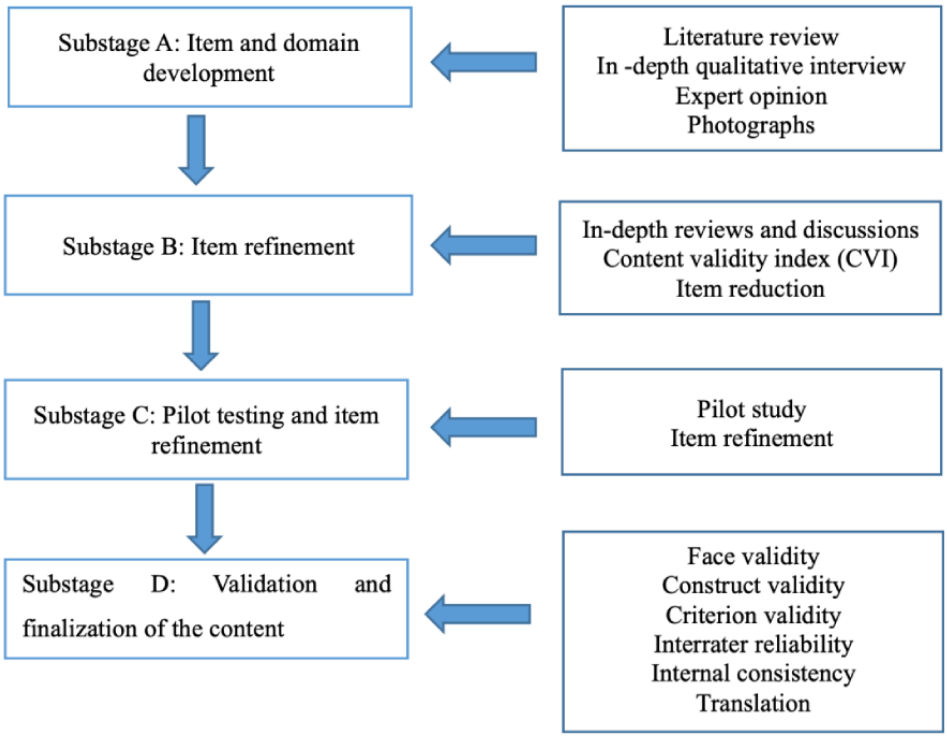
Study Framework

BOHAT will be designed as a paper-based instrument with the inclusion of reference pictures. These reference images serve as visual aids to enhance and facilitate the oral health assessment process**.**

Stage 1: Development and Validation of BOHAT

Stage 1 has 4 substages (Figure 2).

Figure 2. Conceptual framework for the development and validation of the Basic Oral Health Assessment Tool (BOHAT).



Substage A: Item and Domain Development

A literature search will be conducted to obtain data on oral health, oral hygiene, and common dental problems among Indian adult population. An in-depth qualitative interview will be undertaken with nondental health professionals to explore the challenges and complexities inherent in oral health assessment. Additionally, this approach aims to identify key domains that should be incorporated into the BOHAT. Collaboration with oral health care experts from public health dentistry, oral medicine and radiology, oral pathology, oral surgery, periodontics, endodontics, and prosthodontics will identify relevant and essential oral health problems specific to the Indian adult population.

Photographs for BOHAT will be sourced from patients availing of camps organized by the Department of Public Health Dentistry, Manipal College of Dental Sciences, Mangalore. These photographs will cover a vast spectrum of conditions and scenarios pertaining to oral health, thereby presenting a sample of what nondental health professionals might encounter during their assessments. Prior to photographing, proper ethical consent will be obtained from the patients. The photographs will be taken personally by the principal investigator after completing training in intraoral photography. This will help maintain uniformity so that image collection and image capture follow standardized procedures.

The photographic setup for the intraoral photos will include a Canon EOS 90D camera with a Canon EF 100mm f/2.8L Macro IS USM lens. Adequate lighting in the mouth will be provided using a Canon MR-14EX II Macro Ring Lite, which provides lighting without any harsh shadows and gives the best chance of even illumination. The images will have a resolution of 32.5 megapixels and will be saved in both RAW and JPEG formats. This ensures they will provide sufficient detail and can be modified to suit the intended use. The minimum and maximum ISO standards will be set between 100 and 200, aperture will be set at f/22 to ensure enough depth of field, and the shutter speed will be set between 1/125 and 1/200 seconds in order to minimize motion blurs. The custom white balance will be by intraoral light. Each photo will be captured from a distance between 30 cm and 40 cm, and since the ring flash will be used, a fixed distance will be sustained. Each file will be numbered, kept in encrypted digital storage, and secured to ensure data integrity.

Images will be identified and selected by subject matter experts according to the relevance, clarity, and appropriateness of content in relation to the goals of BOHAT. Each image will be critically evaluated to ensure that the wide spectrum of oral health conditions and scenarios that the nondental health care professionals may come across during assessment is captured. This includes ensuring there is sufficient detail and contextual setting in the images for both normal and pathological conditions. Images will further be categorized based on the diagnostic significance, such as specific oral issues like dental caries, periodontal diseases, or mucosa lesions. Selected images will then be further checked for quality assurance to ensure they are educationally valuable, appropriate for educational purposes, and meet ethical standards.

Substage B: Item Refinement and Item Reduction

The items on the BOHAT will undergo rigorous examinations, review, and engagement with the expert panel so that remarks on issues related to clarity, relevance, and appropriateness are captured. Items will also be subjected to systematic refining through discussions of the panels with respect to clarity, relevance, and appropriateness. To evaluate the test's content validity, the content validity index (CVI) will be computed to

measure the relevance of each item. Items with a low CVI (eg, item-level CVI<0.78) will be revised to improve their validity, or only the most relevant items will be retained. There will also be feedback from various stakeholders to enhance the contextual and functional appropriateness of the tool.

Substage C: Pilot Testing and Item Refinement

We will approach 20 nondental practitioners to pilot test the tool for its usability and clarity. This feedback will be used to provide input on the validity and reliability of the tool. Based upon the results of the pilot testing, these improvements will fill in the gaps before formal validation occurs. Descriptive statistics along with qualitative coding of each feedback will be used for initial evaluation of the tool's performance.

Substage D: Measurement Properties and Finalization of the Content

Consensus-Based Standards for the Selection of Health Measurement Instruments Taxonomy

Development and validation will be based on the COSMIN (Consensus-Based Standards for the Selection of Health Measurement Instruments) taxonomy [14]. The COSMIN framework will ensure that this newly developed tool adheres to high methodological standards and permits a rigorous assessment of its primary measurement properties including validity, reliability, and responsiveness.

Validity Testing

For face validity, feedback will be obtained from dental professionals, nondental health professionals, and other stakeholders to establish whether the tool is easy to read, accurate, and relevant. A qualitative assessment will follow, to ensure that the tool is fit for purpose and feasible for end users.

For content validity, content experts will assess the CVI of each item for relevance, clarity, and representativeness. These experts will provide CVI scores as a basis for revision, ensuring objectivity through systematic thresholds, for instance, an item-level CVI≥0.78.

Construct validity of BOHAT will be thoroughly assessed to confirm the extent to which the measure assesses oral health assessment capacity for nondental health care professionals. Exploratory factor analysis will be conducted to determine the underlying structure of the tool by grouping items into the dimensions of knowledge, attitudes, and practices (KAP) of oral health assessments. The appropriateness of the factor structure will be considered with the help of statistical tests such as the Kaiser-Meyer-Olkin test as well as the Bartlett test of sphericity. Confirmatory factor analysis will then validate the identified structure. A root mean square error of approximation ≤0.08 and comparative fit index ≥0.90 will be used to assess fit.

To determine criterion validity, each BOHAT item will be assessed against standardized criteria derived from the World Health Organization (WHO) oral health survey [15]. Each item will be directly mapped to the corresponding items or domains in the WHO oral health survey. For instance, the items measuring dental caries, periodontal health, and oral hygiene status will be benchmarked against the WHO criteria on such conditions. BOHAT and the WHO oral health survey will be administered to the same sample of participants. The sensitivity and specificity parameters will be determined as a statistical measure or estimate of validity for each considered BOHAT item in comparison with the WHO criteria for oral health conditions. Sensitivity and specificity values will show the diagnostic accuracy of the items.

Positive and negative predictive values will provide measures representative of usable or functional utility for each variable under study. Reference variables that form a strong connection with either a positive or negative outcome might be derived from those that create the curves and an area under them in the receiver operating characteristic (ROC) curve using the area under the curve (AUC) as an overall measure of accuracy, such that AUC values ≥0.8 indicate good performance. Items with low sensitivity or specificity will either be reconsidered or removed to obtain the most diagnostically relevant and accurate items.

Reliability Testing

For internal consistency, the Cronbach α will be computed and used as a measure of internal consistency with respect to the degree to which something is being measured as intended. The Cronbach α ranges from 0 to 1. An α near 1 indicates a high internal consistency of the items. Standardization of the scoring criteria for BOHAT, on a consensus basis through collective opinion and expert opinion on subject matter issues, will allow uniformity and objectiveness in assessments.

For interrater reliability, different nondental health professionals will independently use BOHAT with the same patients, and the scores will be checked for their agreement. The ratings proposed by different raters may be statistically analyzed using metrics like the Cohen kappa or the intraclass correlation coefficient (high values [≥0.75] represent excellent agreement).

For test-retest reliability, BOHAT will be evaluated among the same participants at specific intervals to estimate score stability. This will be done using metrics reflecting continuity across time intervals such as intraclass correlations.

Responsiveness of BOHAT

Evaluating the responsiveness of BOHAT will be a vital element in determining the validity of the training for augmenting the oral health assessment skills of nondental health professionals. Differences in scores before and after the training will be assessed using the pre- and posttraining questionnaires as compared with the participants' self-reported changes in confidence and competence of conducting oral health assessments. Focus group feedback will also be analyzed to obtain a sense of perceived skill improvements by participants. Distribution-based methods will be used to evaluate changes in pre- and postintervention scores, including calculation of the effect size (Cohen *d*) to measure the magnitude of change and the standardized response mean to evaluate BOHAT responsiveness to detect clinically meaningful changes. Statistical comparisons of pre- and posttraining scores will be conducted using paired *t* tests or Wilcoxon signed-rank tests. Additionally, minimal clinically important differences will be

determined using ROC curve analysis to interpret thresholds of change in the BOHAT that are considered clinically significant.

Translation of BOHAT

Although BOHAT is primarily in the English language, compliance will ensure proper adaptation of BOHAT for application in Kannada-speaking regions. Adjustments could include providing explanations on linguistic and cultural settings whenever there is a need for clarification. The procedure will likely correspond to the systematic approach provided for the back-translation model by Brislin [16] and comprise the steps outlined in the following sections.

Forward Translation

The test items will be in English; however, key instructions, terms, and technical language will be translated into Kannada by a well-trained bilingual expert who is a native Kannada speaker. This step will provide nondental health care professionals who are comfortable with Kannada the capacity to understand the use and purpose of the tool with ease.

Review by an Expert Team

To ensure cross-cultural equivalence, all translated versions will be reviewed by a multidisciplinary team. A total of 3 oral health experts and nondental health care professionals who have experience with oral health assessments will check the cultural relevance of the terms and concepts with the research team. We will consult 5 nondental health care professionals for practicality and relevance of the tool in the Kannada-speaking health care setting. Any semantic and conceptual changes required will be undertaken based on their feedback, resulting in a first Kannada version of BOHAT.

Back-Translation

A second professional bilingual translator will then back-translate the preliminary Kannada version into English. This translator will be blinded to the original English version to avoid bias.

Comparison and Revisions

The back-translated English version of BOHAT will be compared with the original English version, during which contradictions or deviations will be detected. Revisions will be made when necessary to ensure that the Kannada clarifications correspond to the meaning of the original English version, hence preserving the integrity of the tool items.

Pilot Testing

A refined version of BOHAT in Kannada will be pilot tested with 20 nondental health practitioners in rural and urban PHCs. Each participant will pilot test the tool and provide feedback on items that appear to be unclear or culturally insensitive. The feedback for clarity and utility of additional Kannada content will help determine whether they can understand and use BOHAT properly. The participants will rate each item on a scale from 1 to 5 for relevance, clarity, and specificity. The feedback from this phase will guide further adaptation toward achieving semantic and content equivalence.

The English version will be the final version of BOHAT, supplemented by additional explanatory material in Kannada for users needing language support. This will ensure that the original tool stays in the intended format in English while remaining culturally relevant and accessible to Kannada-speaking health care professionals in the setting.

Stage 2: Capacity Building and User Experience Exploration

Process

The training modules will have details on the purpose of BOHAT, administration procedure, and interpretation of the results. Experts will be given this module, and for content and face validity, they will be invited to classify the need for each question according to a 3-point Likert scale: “necessary,” “useful but unnecessary,” and “unnecessary.” Depending on the experts’ opinion, the content will be modified. The BOHAT training module will adopt a multimodal mode of learning: audio, visual, and audiovisual modes. This will ensure maximum benefits from training sessions so that better understanding and actual application in oral health assessment practices can be achieved.

The module for the training will include how to navigate the tool, interpret the results, and communicate the findings efficiently to patients. Hands-on training sessions will be conducted regarding using the tool. A focus group discussion will be conducted with nondental health professionals to explore the experiences of the participants, challenges faced by them, and perceptions about BOHAT’s usability.

Training Module

This training module is 4 hours long and will be delivered using a combination of audio, visual, and audiovisual aids. The comprehensive training on common problems of oral health among the adult population in India shall draw upon a variety of subjects to provide the necessary background to a health professional. The module will start with an overview of the role of health professionals in disseminating awareness regarding oral health problems and the importance of dental health in relation to overall health. The epidemiology of oral health in India will be presented with data on the most common oral health problems among adults.

The module will consider specific oral health problems often seen in adults. It will cover in-depth the processes of dental caries, periodontal diseases, and tooth sensitivity; the association between tobacco and oral health; potentially malignant disorders and oral cancer; other oral lesions; and the risk factors and lifestyle factors, like diet and lifestyle, affecting oral health. At the same time, emphasis will be placed on early detection and prevention. The module will cover potential solutions to improve access and further incentivize health professionals to incorporate oral health discussions into their practice. The training will be completed with key takeaways underscoring the importance of oral health awareness and preventive measures. An interactive question-and-answer session will be conducted, and participants will have time to share their experiences and discuss special concerns.

Stage 3: Evaluating the Effectiveness of BOHAT

A validated questionnaire will be used by each nondental health professional before the training session to gauge their baseline KAP regarding oral health assessments. The same questionnaire administered after training will help assess the impact and effectiveness of BOHAT on the KAP of nondental health professionals. The scores obtained from the posttest of BOHAT will be compared with benchmarks as observed by dentists. This comparative assessment aims to establish the effectiveness of BOHAT through the tool's degree of conformance with existing standards in dental practice. Retention analysis 3 months after the posttest will evaluate and measure the retained knowledge and acquired skills from the training sessions. Results of the retention analysis will rate how effective the training was when applied and in the long run to help modify or reinforce the practice of oral health assessment.

Statistical Analysis

Chi-square tests will be used to compare the number and percentage of oral health problems detected in a timely manner by nondental health care professionals before and after the training. Referral frequencies before and after training will be used to measure the changes in early referral behavior. Paired *t* tests or Wilcoxon signed-rank tests will be used to analyze any differences found. We will create a reflected quantitative summary of baseline knowledge, and improvement in the KAP of oral health will be evaluated using validated pre- and posttraining questionnaires. Thematic analysis of the qualitative data obtained through the semistructured interviews and focus group discussions will help provide insights into improvements in collaboration with dental and health professionals.

Data from the training assessment and improvements in competence will be analyzed using paired *t* tests, and the reliability of BOHAT will be assessed using the Cronbach α. Referral logs will subsequently be analyzed to gauge increased accessibility to dental care, and trends over time will be evaluated using longitudinal data analysis methods such as linear mixed-effects models. Finally, retention analysis will be conducted 3 months after the training to examine the sustainability of acquired knowledge and skills measured using KAP questionnaires, and time effects will be analyzed using repeated measures ANOVAs.

Ethical Considerations

The Declaration of Helsinki principles will be followed while conducting the research [17]. Ethical approval was sought from the institutional ethics committee of Manipal College of Dental Sciences Mangalore, Manipal Academy of Higher Education (reference number: 24023). Additionally, the Institutional Protocol Approval Committee of the Manipal Academy of Higher Education provided approval for the study (2300400101). Informed consent will need to be provided by every participant after verbal and written information regarding the study is given to them.

All participant data will be anonymized: Names, addresses, or any other forms of unique characteristic directly identifiable in any data collected will be removed from the data set prior to its analysis. In preparation for data coding, all participants will be allocated an ID code that links to personal details using a secure key held separately. For sensitive data that cannot be anonymized, such as qualitative responses or images, access to identifiable data will be strictly limited to authorized research team members. Electronic data shall be stored on secured, encrypted, password-protected devices. Physical records shall be kept in locked cabinets. There shall be no sharing of identifiable data beyond the research team, and the data shall be used only for research.

Participants will not receive monetary compensation for this study, but they will be compensated for any travel costs associated with their involvement in the study. No identifiable characteristics of the participants will be described in the manuscript, supplemental materials, or images.

Results

Study Status

As of January 20, 2025, the study was in the preliminary phase (Substage A: Item and Domain Development). The study will be carried out for a period of 42 months. We have received institutional ethics committee and Institutional Protocol Approval Committee approval for the study. The research team had a meeting with the District Health Officer, Dakshina Kannada District on January 10, 2025, and the study protocol was submitted to the District Health Officer for review. Data collection procedures had not started yet. The study was progressing as per the planned timeline.

Dissemination

This study will be complemented by in-depth qualitative and quantitative analysis. The results of the study will then be presented at relevant scientific conferences and professional meetings as oral presentations and published in academic journals.

Expected Outcomes

The expected outcomes of the study include timely identification of oral health problems and an increase in early referral behavior. This will improve oral health assessments by nondental primary health care providers and oral health KAP of these nondental primary health care providers, leading to enhanced collaboration with dental and other health professionals and improved training and competency. Increased access to dental care is also expected.

Discussion

Overview

Oral health problems can have a significant effect on people's quality of life, interpersonal connections, general well-being, and self-esteem [4]. It is therefore important to address the role of preventive techniques and early diagnosis of oral pathologies in reducing the risk of developing further oral-health-related complications affecting not just oral but also general health. Therefore, oral health assessments are an important part of estimating disease risk, monitoring existing conditions, and improving oral health [5].

The current educational frameworks for these practitioners do not sufficiently cover oral health topics, leading to gaps in knowledge and practice [18]. Health care providers face problems effectively assessing and addressing oral health issues in the population because of a lack of adequate training and inaccessibility of tools specialized for the Indian population.

The Brief Oral Health Status Examination allows carers to monitor the dental health of patients in aged care institutions who are cognitively challenged as well as those who are not. However, the study was conducted in only one nursing home, and the sample size was small [19]. THROAT is another instrument for the oral evaluation of hospitalized older adult patients with medical conditions [6]. OHAT is an assessment tool designed for people with cognitive impairment and is easy to use by nondental staff, such as nurses and caretakers. Nonetheless, OHAT has drawbacks, including nonsignificant and weak correlations and percent agreements for the saliva, oral cleanliness, and dental pain categories [10]. The Oral Health Screening Tool for Nursing Personnel (OHSTNP) evaluates the functioning of the mouth as well as oral health status for inhabitants in long-term care homes. Although the OHSTNP had high specificity for screening the lips, tongue, gums, tissues, saliva, and oral cleanliness, its sensitivity is low, indicating the need for further improvements in these categories [20].

The Minimum Data Set (MDS) is a standardized assessment tool used extensively in long-term care settings that includes an oral health component. Nevertheless, studies have indicated that oral and dental items in the MDS 2.0 lack validity and often underdetect oral health problems among residents of nursing homes [21]. This limitation highlights the importance of developing an instrument like BOHAT, which can both assess oral health conditions with relative accuracy and, most importantly, provide actionable findings for nondental health care workers. The Dental Hygiene Registration (DHR) is a dental hygiene assessment scale suitable for nurses working in institutions [22]. The DHR index requires individual judgment and attendance by a dental professional. The DHR is not an alternative to examinations by dental professionals but an aid for nurses and other caregivers in their daily work [22]. The Oral Assessment Sheet aims to improve the oral health of older adults who require nursing care using 3 items in each of the following 3 categories: oral hygiene, biting and chewing, and oral function [23]. However, challenges concerning its use for oral assessments by care workers have been highlighted [23]. BOHAT seeks to fill these gaps by providing a more credible and valid assessment framework

Within nondental health care settings in India, a critical issue has emerged surrounding the insufficient attention given to oral health due to a lack of adequate training, lack of tools, and underutilization of health care providers for oral care [24]. The role of AYUSH practitioners as nondental health professionals is often underappreciated or even underutilized in the Indian health care setting. Josyula et al [25] pointed out the discrepancies in role perceptions among various health system actors, indicating that AYUSH practitioners are not fully integrated into the public health framework, which limits their ability to effectively contribute to oral health promotion. This lack of integration is echoed in the findings of Kharbanda et al [18], who emphasized that AYUSH professionals, when appropriately empowered with training, can go a long way in promoting oral health. CHWs have a role in addressing oral health issues, but their effectiveness is hindered by poor training and inadequate resources.

According to Najmunnisa et al [26], CHWs can be empowered to serve as oral health literacy workers, but actual knowledge and attitudes toward oral health are often insufficient for promoting preventive behaviors. Reddy and Singh [27] also noted that a comprehensive spectrum of health-promoting behaviors, including oral health, is central to community well-being. The necessity of integrating oral health education in the training of CHWs has thus been demonstrated by these studies, which have shown positive results after CHWs had appropriate structured training [28]. Promotion of oral health by professionals not trained as dentists and by nurses and midwives has also been documented. Villarosa et al [29] discussed how indigenous health workers promote oral health while a woman is pregnant, and their findings suggest that nondental professionals could positively impact maternal oral health. Likewise, only one study conducted by Garry and Boran [30] considered that, to improve the care of older adult patients, enhanced oral health training needs to be incorporated within the nursing curriculum. With a more concrete educational foundation, oral health outcomes could be improved across a variety of demographics.

The challenges that nondental health care providers face in India are not unique to that country. International studies conducted by McGrath et al [31] and Scrine et al [32] showed that health professionals from all disciplines acknowledge their role in oral health, yet they lack the training and resources to effectively develop programs. Therefore, there is a universal demand for cross-disciplinary collaboration and training to ensure that oral health receives adequate emphasis in broader health initiatives.

Insufficient research has been conducted to determine how oral health assessment tools can be integrated into the routine practice of nondental health care professionals. Furthermore, the existing literature does not adequately address the training needs to attain effective tool use among these professionals. Evidence pertaining to the validation of the oral health assessment tools in varying clinical scenarios and patient populations is also lacking. Finally, there is a lack of literature investigating the effectiveness of enhanced oral health assessments on overall patient outcomes and preventive care. These gaps in research provide the rationale for the development and validation of BOHAT to fill these gaps with a culturally appropriate tool that can be efficiently used by nondental health care professionals in India.

Beyond dentistry, oral health is important for general well-being and good health [33]. Unfortunately, the absence of specialized instrumentation for nondental health care providers often creates a barrier to early detection and treatment of oral health diseases. This calls for a comprehensive and easy-to-use instrument; hence, the need exists for BOHAT. It allows nondental health care professionals to conduct effective oral health assessments, thus addressing the need for holistic approaches to health care.

Challenges and Solutions

A major challenge can be a lack of awareness of the importance of oral health care among nondental health professionals. There is a need to conduct an awareness drive with campaigns aimed at professional groups and the community. Conducting a media campaign on television, radio, print media, and social media regarding the importance of oral health and its interlinkage with general health will be very useful. Another challenge is resources and funding. A possible solution for this challenge can be the exploration of grants aimed at health care innovations and public health improvements. Integration into current health care systems presents yet another possible obstacle. Integration issues can be identified and dealt with by working closely with health care administrators to ensure the integration of BOHAT into existing workflows, developing clear protocols and guidelines on implementation, then piloting the program in a few centers prior to a wider area. There can be difficulties relating to the collection and management of data. These may be overcome by ensuring strong systems for data management and error-free and effective data collection, training health professionals in data entry and management, and digitizing tools for data collection and analyses. For its sustainability, this program will require a long-term sustainability plan that includes periodic training and follow-up support for health professionals. A monitoring and evaluation framework should also be developed to check the program's impact, make necessary adjustments, and create community ownership and involvement to help sustain interest and participation.

Strengths of the Study

The BOHAT study fosters holistic health care that is interdisciplinary in nature by its inclusion of nondental health care professionals, therefore providing the basis for oral health to become part of general health assessments. It builds the capacity of nondental health professionals with training and education for better health outputs. This study aims to enhance the capacity of nondental health professionals in relation to the identification and referral of oral health conditions and increase access to dental care, particularly in underserved areas. This way, early identification and intervention will help prevent the progression of these oral diseases and reduce the health care system burden—improving the quality of life of patients. The research conducted here contributes to many sustainable development goals (SDGs) that pertain to good health, quality education, reduced inequalities, and effective partnerships.

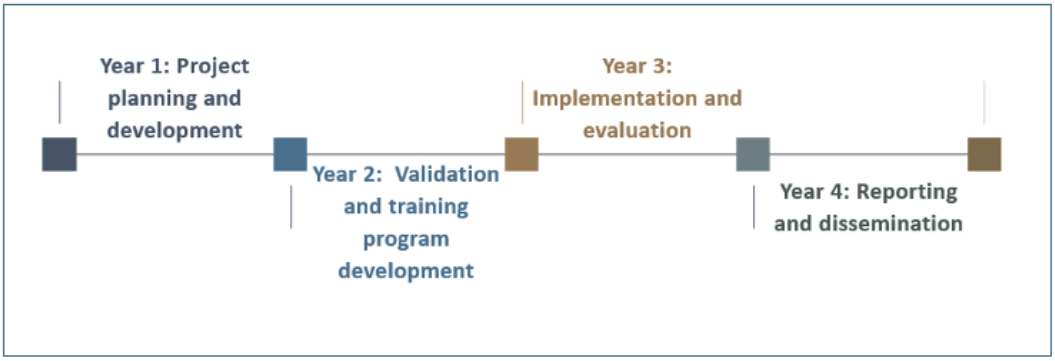
Link to SDGs

Oral health assessments are crucial for identifying problems early and preventing more severe oral and general health conditions [34]. Therefore, BOHAT is linked with many SDGs. BOHAT will support the attainment of several health and well-being SDGs. It will help support SDG 3: "Good health and well-being" by providing a systematic approach for performing oral health assessments [35]. It will help with the early diagnosis and prevention of oral diseases by building the capacity of nondental health professionals, hence promoting health and well-being. This study aligns with SDG 4: "Quality education" by training nondental health care professionals on the use of BOHAT and promoting continued education and capacity building, ensuring that health care professionals have the proper skills to manage oral health [36]. The study will help reduce inequalities in oral health, working in concert with SDG 10: "Reduced inequalities" [37]. Hence, it will reduce health disparities in oral health outcomes but ensure equitable access to quality health care. This will add depth to the exploration of oral health practices within a specified region, like Mangaluru Taluk, and establish ways to reduce health inequalities. Thus, working with the main stakeholders—nondental health professionals, PHCs, and people within the community—shall further stress the importance of partnership in line with SDG 17: "Partnership for goals" [38]. This will help underscore the indispensability of collaborative efforts in securing SDGs.

Research Timeline

Figure 3 shows the research timeline for the proposed study including the order of the main activities and the study milestones over time. The developed timeline spans a duration of 42 months, making sure that each of the stages of implementing such a research project takes place in a highly systematic, organized, and timely manner, making it easy to adapt to changes and solve eventual problems.

Figure 3. Research timeline.



Conclusion

The BOHAT study holds considerable potential for promoting oral health care through collaborative and interdisciplinary approaches. It will facilitate early diagnosis, timely referrals, and comprehensive care by integrating assessment actions for oral health into routine practice by nondental primary health care professionals. This work is a large step toward the

integration of oral health into general health care, by emphasizing general health and well-being and the reduction of health disparities. This study can, therefore, serve as a model for similar efforts elsewhere in the world and help to ensure good oral health outcomes and excellent quality of life for diverse populations.

Acknowledgments

The authors extend their appreciation to Prince Sattam bin Abdulaziz University for funding this research work through project number PSAU/2024/01/922576.

Conflicts of Interest

None declared.

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Abbreviations

AUC: area under the curve
AYUSH: Ayurveda, yoga, naturopathy, Unani, Siddha, and homeopathy
BOHAT: Basic Oral Health Assessment Tool
CHW: community health worker
COSMIN: Consensus-Based Standards for the Selection of Health Measurement Instruments
CVI: content validity index
DHR: Dental Hygiene Registration
KAP: knowledge, attitude, and practice
MDS: Minimum Data Set
OHAT: Oral Health Assessment Tool
OHSTNP: Oral Health Screening Tool for Nursing Personnel
PHC: Primary Health Center
SDG: sustainable development goal
THROAT: the Holistic Reliable Oral Assessment Tool
WHO: World Health Organization

Edited by A Schwartz, GRM La Rosa; submitted 21.06.24; peer-reviewed by S Anitasari, A Pai; comments to author 18.11.24; revised version received 01.01.25; accepted 04.01.25; published 13.02.25.

Please cite as:
Basheer N A, Jodalli P, Shetty S, Shenoy R, Rao A, Pai M, Gowdar IM, Almalki SA
Development and Validation of the "Basic Oral Health Assessment Tool" (BOHAT) for Nondental Health Care Professionals to Use With the Indian Adult Population: Protocol for a Mixed Methods Study
JMIR Res Protoc 2025;14:e63480
URL: https://www.researchprotocols.org/2025/1/e63480
doi:10.2196/63480
PMID:

Protocol

Assessing Preparedness for Self-Management of Oral Anticoagulation in Adults With the PERSONAE Scale: Protocol for a Development and Validation Study

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Abstract

Background: Optimal anticoagulation using vitamin K antagonists prevents strokes associated with atrial fibrillation and heart valve replacements. Preparedness for self-monitoring and self-management could improve outcomes, but this remains a challenge.

Objective: This study aimed to outline the methodology for developing and validating the PERSONAE scale, a self-report measure designed to assess the preparedness for self-monitoring and self-management of oral anticoagulation in adult patients.

Methods: This study comprises 2 main phases, and it adheres to the "COnsensus-based Standards for the selection of health Measurement INstruments" (COSMIN) guidelines for instrument development. The first phase involved the conceptualization of the PERSONAE scale, where a comprehensive literature review and a consensus meeting among experts were conducted to draft the initial items. Face and content validity were then established through an expert panel review. In the second phase (ongoing), a detailed sampling methodology will be used, targeting adult Italian patients on long-term oral anticoagulation. According to a performed simulation-based power analysis, the study aims to recruit a sample size of approximately 500 participants by using a combination of convenience and snowball sampling. Data collection will be facilitated through web-based surveys distributed through social media and patient networks, ensuring a wide and representative sample. Analytical procedures will include Mokken scaling analysis for item selection and confirmatory factor analysis to validate the scale's structure. In addition, internal consistency will be assessed using Molenaar Sijtsma statistics.

Results: The scale's content derived from phase 1 (process completed in December 2023) is grounded in a comprehensive literature review and based on the assessments of a panel of 12 health care expert professionals. The PERSONAE scale derived from phase 1 encompasses 20 items reflecting essential behaviors needed to assess the preparedness for self-monitoring and self-management of oral anticoagulation. Each item obtained a content validity ratio higher than 0.67, which is the critical content validity ratio indicating the minimum level of agreement among the experts for an item to be considered essential beyond the level of chance at a significance level of .05 for a 1-tailed test. From January 2024 to May 2024, we conducted the initial round of data collection and use Mokken scaling analysis to select items. A second round of data collection for confirmatory factor analysis was scheduled from June 2024 to September 2024, which will validate the scale's unidimensional structure. We expect to achieve robust psychometric properties, including high internal consistency and validated constructs.

Conclusions: The PERSONAE scale will be a valuable tool to assess patients' preparedness for self-monitoring and self-management of oral anticoagulation. The study's insights into technology-assisted learning preferences will inform the design of future educational interventions to enhance preparedness in adult patients.

Trial Registration: ClinicalTrials.gov NCT05973240; https://clinicaltrials.gov/study/NCT05973240

International Registered Report Identifier (IRRID): PRR1-10.2196/51502

(JMIR Res Protoc 2025;14:e51502) doi:10.2196/51502

KEYWORDS

self-monitoring; self-management; oral anticoagulation; vitamin K antagonists; preparedness; validation

Introduction

Vitamin K antagonists (VKAs), such as warfarin, are a group of medicines used to thin the blood, preventing the formation of harmful blood clots that can lead to stroke [1]. They function by inhibiting Vitamin K-dependent coagulation factors, which are essential for blood clotting. This class of medications is particularly vital for reducing the risk of stroke associated with atrial fibrillation and heart valve replacements, especially when direct oral anticoagulants are unsuitable for certain individuals, such as adults with multiple morbidities [1]. The use of oral anticoagulants globally is on the rise, reflecting an increasing need to manage conditions predisposing individuals to increased thromboembolic risks. Currently, about 2 out of every 100 Italians are on oral anticoagulants [2], including both direct and indirect agents [3]. This increasing prevalence underscores the necessity for regular monitoring of prothrombin time and appropriate dose adjustments, as inadequate monitoring and dose management could lead to serious adverse reactions and complications. Several studies have highlighted the risks associated with insufficient monitoring in the last 2 decades [4,5]. For instance, it was highlighted that patients on warfarin who did not have their prothrombin time regularly monitored were at a higher risk of major bleeding complications [4]. A meta-analysis published in 2020 confirmed that with the rising number of patients on oral anticoagulants, there is a proportional increase in adverse events related to inadequate monitoring [5].

People on long-term oral anticoagulation can use point-of-care testing equipment (POCT) to monitor their blood clotting time, typically measured by the international normalized ratio (INR) [6]. In managing their anticoagulant medication, these individuals have 2 primary options: self-management, where they adjust their medication dosage based on a predetermined dose-INR schedule, allowing them greater autonomy and immediate response to INR readings, or self-monitoring, where they measure their INR levels independently but consult health care providers to make dosage adjustments [7]. This distinction is crucial as self-management empowers patients to take full control of their therapy, potentially improving their adherence and outcomes, while self-monitoring still relies on professional guidance for dose adjustments [8,9].

Numerous studies and systematic reviews have demonstrated that these self-testing approaches are equally effective, if not superior, to routine physician-managed anticoagulation monitoring, providing evidence that patient-led monitoring can enhance therapy management and patient satisfaction [8,9]. For instance, a systematic review reported that patients who self-managed their oral anticoagulation therapy had significantly better control over their INR levels and fewer thromboembolic events than those who relied on professional monitoring [10]. In this context, a solid randomized controlled trial found that self-management was associated with higher patient satisfaction and better quality of life due to increased control over their health [11]. However, the choice between self-management, self-monitoring, and physician-managed care should be individualized based on patient characteristics. Recent researches highlight that health-related quality of life in anticoagulated patients varies significantly, indicating how some patients may benefit more from self-management while others may find self-monitoring or physician-managed care more suitable [9,12,13]. In addition, the quality of anticoagulation control, traditionally assessed by the time in the therapeutic range (%TTR), is enhanced by using recommended coagulometers like CoaguChek XS, which are globally endorsed, particularly in response to the COVID-19 pandemic [14,15].

While self-monitoring and self-management approaches have garnered strong evidence for their effectiveness and cost-effectiveness, a Cochrane review highlighted the need for further research into factors influencing individuals' preparedness for self-testing [8]. These factors include both psychological preparedness and preparedness in terms of objective equipment. Psychological preparedness encompasses patients' self-management knowledge, motivations for medical attention, health literacy, self-efficacy, and perceived and actual support systems [13,16]. Specifically, patients' knowledge about self-management affects their ability to understand and manage their treatment, while motivations for seeking medical attention could influence their commitment to regular monitoring. Health literacy impacts their ability to comprehend medical instructions and make informed decisions, and self-efficacy relates to their confidence in performing self-testing tasks [17]. Finally, perceived and actual support systems are crucial in providing the necessary resources and emotional support for effective self-management. Preparedness in terms of objective equipment involves access to and familiarity with POCT devices and other necessary tools. Evaluating preparedness for self-management and self-monitoring is therefore crucial in tailoring health care delivery, enhancing efficiency, and adequately preparing patients for self-testing [18]. The interaction between psychological preparedness and preparedness regarding objective equipment is critical. Patients who are psychologically ready but lack the necessary equipment, or vice versa, may not effectively self-manage their condition. Therefore, both aspects must be

addressed to ensure successful self-management and self-monitoring.

In Italy, for instance, adopting self-testing is complicated by organizational and professional barriers, such as the cost of POCT devices and concerns regarding the loss of direct control over treatment management [12]. Addressing this gap is essential, as enhancing patient preparedness through targeted interventions could substantially improve the effectiveness and patient outcomes of self-management programs, ultimately transforming anticoagulation therapy practices globally. The PERSONAE scale specifically addresses these gaps by assessing domains of preparedness and providing its comprehensive measure for self-management and self-monitoring. Thus far, no measures of the preparedness for self-monitoring and self-management exist in relation to this population. Therefore, the aim of this protocol is to outline the methodological steps for the development and validation of the PERSONAE scale, a self-report measure intended to assess the preparedness for self-monitoring and self-management of oral anticoagulation in adult patients. The study is currently focused on the Italian adult patient population, carefully considering the scalability and adaptability of the PERSONAE scale for diverse age groups and international settings. In addition, it aims to pinpoint the most favored technology-assisted learning options among patients undergoing anticoagulation therapy. The PERSONAE scale is expected to improve existing self-management protocols and practices by identifying areas where patients may need additional support or resources after a detailed assessment of patient preparedness. The findings from this pioneering research will lay the groundwork for innovative technology-assisted educational programs designed specifically to boost preparedness for self-monitoring and self-management of oral anticoagulation, marking a significant advancement in patient-centered health care solutions.

Methods

Study Design

This methodological, multiphase study comprises 2 main phases to develop and validate the PERSONAE scale for assessing the preparedness for self-monitoring and self-management of oral anticoagulation in adult patients. The protocol adheres to the "COnsensus-based Standards for the selection of health Measurement INstruments" (COSMIN) guidelines for instrument development [19].

Phase 1 focused on conceptualizing the PERSONAE scale through a developmental methodological approach involving 3 primary steps. First, a literature review was conducted to identify all relevant elements related to the preparedness for self-monitoring and self-management of oral anticoagulation (anticipated between May 2023 and July 2023). This review was recently published elsewhere [13]. Second, a consensus meeting among developers was held to examine the findings of the literature review and endorse its synthesis (anticipated time: September 2023). Finally, the situations representing patients' preparedness will be operationalized, and an external panel of experts, including nurses, physicians, and pharmacists, will determine the face and content validity of the newly developed scale (anticipated time: October 2023). Phase 2 focused on the validation procedures. Initially, the PERSONAE scale, containing items with acceptable content validity, was used for cross-sectional data collection from January to May 2024. The Mokken scaling analysis (MSA) procedure will be used to assess how the items in the first version of the scale behave in response to varying levels of the theoretical latent trait (preparedness). MSA is preferred over exploratory factor analysis in this study as it allows selecting items with the highest scalability, leading to a brief, unidimensional measure computed in a single score. Once a stable unidimensional PERSONAE scale is developed, a second round of cross-sectional data collection was performed from June to September 2024 to cross-validate the plausible unidimensional structure of the scale.

Participants and Procedures

In phase 1, a panel of 8-12 experts, comprising nurses, physicians, and pharmacists, evaluated the relevance and clarity of the proposed items derived from the literature review (content validity). The experts provided written consent to use their sociodemographic and professional characteristics for scientific reporting, as content validity is closely linked to the characteristics of the involved experts. This phase cannot be anonymous to ensure transparency, and variables such as sex, age, academic title, experience in studies testing content validity, and experience in oral anticoagulation were collected.

Once adequate content validity was established (December 2023), data collection commenced at the IRCCS (Istituto di Ricovero e Cura a Carattere Scientifico [Institute for Research and Healthcare]) Policlinico San Donato, using 2 cross-sectional data collection rounds using web surveys. A convenience sampling procedure was used, disseminating the web surveys through social media campaigns, newsletters, and flyers of associations involving anticoagulated patients, such as "Associazione Italiana Cardiopatici Congeniti" (AICCA). Participants for the second round were selected based on the same approach, with communication to prevent overlapping responses from participants who completed the survey.

Quality control measures have been implemented to ensure the integrity and quality of the data collection process: automatic data validation checks are included in the survey software to ensure that all responses are complete and adhere to the required format; unique identifiers were used for each participant to prevent duplicate responses in the dataset; and after data collection, statistical analyses were performed to identify any outliers or inconsistencies in the responses, which were then reviewed for accuracy.

Sampling Procedure

The sampling procedure will use a cloud-data recording system and web surveys disseminated through social media campaigns, newsletters, and flyers. The local study coordinator and the principal investigator will manage the sampling procedure following good clinical practice principles. An expected response rate of approximately 60% is anticipated, which is considered adequate [20]. This expectation is based on several considerations, including using targeted engagement strategies such as precontacting potential participants and leveraging

multiple dissemination channels. In fact, this rate aligns with the upper bound of the confidence interval from a recent meta-analysis, which reported an average response rate of 44.1% across 1071 studies in educational research [20]. Studies achieving similar response rates are those that have successfully implemented strategies to engage participants actively.

Sample Size

The sample size for phase 1 will be 8-12 experts. The sample size required for phase 2 to perform the Mokken scaling analysis was determined considering the 20 items derived from phase 1 (content validity phase). A simulation-based power analysis was performed in R (R Foundation for Statistical Computing; library "Mokken"), as shown in Multimedia Appendix 1. The aim of the simulation was to estimate a sample size that would provide sufficient statistical power, set at 0.8, to detect a minimum H coefficient of 0.3, indicative of a moderate scale according to Mokken's hierarchy. The H coefficient in Mokken scaling analysis measures the strength of the hierarchical relationship among items in a scale as it quantifies the extent to which items form a cumulative scale. A custom simulation function was created using R statistical software, with the following parameters defined: 20 items, initial sample (n= 200), number of simulations=100, desired power=80%, minimum H coefficient=0.3, and maximum number of iterations=30. For each simulation iteration, the function generated a matrix of binary data representing responses to the 20 items, with responses simulated under a simple random model (ie, the probability of success was 0.5 for each item). The results from the simulation suggested that a sample size of 500 patients would be needed to achieve the desired power of 0.8 for our MSA. The MSA procedure will help reduce the number of items to the first 10-15 items that define the preparedness for self-monitoring and self-management of oral anticoagulation in adult patients. The required sample size for the second round of data collection will be determined through Monte Carlo simulations, aiming to achieve a power of 0.8 for the confirmatory factor analysis (CFA) model.

Eligibility Criteria

In phase 1, experts must have at least 1 year of experience in managing patients with VKAs, hold at least a master's degree in nursing, pharmacy, or an MD degree, and have proficiency in the Italian language. Exclusion criteria for experts include conflicts of interest regarding the topic. In phase 2, patients aged 18 years and older will be included under oral anticoagulation treatment in an anticoagulation clinic for at least 3 months, with appropriate cognitive functioning and the ability to provide informed consent. Patients will be excluded based on more specific criteria to ensure the homogeneity and reliability of our data: those with a high Charlson Comorbidity Index (CCI>4), indicating severe concurrent medical conditions that could confound the study outcomes; patients undergoing any other experimental treatment affecting coagulation; and those with a history of noncompliance with medical regimens as reported by their health care providers.

Study Procedures for Cross-Sectional Data Collections

Patients who agree to participate will access a web-based survey (SurveyMonkey) through social media channels, mobile messages, or emails. The invitation will include all relevant information about the study's aim, methods, and tasks required for participation. Patients will confirm the inclusion and exclusion criteria during the initial access, and those who do not meet the criteria can opt out.

The data collection tools will include the PERSONAE scale derived from the content validity phase, a sociodemographic and clinical data form, and a graphic rating scale for assessing patients' preferences for technology-assisted learning options. Sociodemographic data will include age, sex, marital status, educational level, and occupation, while clinical variables will encompass time in oral anticoagulation, clinical indication for anticoagulation, %TTR, and history of thromboembolic or bleeding complications in the last 3 months. These clinical variables are consistent with previous research, such as the studies that developed measures of knowledge in the same population [21,22], which examined similar sociodemographic and clinical factors to assess anticoagulation knowledge in the Italian population. This alignment ensures that our data collection is grounded in established theoretical frameworks and allows authors to generate hypotheses relevant to our target population.

Data Analysis

The data analysis will involve the use of various statistical methods to develop and validate the PERSONAE scale.

For the first data collection round, MSA will be conducted using the "mokken" package in R [23]. MSA allows for the hierarchical evaluation of items, and the most relevant items that measure preparedness for self-monitoring and self-management of oral anticoagulation will be selected for the PERSONAE scale [24]. Loevinger's coefficient of homogeneity function will be used to assess the scalability of the items. Monotonicity violations will be checked, and violations below 80 will be consistent with the requirements of a Mokken scale [23,25]. Loevinger's coefficients of homogeneity (H) at the scale, item, and pairs of items level will be computed, where H values equal to or greater than 0.3, 0.4, or 0.5 indicate weak, moderate, or strong scales, respectively [23,25]. Item pairs violating monotonicity will be excluded, and floor and ceiling effects in data distribution will be assessed. Invariant item ordering (IIO) will be performed to further narrow down the pool of questions based on monotone homogeneity [25]. The IIO procedure will remove items one at a time until no significant violations are found. The Htrans (H^T) coefficient will express the accuracy of the IIO selection, and H^T>0.3 will denote proper IIO process and consistent Mokken scales. The final set of questions will be used to calculate ρ coefficients for reliability using the Molenaar-Sijtsma technique [26]. This approach is particularly adequate for assessing reliability in MSA because it provides a robust estimate of the internal consistency for nonparametric scales. The Molenaar-Sijtsma technique is well-suited for evaluating the scalability and reliability of the items within the scale, ensuring that the

PERSONAE scale reliably measures the construct of preparedness for self-monitoring and self-management of oral anticoagulation.

CFA will be used to cross-validate the plausible unidimensional structure of the PERSONAE scale derived from the MSA, theoretically containing 10-15 items, using Mplus 8.1 (Muthén and Muthén, 2017). An unrestricted and unspecified model will be used with a maximum likelihood robust estimation of parameters. A confirmatory factor analysis with covariates will be used to estimate measurement invariance between subgroups if linear relationships between participant characteristics and the scale's total score are detected [27]. Modification indices will be explored to identify items causing a violation of invariance. Items causing invariance will be evaluated for possible deletion from the final scale. The adequacy of confirmatory factor analyses in explaining sample statistics will be assessed using various fit indices, such as chi-square, chi-square/degree of freedom, comparative fit index, Tucker-Lewis index, and root mean square error of approximation [28]. Invariance testing based on different levels of CCI and other potential confounders will be considered if needed and is feasible to ensure that the scale functions equivalently across groups with varying levels of comorbidity and demographics.

Missing data will be managed using an available-case approach for missingness lower than 5% or regression imputations for missingness equal to or higher than 5%, assuming missing at random. The significance level for all analyses will be set at 5%. The software used for the analysis will include Mplus (version 8.1, Muthén and Muthén), IBM SPSS Statistics for Microsoft Windows version 27, and R (version 4.2.1, R Foundation for Statistical Computing).

Ethical Considerations

The present protocol was approved by the Ethical Committee of Ospedale San Raffaele (protocol number 52/INT/2023). Ethical considerations will be carefully adhered to throughout the research process.

In the first stage of the study, which involves experts assessing the content validity [29,30], written informed consent will be obtained from each expert. They will be fully informed about the study's objectives and their voluntary participation in the process. During the second part of the study, data collection will be carried out through anonymous web surveys. As per European Regulation 2016/679 and Legislative Decree 101/2018, this type of study ensures anonymity and does not require individual written informed consent from the participants [31]. However, to ensure transparency and participant understanding, a simple and clear presentation page will be provided to patients before they proceed to complete the web-based questionnaire. This page will explain the study's purpose, the voluntary nature of their participation, and the anonymity of the survey.

The research team will prioritize the confidentiality and privacy of all participants involved in the study, adhering to the ethical principles outlined in the Declaration of Helsinki. Personal data will be handled with utmost care, and all data collected will be stored securely and accessible only to authorized personnel involved in the study. Any potentially identifying information will be removed from the dataset to ensure complete anonymity. Throughout the study, participants' rights and welfare will be protected, and any potential risks will be minimized. The study findings will be reported and disseminated in a manner that preserves anonymity and confidentiality. Researchers will act responsibly, maintaining the highest ethical standards and ensuring that the study is conducted with integrity and respect for the participants' rights and well-being.

Results

The PERSONAE scale development and validation protocol has been fully funded by the "Fondazione Insieme per Vita agli Anni" with additional support from the Ricerca Corrente funding by the Italian Ministry of Health in 2023 (no specific grant number). The summary of the results is shown in Textbox 1.

Textbox 1. Results summarized per main categories.

Conceptual framework

- Defined by the literature summarized in a literature review published elsewhere, describing self-care behaviors in patients on oral anticoagulant therapy [13].

Focus of PERSONAE measure

- Assess how ready patients feel about undertaking and managing the tasks associated with their anticoagulation therapy by translating the behavioral content identified in the review into terms of preparedness (refer to Multimedia Appendix 1).

Item pool drafting

- November 2023

Expert panel for validation

- Date of content validation: December 2023.
- Median age: 36 (IQR 29-45) years.
- Education qualifications: 25% (n=3) with a master of science, 25% (n=3) with a doctor of philosophy, and 50% (n=6) medical doctors.
- Specialties: 16.67% (n=2) in cardiology, 50% (n=6) in nursing, 16.67% (n=2) in pharmacy, and 16.67% (n=2) in internal medicine.
- Experience: All experts with more than 6 years in oral anticoagulation.
- Sex distribution: 66.67% (n=8) females.
- Conflict of interest: None reported (100%, n=12).
- Content: 50% (n=6) in nursing, 16.67% (n=2) in pharmacy, and 16.67% (n=2) in internal medicine.
- Experience: all experts with more than 6 years in oral anticoagulation.
- Sex distribution: 66.67% (n=8) females.
- Conflict of interest: none reported (100%, n=12).
- Content validity ratio (CVR): All 20 items obtained adequate CVR (refer to Multimedia Appendix 1 for additional details).

Scale question

- “How prepared do you feel to independently monitor and manage your oral anticoagulation therapy for each of the following statements?”

Rating scale

- A 5-point Likert scale ranging from 1 (not at all prepared) to 5 (extremely prepared).

Data collection for phase 2

- Ongoing, anticipated completion by September 2024.

Impact of PERSONAE scale

- The PERSONAE scale will offer a comprehensive and validated tool to assess the preparedness of patients for self-monitoring and self-management of oral anticoagulation, aiding clinicians in tailoring interventions. Health care providers can empower patients to take an active role in their anticoagulation therapy, potentially improving treatment outcomes and reducing health care costs by encouraging safe and effective practices of self-monitoring and self-management.

Dissemination of results

- Upon successful validation, the results will be disseminated through peer-reviewed publications and presentations at international conferences. The research team plans to engage with professional societies and patient advocacy groups to promote the implementation of the PERSONAE scale in clinical practice globally.

The conceptual framework was defined by the literature summarized in a literature review published elsewhere, describing self-care behaviors in patients on oral anticoagulant therapy [13]. The focus on preparedness encapsulates the ability to perform specific self-care tasks and integrates the confidence and knowledge necessary to manage treatment proactively. In other terms, the version of the PERSONAE measure derived from phase 1 aims to assess how ready patients feel about undertaking and managing the tasks associated with their anticoagulation therapy by translating the behavioral content

identified in the review into terms of preparedness (Multimedia Appendix 1). Once the pool of items was drafted (November 2023), an expert panel for validating the PERSONAE scale was involved, and it consisted of 12 professionals with diverse qualifications and backgrounds in health care. The process of content validation was performed in December 2023. The median age of the experts was 36 (IQR 29-45) years. Regarding higher education qualifications, 25% (3/12) held a master of science degree, another 25% (3/12) had earned a doctor of philosophy degree, and the remaining 50% (6/12) were medical doctors. Expertise among the panel members varied, with representation from multiple disciplines critical to managing oral anticoagulation therapy. Specifically, 16.67% (2/12) specialized in cardiology, the majority, 50.00% (6/12), were from nursing, 16.67% (2/12) practiced pharmacy, and 16.67% (2/12) were from internal medicine. When considering potential conflicts of interest, it was noted that 100% (12/12) of the experts reported none. All experts had substantial experience with oral anticoagulation, with each member having more than 6 years of experience in the field, which provided a solid foundation for their evaluative contributions. Regarding sex distribution, the panel was predominantly female, with 66.67% (8/12) of the members being women. All content validity ratio (CVR) of the 20 items obtained adequate content validity based on the evaluation of the experts (Multimedia Appendix 1; all observed CVR were equal or higher to the critical CVR, indicating the minimum level of agreement among the experts for an item to be considered essential beyond the level of chance at a significance level of .05 for a 1-tailed test).

The question guiding the self-report assessments derived from phase 1 is: “How prepared do you feel to independently monitor and manage your oral anticoagulation therapy for each of the following statements?” Therefore, the scale is designed for the patients. In the current form of the scale, patients are asked to rate their level of preparedness on a 5-point Likert scale ranging from 1 (not at all prepared) to 5 (extremely prepared). Therefore, the scale prompts patients to consider their proficiency across a spectrum of 20 activities (items) vital to the effective self-management of their treatment, from medication adherence to lifestyle adjustments and the use of technology.

The data collection for phase 2 is ongoing, and it is anticipated to be completed in September 2024. The PERSONAE scale will fill a critical gap by offering a comprehensive and validated tool to assess the preparedness of patients for self-monitoring and self-management of oral anticoagulation. Clinicians will be able to use this scale to identify patients who may benefit from self-testing approaches and tailor interventions accordingly. Health care providers can empower patients to take an active role in their anticoagulation therapy, potentially improving treatment outcomes and reducing health care costs by encouraging safe and effective practices of self-monitoring and self-management.

Upon successful validation, the results will be disseminated through peer-reviewed publications and presentations at international conferences. The research team plans to engage with professional societies and patient advocacy groups to promote the implementation of the PERSONAE scale in clinical practice globally.

Discussion

Principal Findings

This study outlines a methodological approach to developing and validating the PERSONAE scale, a self-report measure aimed at assessing the preparedness for self-monitoring and self-management of oral anticoagulation in adult patients. This novel scale aims to help health care providers discern patients’ preparedness for autonomous oral anticoagulation management, potentially leading to customized treatment strategies that enhance patient independence and treatment adherence. High scorers on the PERSONAE scale might be suitable for self-testing and adjusting their medication. At the same time, those with lower scores could benefit from targeted educational programs to improve their management capabilities, pending further research to establish specific scale cutoffs for optimal outcomes. It is important to note that the practical application of this scale and its cutoff points require empirical testing in future research to assess criterion validity and establish effective thresholds for different patient outcomes.

Phase 1 of the research protocol, based on a developmental methodological approach, was based on a literature review [13], followed by a consensus meeting among developers who have operationalized the literature into 20 measurable items of preparedness, leading to the initial version of the scale as per previous research focused on developing new self-report measures [32,33]. An expert panel consisting of 12 professionals from diverse health care disciplines (cardiology, nursing, pharmacy, and internal medicine) validated the content of the PERSONAE scale in December 2023. The experts, who brought a wealth of experience from their respective fields, ensured that the scale’s content was relevant and applicable to various professionals involved in anticoagulation management. This multidisciplinary approach enriched the scale’s content validity, ensuring comprehensive coverage of the necessary competencies for effective self-management. This phase was instrumental in creating a scale that is scientifically sound and clinically meaningful. This initial phase set a solid foundation for the subsequent validation phase, aiming to confirm that the scale accurately measures preparedness in a way that is predictive of patients’ ability to manage their anticoagulation therapy effectively.

In phase 2, validation procedures will be conducted to ensure the reliability and validity of the scale, and it is anticipated to end in September 2024. This process will require 2 cross-sectional data collections among Italian adult patients currently undergoing oral anticoagulation treatment. The collected data will be used to assess the scale’s psychometric properties and determine its performance in measuring preparedness for self-monitoring and self-management of oral anticoagulation [34]. More precisely, the first cross-sectional data collection will provide the needed power to perform the MSA procedure and determine item behavior in response to varying levels of the theoretical latent trait (preparedness) [35]. The second data collection will be based on the version of the scale updated from the analytics of the first data collection, and a CFA will be used to cross-validate the unidimensional

structure of the PERSONAE scale. Cross-validation helps assess the generalizability of the scale's results and allows researchers to determine if the validity holds true beyond the initial sample used for scale development [36].

Limitations

Several limitations should be acknowledged. First, the sample size for the validation phase was based on a power-based simulation and Monte Carlo simulations, which may have inherent assumptions that could affect generalizability. Expanding future studies to include larger and more diverse populations could enhance the scale's validity across varied demographics and age groups. Second, the use of web surveys for data collection may introduce response biases, particularly biases associated with self-reporting, such as recall bias and social desirability bias. Although measures such as ensuring participant anonymity and confidentiality are planned to mitigate these issues, the influence of these biases cannot be entirely eliminated. In addition, further exploration into potential sources of bias, including sampling biases due to nonrandom selection methods and the impact of the data collection medium on participant engagement and accuracy, is necessary. Limitations stemming from the analysis methods, such as potential confounding factors not accounted for in the statistical models, should also be critically evaluated. Future research should aim to address these limitations by adopting more robust sampling frameworks, using mixed methods for data collection, and applying comprehensive analytical techniques to provide a deeper understanding of the scale's applicability and accuracy.

Comparison With Previous Work

While previous studies have explored various components of oral anticoagulation therapy, such as patient knowledge, health literacy, and self-efficacy in self-management, the PERSONAE scale introduces a unique comprehensive measure [2,7-9,17]. It is the first self-report tool designed to assess both self-monitoring and self-management preparedness among adult patients on oral anticoagulation therapy. This distinction sets the PERSONAE scale apart from existing scales that typically focus on isolated aspects of anticoagulation management. Existing measures often independently evaluate patient knowledge or health literacy, which does not necessarily translate to practical, actionable patient readiness. In contrast, the PERSONAE scale encompasses a broader spectrum of preparedness, integrating aspects of knowledge, self-efficacy, and practical application capabilities into a single measure. This integrative approach not only aids health care providers in identifying well-prepared patients but also pinpoints those who might benefit most from targeted educational interventions. Furthermore, the development methodology of the PERSONAE scale enhances its robustness and applicability. The scale was crafted to ensure scientific soundness and clinical relevance through a rigorous, multiphase approach that included a literature review, expert consensus, and external validation. This methodological solidity supports its potential for widespread adoption and use in clinical settings, distinguishing it further from other tools that may lack such comprehensive validation.

Conclusions

The PERSONAE scale represents a significant advancement in the management of oral anticoagulation therapy. It is the first comprehensive self-report measure specifically designed to assess the preparedness of adult patients for self-monitoring and self-management. This tool will enable health care providers to better identify patients ready to manage their treatment autonomously, possibly enhancing patient outcomes and optimizing therapy adherence. Our study aims to determine the scale's robust psychometric properties, which underscore its reliability and applicability in clinical settings. The PERSONAE scale's ability to encompass a broad spectrum of preparedness, from patient knowledge to self-efficacy and practical application skills, sets it apart from existing tools focusing on narrower anticoagulation management aspects. Looking forward, the PERSONAE scale has the potential to transform patient management in clinical practice globally. By facilitating the identification of patients suited for self-testing, the scale supports tailored educational interventions that can improve self-management skills among those less prepared. This approach promises to enhance patient autonomy and aims to reduce health care costs by improving treatment efficiency and satisfaction. Future research should focus on validating the scale across diverse patient populations to ensure its broader applicability. In addition, integrating the PERSONAE scale into routine clinical practice will be crucial for evaluating its impact on long-term patient outcomes and health care systems. Ultimately, the scale is poised to play a pivotal role in advancing patient-centered health care solutions in anticoagulation therapy.

Acknowledgments

The authors would like to acknowledge the generous support of "Fondazione Insieme per Vita agli Anni" and the partial support by Ricerca Corrente funding from Italian Ministry of Health to IRCCS Policlinico San Donato.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Additional information.
[DOCX File , 27 KB - resprot_v14i1e51502_app1.docx]

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Abbreviations

%TTR: time in the therapeutic range
AICCA: Associazione Italiana Cardiopatici Congeniti (Italian Association of Congenital Heart Disease Patients)
CCI: Charlson comorbidity index
CFA: confirmatory factor analysis
COSMIN: COnsensus-based Standards for the selection of health Measurement INstruments
CVR: content validity ratio
IIO: invariant item ordering
INR: international normalized ratio
IRCCS: Istituto di Ricovero e Cura a Carattere Scientifico (Institute for Research and Healthcare)
MSA: Mokken scaling analysis
POCT: point-of-care testing
VKA: vitamin K antagonist

Edited by A Mavragani; submitted 03.08.23; peer-reviewed by R Meng, N Mirabootalebi; comments to author 11.03.24; revised version received 11.04.24; accepted 08.07.24; published 26.02.25.

Please cite as:
Caruso R, Conte G, Castelvecchio S, Baroni I, Paglione G, De Angeli G, Pasek M, Magon A
Assessing Preparedness for Self-Management of Oral Anticoagulation in Adults With the PERSONAE Scale: Protocol for a Development and Validation Study
JMIR Res Protoc 2025;14:e51502
URL: https://www.researchprotocols.org/2025/1/e51502
doi:10.2196/51502
PMID:

Protocol

Developing a Multisensor-Based Machine Learning Technology (Aidar Decompensation Index) for Real-Time Automated Detection of Post–COVID-19 Condition: Protocol for an Observational Study

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Abstract

Background: Post–COVID-19 condition is emerging as a new epidemic, characterized by the persistence of COVID-19 symptoms beyond 3 months, and is anticipated to substantially alter the lives of millions of people globally. Patients with severe episodes of COVID-19 are significantly more likely to be hospitalized in the following months. The pathophysiological mechanisms for delayed complications are still poorly understood, with a dissociation seen between ongoing symptoms and objective measures of cardiopulmonary health. COVID-19 is anticipated to alter the long-term trajectory of many chronic cardiovascular and pulmonary diseases, which are common among those at risk of severe disease.

Objective: This study aims to use a single, integrated device—MouthLab, which measures 10 vital health parameters in 60 seconds—and a cloud-based proprietary analytics engine to develop and validate the Aidar Decompensation Index (AIDI), to predict decompensation in health among patients who previously had severe COVID-19.

Methods: Overall, 200 participants will be enrolled. Inclusion criteria are patients in the US Department of Veterans Affairs health care system; "severe" COVID-19 infection during the acute phase, defined as requiring hospitalization, within 3-6 months before enrollment; aged ≥18 years; and having 1 of 6 prespecified chronic conditions. All participants will be instructed to use the MouthLab device to capture daily physiological data and complete monthly symptom surveys. Structured data collection tables will be developed to extract the clinical characteristics of those who experience decompensation events (DEs). The performance of the AIDI will depend on the magnitude of difference in physiological signals between those experiencing DEs and those who do not, as well as the time until a DE (ie, the closer to the event, the easier the prediction). Information about demographics, symptoms (Medical Research Council Dyspnea Scale and Post-COVID-19 Functional Status Scale), comorbidities, and other clinical characteristics will be tagged and added to the biomarker data. The resultant predicted probability of decompensation will be translated into the AIDI, where there will be a linear relationship between the risk score and the AIDI. To improve prediction accuracy, data may be stratified based on biological sex, race, ethnicity, or underlying clinical characteristics into subgroups to determine if there are differences in performance and detection lead times. Using appropriate algorithmic techniques, the study expects the model to have a sensitivity of >80% and a positive predicted value of >70%.

Results: Recruitment began in January 2023, and at the time of manuscript submission, 204 patients have been enrolled. Publication of the complete results and data from the study is expected in 2025.

Conclusions: The focus on identifying predictor variables using a combination of biosensor-derived physiological features should enable the capture of heterogeneous characteristics of complications related to post–COVID-19 condition across diverse populations.

Trial Registration: ClinicalTrials.gov NCT05220306; https://clinicaltrials.gov/study/NCT05220306

(JMIR Res Protoc 2025;14:e54993) doi:10.2196/54993

KEYWORDS

Aidar Decompensation Index; AIDI; biophysical biomarkers of worsening health; biosensor-based physiological monitoring; cardiorespiratory, metabolic, renal, and neurological complications after COVID-19; early warning signs of clinical decompensation; long COVID; noninvasive monitoring of physiology; postacute sequelae of COVID-19; PACS; rapid assessment tool; risk triaging related to long COVID

Introduction

Severe complications of postacute COVID-19 infection like thrombosis, respiratory failure, and cardiac and vascular damage increase the likelihood of future morbidity and mortality in recovered patients. In one study of individuals who had been hospitalized with COVID-19, nearly a third (14,060/47,780, 29.4%) of individuals who were discharged from the hospital after acute COVID-19 were readmitted, and more than 1 in 10 (5875/47,780, 12.3%) died over a follow-up period of 140 days after discharge [1]. These events occurred at rates 4 and 8 times greater, respectively, than in the matched control group from the general population. In another study, the 6-month incidence of a new hospitalization among patients previously hospitalized with COVID-19 was found to be 29.8% [2]. SARS-CoV-2 infection can also lead to postacute development of substantial cardiac cellular abnormalities and cardiovascular clinical sequelae, including dysrhythmias, ischemic heart disease, heart failure, pericarditis, myocarditis, and thromboembolic disease [3]. Glycometabolic abnormalities are also evident in many survivors of acute COVID-19 and, in some cases, manifest as overt new-onset diabetes mellitus [4].

Risks of complications are higher among patients with comorbidities like congestive heart failure, chronic obstructive pulmonary disease, asthma, chronic kidney disease, diabetes, and hypertension [1,5,6]. Thus, although the current rate of new COVID-19 infection has dropped, the risk of morbidity, mortality, and organ dysfunction among the survivors of COVID-19 infection is high, especially among those with preexisting illnesses. Compelling evidence suggests that the pandemic may lead to new-onset kidney disease (and other noncommunicable chronic diseases including diabetes, cardiovascular disease, and neurological disease) in the millions. Given the scale and the chronic nature of several of its sequelae, post–COVID-19 condition (also known as “long COVID” or “postacute sequelae of COVID-19”) will reverberate with us for decades and will have broad and deep social and economic impact long after the COVID-19 pandemic abates [7]. Thus, it would be appropriate to infer that the next wave related to COVID-19 may not necessarily be a new strain but rather the surge of hospitalizations due to postacute complications. Developing strategies to prevent decompensation among high-risk survivors of COVID-19 has emerged as an unmet need.

One approach to the prevention of decompensation is to monitor for worsening in physiological parameters after hospital discharge. However, collecting such data longitudinally for prediction poses several challenges. First, only a limited number of parameters can be easily collected (eg, blood pressure, heart rate, oxygen saturation, etc), although additional parameters such as heart rate variability and lung function may provide additional prognostic data. Second, even if patients or families are able to collect these parameters longitudinally, there is no automated, validated method to analyze those data concurrently and provide a quantitative assessment of decompensation risk over time. These limitations hinder the sensitivity and thus the utility of current approaches to using physiologic parameters to predict decompensation risk among patients after COVID-19.

The overall objective of this study (trial registration: ClinicalTrials.gov NCT05220306) is to use a handheld, multisensor device—MouthLab, which measures 10 vital health parameters in 60 seconds—and a cloud-based proprietary engine to develop and validate the Aidar Decompensation Prediction Index (AIDI). MouthLab measures oral temperature, single-lead electrocardiogram, heart rate, breathing rate, heart rate variability, respiratory flow morphology, oxygen saturation, pulse rate, and basic lung function (forced expiratory volume in the first second and peak expiratory flow rate). The study will collect MouthLab data from patients previously hospitalized with COVID-19 (“severe COVID-19”) in order to identify decompensation predictor variables. These variables will be used to develop the AIDI to accurately predict decompensation events (DEs) related to post–COVID-19 condition. Index development will follow best practices in machine learning and algorithmic development, where the main outcome is any COVID-19–related event that leads to an emergency department (ED) visit, hospitalization, or the need for escalated care (new diagnosis or change in intervention to manage the chronic conditions). These DE cases will help inform the final set of predictor variables to develop the AIDI. In the future, early prediction and real-time risk triaging using the AIDI may support better clinical decision-making, thus preventing complications, controlling disease progression, and improving outcomes. The aim of this paper is to describe the protocol for this study to develop and validate the AIDI.

Methods

Study Design

This is a national, longitudinal, observational study. Potentially eligible patients will be identified using the US Department of Veteran Affairs (VA) Corporate Data Warehouse (CDW) and the COVID-19 Shared Data Resource. A total of 200 patients who have a history of “severe” COVID-19 infection in the previous 3-6 months and at least 1 of the specified comorbidities will be recruited. Severe COVID-19 is defined as requiring hospitalization for acute COVID-19 or its complications.

Participants will be required to use the MouthLab device twice daily and to complete monthly surveys administered remotely either by phone or through a web portal. Data will be used to develop a machine learning–based algorithm to detect DEs among patients in the postacute COVID-19 phase.

Study Setting

The VA is the largest integrated health system in the United States, with over 9 million patients enrolled. VA delivers care to US military veterans across 171 VA Medical Centers and 1113 outpatient care sites across the United States and Puerto Rico, Guam, and other US territories [8]. Nearly 50% of enrolled veterans are aged 65 years or older; 91.1% are male and 8.9% are female; and overall, veterans bear a greater burden of physical and mental health comorbidities than nonveterans [9,10].

Sample Size

To develop the AIDI algorithm, the study will collect longitudinal parameters that lead up to a DE with the MouthLab device. Because the actual multiparametric changes are unknown and are, in fact, the outcome of the study, the study aims to obtain as much data as possible from those who experience a DE. For this study, we estimate that 100 individual DEs would be sufficient to create a statistical algorithm to predict decompensation. The ultimate goal is to have the algorithm produce no false negatives (ie, if someone is at risk of decompensation while the algorithm says that they are not) and less than 10% false positives (ie, if someone is *not* at risk of decompensation while the algorithm says they are). That is, we do not want to miss any DEs at the cost of having some nonevents classified as being risky.

Al-Aly Z et al [11] observed that the risk and associated burden of pulmonary and extrapulmonary manifestations increase across the disease spectrum of acute COVID-19 infection (from nonhospitalized individuals to hospitalized individuals and then to those admitted to intensive care). The study implemented a comparative approach to examining postacute sequelae in individuals who are hospitalized with COVID-19 versus individuals with seasonal influenza (using a high-dimensional approach and through examination of prespecified outcomes). Results suggested that there is a substantially higher burden of a broad array of postacute sequelae in the individuals who are hospitalized with COVID-19, which provides features that differentiate post–COVID-19 condition (both in the magnitude of risk and the breadth of organ involvement) from postinfluenza viral syndrome [11]. A study by Mainous et al [2] demonstrated a hospitalization rate of 29.8% among survivors of “severe COVID-19.” Given that the AIDI study has defined “decompensation” more broadly than hospitalization alone, we anticipate higher decompensation rates among our study population. Conservatively estimating 1 DE per any participant, with an event rate of 60%, we would need 168 participants to complete the study in order to capture 100 DEs. Since we anticipate up to 15% dropout, we will aim to recruit 200 participants.

Eligibility Criteria

The inclusion and exclusion criteria are shown in Textbox 1.

Textbox 1. Inclusion and exclusion criteria.

Inclusion criteria

- Aged 18 years and older
- Were hospitalized for treatment of acute COVID-19 or its complications in the prior 3-6 months
- At least one of the following comorbidities:
  - Hypertension
  - Asthma
  - Chronic obstructive pulmonary disease
  - Heart failure
  - Chronic kidney disease
  - Diabetes mellitus
- English fluency
- Comfortability with using technology
- Basic literacy with electronic platforms

Exclusion criteria

- Any motor disability that would impede the use of the MouthLab device as required with the left hand
- Pregnancy
- Cognitive deficits that would impede the ability to provide informed consent
- Alzheimer disease or other dementia
- Pacemakers and implantable cardioverter-defibrillators

Recruitment

This study will recruit participants from across the country who receive care at the VA. A waiver of the Health Insurance Portability and Accountability Act (HIPAA) and informed consent for screening will be obtained for recruitment. Three modes of recruitment will be used. First, eligible patients will be identified via the CDW and sent letters with information about the study and a number to call if they are interested in learning more. Second, those who have authorized the VA through any partnership programs (eg, COVID-19 research volunteer registry) to receive communication on research opportunities may be contacted for this study. Third, study flyers will be posted at three of the VA's post–COVID-19 condition clinics. The selection process will include best efforts to ensure equitable inclusion of different races, ethnicities, and age groups among the participants.

Ethical Considerations

The protocol was approved by the Central Institutional Review Board of the Veterans Healthcare Administration, on December 21, 2022 (1720625-1). Since this is a multisite study, individual institutional review boards at the VA Bedford Healthcare System and the VA Providence Healthcare System also reviewed and approved the study. Informed consent will be obtained from all eligible participants prior to shipping the MouthLab device, administering baseline surveys, and collecting any patient data. Upon obtaining consent, the research team will also obtain HIPAA authorization. No study-related tasks will be performed before obtaining both consent and HIPAA authorization. A member of the research team will send the informed consent form (ICF) to the patient via DocuSign and read through the form with the participants on the WebEx (Cisco) consent call. The person obtaining consent will review the ICF in depth and solicit all questions before the participants sign the ICF via DocuSign. Participants will receive an executed copy via email, and those who prefer to sign a physical copy will be mailed a consent form. This approach will allow participants sufficient time to follow up with questions and discuss before officially signing the consent form. Participants will receive US $85 at the end of months 1-5. At the end of month 6, upon the completion of study tasks (survey and device return), participants will receive US $175. The total potential compensation is US $600, paid by check.

Study Timeline

The timeline of the study is provided in Table 1.

In addition to MouthLab and survey data (Table 2), data will be collected from the CDW on patient demographics, comorbidities, medications, and potential DEs. The main DEs of interest are any COVID-19–related events that lead to an ED visit, hospitalization, or the need for escalated care (new diagnosis or change in intervention to manage the chronic conditions).

The study will collect information about the index hospitalization, related to COVID-19 either as a primary or secondary diagnosis, from the CDW. This information will include medications (including oxygen therapy), vitals, and the use of mechanical ventilation. Additionally, the index hospitalization will be classified as an intensive care unit–level admission or not.

Table 1. Timeline of patient data collection for the Aidar Decompensation Index study.

	Phone screening	Consent	Patient intake form	Training on the MouthLab device	MRC[a] Dyspnea Scale [12]	Post-COVID-19 Functional Status Scale [13]	VR-12[b] [14]	User experience survey
First contact and screening	✓							
Consenting and HIPAA[c] authorization		✓						
Baseline and BP[d] calibration				✓				
Monthly follow-ups and data collection			✓[e]		✓[f]	✓[f]	✓[e,g]	✓[g]
Termination								

[a]MRC: Medical Research Council.

[b]VR-12: Veterans RAND 12-Item Health Survey.

[c]HIPAA: Health Insurance Portability and Accountability Act.

[d]BP: blood pressure.

[e]First month: patient intake form and first VR-12.

[f]Monthly: MRC Dyspnea Scale and Post COVID-19 Functional Status Scale.

[g]Sixth month: second VR-12 and user experience survey.

Table 2. Survey data to be collected for Aidar Decompensation Index study.

Survey data	Instrument or measure	Time points
MRC[a] Dyspnea Scale (score 1-5)	A 5-point scale that has been used to classify dyspnea, mainly used in grading COPD[b] progression	Every 4 weeks
Post-COVID-19 Functional Status Scale (0-4 grade scale)	Functional status questionnaire that measures the impact of post–COVID-19 condition on ADL[c] along with psychological symptoms	Every 4 weeks
VR-12[d] Quality of Life Assessment	Patient self-report	At the start and end of study
MouthLab Usability Survey	MCQs[e] to ascertain the information of the physical and usage aspects of the MouthLab device	Study conclusion
User feedback on remote physiological monitoring technology	General perception about remote monitoring technologies (wearable and spot-check)	Study conclusion
Index hospitalization	Collected laboratory data, diagnoses, investigation report, medications, oxygen therapy, clinical notes, and vital signs data	Study conclusion

[a]MRC: Medical Research Council.

[b]COPD: chronic obstructive pulmonary disease.

[c]ADL: activities of daily living.

[d]VR-12: Veterans RAND 12-Item Health Survey.

[e]MCQ: multiple-choice question.

Evaluation of DEs

Data on outcomes (DEs) will be collected at the end of the data collection period via the CDW, records obtained from non-VA hospitalizations and ED visits, and monthly and end-of-study surveys.

A DE is defined as a complication related to organ dysfunction induced by SARS-CoV-19 that establishes the need for a change in treatment or intervention. To identify these events, we will first identify all new diagnoses and treatments, including medications, health care visits, and changes in level of service (eg, outpatient, inpatient, and hospital at home), for each patient during the study period using national CDW data. The data reviewed will be limited to those linked to relevant service types (eg, emergency care, urgent care, primary care, cardiology, and pulmonology). A study staff member will review these outcomes with guidance from the principal investigator or other team member with medical training to establish which are highly likely, somewhat likely, and not likely to be related to COVID-19. The full set of outcomes (Table 3) will be used as one outcome in one approach to the development of the predictive algorithm, and the subsets of highly likely and somewhat likely DEs will be used in a second approach to development.

Table 3. Study outcomes.

Outcomes	Instrument or measure
Primary outcomes	
All-cause, higher-level health care use (hospitalization, ED[a], or urgent care visits within the VA[b] system)	Participant self-reporting, confirmed through EMRs[c]
All-cause health care use (within and outside the VA system)	Participant self-reporting, confirmed through record requests and EMRs
Highly likely COVID-19–related health care use	As evaluated by the PI[d] and subinvestigators
Highly likely and somewhat likely COVID-19–related health care use	As evaluated by the PI and subinvestigators
Secondary outcomes	
Highly likely and somewhat likely COVID-19–related health care use	As evaluated by the PI and subinvestigators
Highly likely COVID-19–related diagnoses, treatment, use, and medication	As evaluated by the PI and subinvestigators and confirmed in EMRs

[a]ED: emergency department.

[b]VA: Department of Veteran Affairs.

[c]EMR: electronic medical record.

[d]PI: principal investigator.

Data Blinding

Participants and physicians are blinded to the data from the MouthLab device. Participants will be informed that they are not restricted from seeking any level of care. There will be no medical intervention provided during or after the study as a consequence of any unfavorable trends in the MouthLab data, as these data are not being surveilled during the study.

Participant Data Protection

The confidentiality of participants will be maintained throughout the study. All participants will be assigned a unique subject ID by the data analyst. The crosswalk that matches the participant ID to the participant's name will be secured behind the VA firewall. Any data that may be published in abstracts and scientific journals or presented at medical meetings will reference the unique participant ID or will be aggregated, so to not reveal the participant's identity. Patient identifiable information such as name, address, email address, and phone number will only be used to support device shipment and return–related activities. Participants' unique identifiers, rather than personal information, will be connected to their device and survey data as well as any other data obtained from the electronic medical record. To protect participants' privacy, the Aidar Connect dashboard will not collect any patient identifiable information during registration, and pairing of MouthLab devices will be performed against the participants' IDs.

Safety Monitoring

During the monthly health surveys sent via the VA Office of Research and Development Qualtrics platform, participants will report any potential adverse events (AEs) that are possibly related to their COVID-19 diagnosis, as well as to any hospitalizations or medical care use. Study coordinators will follow up with participants to gather more information and have participants sign a Release of Information if needed. The investigator or study coordinator will determine whether the AE or serious AE meets the criteria for reporting; submit to the sponsor and VA Central Institutional Review Board all associated information and documentation related to each AE or SAE; and execute corrective actions as necessary.

Statistical Analysis

Feature Engineering and Selection

For each patient, baseline readings will be based on their first few MouthLab measurements. The number of observations used to establish the baseline will depend on the variability in each patient's reading. We will then summarize the patient's parameters obtained from the MouthLab data collection. At each time t, we will include the most recent observations, changes since the last reading, trends, variability in values, and comparison to the patient's baseline. Additionally, we will include information about demographics, symptom scores, other clinical characteristics, as well as key comorbidities. We anticipate that variable interactions will be important. Given the cohort size and the number of different features, regularization will be applied to avoid overfitting.

Outcome Modeling

We will define the outcome as patients experiencing a DE within τ time units (DEτ). For different values of τ, we will deploy a series of more sophisticated models in order to explore the predictive ability of different approaches, as detailed below. We will split up the data into training and testing datasets based on the time of enrollment. We anticipate an 80:20 split; in other words, we will set aside 20% of the data to evaluate the model performance. For each τ, we will construct a training dataset consisting of multiple overlapping time segments for each patient, which we refer to as the observation period (eg, 2 weeks), and multiple nonoverlapping time segments leading up to the outcome for the patients that experience the outcome, one of which contains the outcome.

Second, we will explore several other machine learning algorithms, including classification trees, random forest, and boosting approaches, to understand whether these more flexible modeling approaches have an advantage over the logistic regression approach. The output of any of these approaches is a predicted probability of a DE occurring within the following τ days given observations of a fixed observation interval (eg, up to 30 previous measurements, or ~2 weeks). As stated earlier, the goal is to develop the AIDI to predict worsening health. The detailed analysis laid out above will allow us to understand the ability of early prediction, that is, the critical time frame just prior to decompensation during which the probability of hospitalization becomes increasingly predictive.

The initial exploratory analysis will inform the selection of proper features for the analysis. We will model the patient's risk of hospitalization as a function of their physiological values, short-term changes in those values, changes from the baseline, etc. The initial exploratory analysis will inform features such as the appropriate time ranges (eg, should short-term changes be captured since the last reading or over the last 24 hours).

Performance Evaluation

In case of a lower-than-expected number of observed outcomes, or smaller differences than expected between those who experience the outcome and those who do not, we may revert from our 80:20 split to use cross-validation to measure performance. In that case, we will evaluate the algorithm using the leave-one-out cross-validation technique. We will implement this approach by leaving out one patient at a time (corresponding to potentially multiple observation periods to avoid fitting the model on data from the same patient as the model is being evaluated). The leave-one-out cross-validation technique facilitates cross-validation evaluation of the algorithm structure to assess its robustness to changes. This validation step will remake the algorithm for every patient left out of the algorithm development iteration. In short, this approach fits each algorithm using all available data except for (in our case) the data of one patient and then summarizes whether the algorithm predicts the correct classification of decompensation or nondecompensation for each observation period. This process is repeated over all available patients. For each τ, we will summarize the accuracy, false positives, and false negatives.

The resulting predicted probabilities of decompensation will then be translated into the easy-to-communicate AIDI, where there is a linear relationship between the risk score and the AIDI. At the conclusion of phase 3, the final COVID-19 DE detection performance of the AIDI will be evaluated using standard measures including sensitivity, specificity, and positive predictive value across a wide range of risk cutoff values. Overall, AIDI DE detection performance and lead time statistics will be examined across study populations as well as within subgroups. If necessary, to improve prediction accuracy, data may be stratified based on biological sex, race, ethnicity, or underlying clinical characteristics into subgroups to determine if there are differences in performance and detection lead times among the groups.

Results

Recruitment began in January 2023, and the first patient was enrolled in January 2023. At the time of manuscript submission, 204 patients have been enrolled. Publication of the complete results and data from the study is expected in 2025.

Discussion

Expected Findings

The AIDI study seeks to address a substantial challenge, that is, to develop an affordable, scalable, technology-assisted remote monitoring solution to facilitate early identification of abnormalities and timely intervention by clinicians to improve quality of life, functional status, and health outcomes and, ultimately, to reduce the burden of post–COVID-19 condition in the United States and elsewhere. We hypothesize that monitoring participants for 6 months and capturing critical cardiorespiratory parameters on a daily basis in conjunction with subjective and clinical data will enable the development of an index, the AIDI, that will empower high-quality clinical care using the MouthLab device as a rapid and early assessment tool. The outcomes of this research have the potential to redefine the care delivery for COVID-19 and potentially other conditions in the future, as well as push the boundaries of prevention and care beyond traditional care settings into the home.

Limitations

Self-selection bias may be a limitation of this study as participation is voluntary, and participants already comfortable with using technology might be especially motivated to participate in digital intervention studies. Patients who are particularly ill may not enroll due to difficulty managing the device, and those without cellular service will not be able to participate.

Strengths

Fully remote study procedures will enhance the accessibility of eligible research participants living in rural or remote locations away from large metropolitan areas. The MouthLab device has built-in SIM cards offering cellular data, thus requiring no other accessory, such as mobile phones, to transmit data to the Aidar Cloud. Using a web application dashboard will allow easier visualization of MouthLab data from all participants, providing us with the opportunity to intervene immediately in the event of absent data or noncompliance.

Conclusions and Future Work

The findings from this study will result in a predictive algorithm (AIDI) to predict decompensation among high-risk patients who previously had severe COVID-19. In the short term, this could be applied to monitoring such patients during the hospital-to-home transition or for longer periods at home. In the long term, we will adapt and validate the AIDI for monitoring other conditions. Our work will generate insight and guidance for scalable and easy-to-use digital monitoring solutions for remote management of chronic diseases to control disease progression, limiting the impact of comorbidities and, ultimately, improving health outcomes among high-risk populations.

Acknowledgments

The study used data from the Department of Veteran Affairs (VA) COVID-19 Shared Data Resource.

This clinical trial is funded in part with federal funds from the Department of Health and Human Services; Office of the Assistant Secretary for Preparedness and Response; and Biomedical Advanced Research and Development Authority, under contract 75A50121C00062. The clinical trial will be completed by the VA under contract with Aidar Health, Inc. and supported with resources and the use of facilities at the VA Bedford Medical Center and the VA Informatics and Computing Infrastructure (VA HSR RES 13-457).

The content is the sole responsibility of the authors and does not necessarily represent the official views of the VA, the National Institutes of Health, the Department of Health and Human Services, or the US Government.

Data Availability

Datasets generated or analyzed during the study described by this protocol may be made available from the corresponding author on reasonable request.

Authors' Contributions

JM and SE acquired the funding. JM and SE conceptualized the study with input from VGV. JM, JAP, and VGV drafted the paper with input from LKW, KL, and AJL. All authors contributed to reviewing and editing the final version.

Conflicts of Interest

Two authors (JM and SE) are employees of Aidar Health, Inc., which is the company that manufactured the technology being used in the research study (device and the software platform).

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Abbreviations

AE: adverse event
AIDI: Aidar Decompensation Index
CDW: Corporate Data Warehouse
DE: decompensation event
ED: emergency department
HIPAA: Health Insurance Portability and Accountability Act
ICF: informed consent form
SIM: Subscriber Identity Module
VA: Department of Veteran Affairs

Edited by T Leung; submitted 01.12.23; peer-reviewed by Z Ding, T Abd El-Hafeez; comments to author 13.02.24; revised version received 05.12.24; accepted 22.02.25; published 27.03.25.

Please cite as:
Mathew J, Pagliaro JA, Elumalai S, Wash LK, Ly K, Leibowitz AJ, Vimalananda VG
Developing a Multisensor-Based Machine Learning Technology (Aidar Decompensation Index) for Real-Time Automated Detection of Post–COVID-19 Condition: Protocol for an Observational Study
JMIR Res Protoc 2025;14:e54993
URL: https://www.researchprotocols.org/2025/1/e54993
doi:10.2196/54993
PMID:

Protocol

Evaluation of the Transition-to-Practice Arrangements for Novice Perioperative Nurses: Protocol for a Mixed Methods Study

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Abstract

Background: Transitioning into the first year of clinical practice as a nurse or changing specialties in the nursing career presents a critical phase for novice nurses characterized by excitement, apprehension, and the phenomenon of “transition shock.” Within perioperative nursing, this transition phase takes on distinctive challenges. However, there is a lack of empirical evidence on transition programs and arrangements.

Objective: This study aimed to evaluate the current transition-to-practice (TTP) arrangements available to new graduate and novice nurses within Australian perioperative nursing settings.

Methods: This study uses an exploratory mixed-method, multilevel triangulation with a sequential phase design to address 4 research questions. Phases 1 to 3 will use document analysis, surveys, and semistructured interviews to establish the findings of the research questions. Phase 4 will use meta-inference and triangulation to aggregate and analyze the data from all preceding phases. These findings will be the foundation for developing a framework to inform future TTP arrangements. This robust framework will embed empirical evidence, existing literature, and sound learning and teaching pedagogy. Results emerging from this study will be reported using the Good Reporting of Mixed Methods Study guidelines.

Results: This project received approval in June 2023. Following this, Human Research Ethics Committee approval was sought for phases 1 and 2, and recruitment began. As of August 2024, phase 1 has collected 50 responses and phase 2 has collected 69 responses. Data collection for phase 3 is projected to commence in May 2025 once data from phases 1 and 2 have been analyzed. Phase 4 is projected to occur in 2026. Each phase is anticipated to have a results manuscript submitted for publication once data are analyzed and written up.

Conclusions: The findings of this study will provide an in-depth exploration of TTP arrangements within perioperative nursing in Australia and provide a framework to guide the future development of TTP arrangements.

Trial Registration: OSF Registries osf.io/zm432; https://osf.io/54s36

International Registered Report Identifier (IRRID): DERR1-10.2196/64970

(JMIR Res Protoc 2025;14:e64970) doi:10.2196/64970

KEYWORDS

transition to practice; perioperative nursing; novice nurses; nurse educators; mixed methods research; protocol; document analysis; semistructured interviews; pedagogy

Introduction

Transitioning from undergraduate nursing studies or other nursing specialties into perioperative nursing is a pivotal phase in a nurse's career journey. This critical period in a novice nurse's career is often filled with excitement, nervousness, and apprehension. It is not uncommon for novice nurses to experience transition shock during this period, a term that describes a state of emotional and physical shock [1]. Novice nurses often describe transition as feeling like they are "drowning", "terrified," or "scared to death" [1]. Within the specialized field of perioperative nursing, transition challenges take on a unique dimension. Perioperative nurses play a vital role in surgical settings, where precision, attention to detail, and seamless care coordination are paramount. Professional health care organizations recognize the unique nature of critical care environments, such as perioperative nursing, that require specialized clinical competence and an understanding of the environment [2,3].

Transition shock in novice nurses arises from the sudden shift from a structured, academic environment to the complex and high-pressure demands of real-world practice, which often differ greatly from their expectations [1]. Without the support systems novice nurses rely on as students, novices can feel isolated, anxious, and insecure in their abilities. The disconnect, paired with high responsibility and fear of making mistakes, contributes to self-doubt, stress, and sometimes burnout in the early months of their job [1].

It is common practice for novice nurses to gain employment opportunities that offer the prospect of completing structured transition-to-practice (TTP) arrangements [4]. TTP arrangements serve as vital conduits connecting the theoretical knowledge acquired during undergraduate nursing education with the knowledge and skill requirements of real-world clinical practice. TTP arrangements play a pivotal role in nurturing the growth of novice perioperative nurses by providing mentorship, tailored training, and a supportive environment where new graduates can gain hands-on experience and develop the competence and confidence necessary for successful nursing practice [5,6].

A lack of empirical evidence regarding TTP arrangements within the perioperative nursing setting was noted during the literature search [7]. Transition arrangements and the impacts of transition shock are well defined within the literature [5,6]; however, there was a paucity of empirical literature that discussed the perioperative TTP arrangements. Most of the literature identified were discussion pieces [7]. Second, the "Educating the Nurse of the Future" report described the significant variability between TTP arrangements and their providers [8]. In this report, it was identified that there is no set standard for the length of transition arrangements, the content taught, how the content is taught, or the other supporting mechanisms available to novice nurses.

This study will address the 2 critical gaps in the literature and transition practices, as identified above. This paper provides a detailed overview of the methods to be used and a discussion of how the study will systematically investigate current practices in transition arrangements and the efficacy of these arrangements. It seeks to explore the perspectives of novice perioperative nurses and perioperative nurse educators regarding transition arrangements.

Methods

Study Aim

The proposed research study aims to evaluate the current TTP arrangements available to new graduate and novice nurses (hereafter referred to both groups as novice nurses) within Australian perioperative nursing settings and draw on these findings to develop recommendations and a theoretical framework to guide the design, development, and implementation of future transition arrangements within the perioperative nursing specialty.

Study Objectives

The following research objectives stem from the research aim and have been used to guide the development of the research questions. The research objectives are (1) to develop an understanding of the transition to practice arrangements in the perioperative environment; (2) to engage key stakeholders to share their opinions, expertise, and experiences on transition arrangements within the perioperative nursing environment in Australia; (3) to undertake critical analysis of the transition arrangements available in Australia to support novice nurses entering perioperative nursing; and (4) and to develop a framework and model that provides evidence-based educational, social, and holistic transition arrangements for novice nurses entering perioperative nursing.

Research Questions

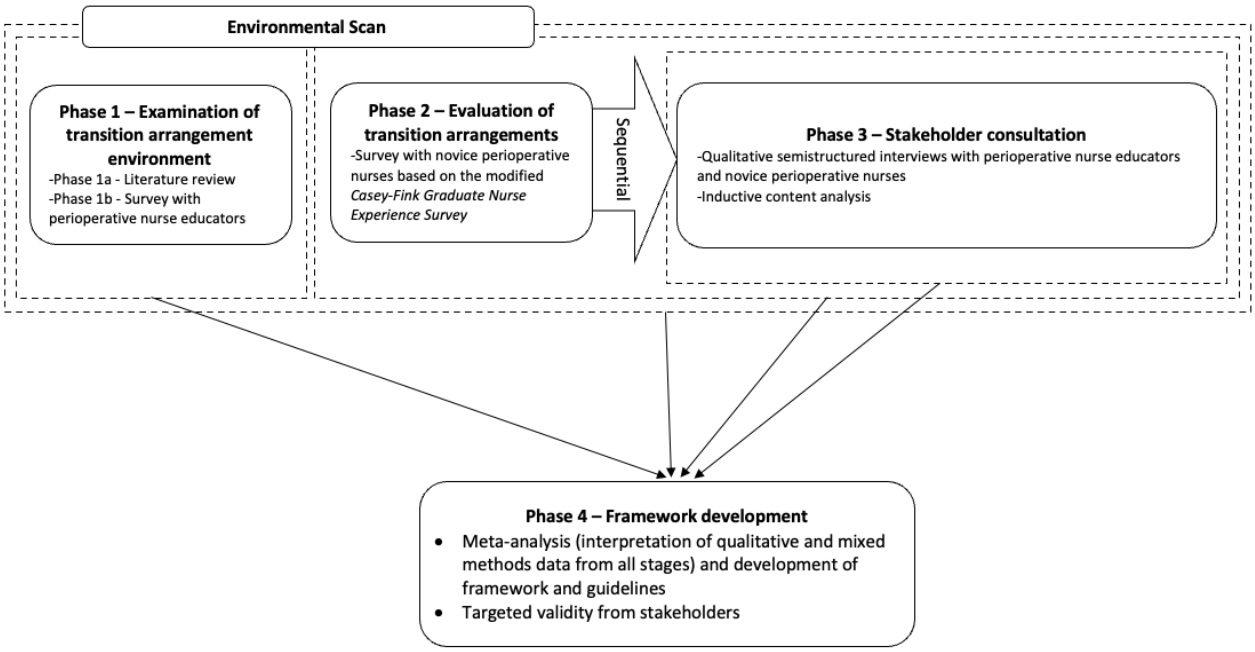
The following research questions (RQs) are designed to meet this study's aims and objectives:

- RQ1: What are the current TTP arrangements available to novice perioperative nurses within Australian health care organizations?
- RQ2: What are the content, methods, and educational philosophies used within these TTP arrangements?
- RQ3: How effective are TTP arrangements in supporting novice perioperative nurses and guiding them throughout the transition period?
- RQ4: What support do novice perioperative nurses undertaking TTP arrangements require to become competent and confident clinicians?

Design

This study uses an exploratory sequential mixed-method, multilevel triangulation design (Figure 1). This methodology combines both qualitative and quantitative data to yield a deeper understanding of the research questions [9]. By mixing qualitative (subjective) and quantitative (objective) research, the researcher is provided with the flexibility to explore complex issues and answer multifaceted research questions, thus bridging the divide between the 2 individual research approaches [10]. Several multifaceted research questions need to be answered within this study, which would not be feasible by using only quantitative or qualitative data sources.

Figure 1. Overview of the exploratory mixed-method, multilevel triangulation design with sequential phases.



This research study has 4 phases (Figure 1). The sequential design will be applied between phase 2 and phase 3 [11]. Phase 1 involves document analysis and surveys to establish the existing TTP arrangements for perioperative nursing in Australia. Phase 2 involves surveys with novice perioperative nurses to determine the effectiveness of TTP arrangements. The findings from these phases will inform the development of interview questions for phase 3. Phase 4 of this study will involve a meta-analysis of all the data collected, which will be used in the development of a framework. An overview of this research design is represented in Figure 1, illustrating the research questions being addressed and the primary method used at each phase. Ethics approval will be sought for phases 1 and 2, as these will run concurrently, and for phase 3.

Phase 1: Transition-to-Practice Arrangement Analysis

The first phase of the study will address RQ1 (what are the current TTP arrangements available to novice perioperative nurses within Australian health care organizations?) and RQ2 (what are the content, methods, and educational philosophies used within these TTP arrangements?) using document analysis techniques and a mixed methods survey. As most health care organizations do not publicly publish their transition arrangements, a survey was designed to collect data about TTP arrangements from perioperative nurse educators. The research team had access to their local TTP arrangements; however, surveying perioperative nurse educators will ensure that this study is not geographically confined. Using 2 data collection methods ensures sufficient results are obtained to understand the TTP arrangements used within the Australian perioperative environment.

Participants, Sample Size, and Recruitment

Data will be collected from 2 separate sources. First, the document analysis, which seeks to explore and understand TTP arrangements from within Australia. These TTP arrangements will be purposefully selected to ensure completeness and that they are currently used in novice perioperative nurses' training and transition support.

Second, a survey will be undertaken with a convenience sample of Australian perioperative nurse educators. Sample size calculations indicate an ideal sample size of 28 participants will be required using a confidence level of 95% and a margin of error of 5%) [12] to capture adequate responses to generalize TPP arrangement practices in Australia. Perioperative nurse educators who participate in this survey must be currently used within an Australian perioperative department in a role that allows them to provide nursing education, management, or support to novice perioperative nurses. Participants will be recruited through snowball sampling techniques and social media such as LinkedIn, Facebook (Meta), and Twitter (rebranded as X) [13]. In addition, professional nursing organizations and peak bodies for perioperative nursing will be approached to disseminate the survey.

Data Collection and Analysis

Manual searching of gray literature search engines, professional organizations, and health service websites will be used to identify suitable TTP arrangements for the document analysis component of this phase. Data collection for the document analysis and survey will be completed using a fit-for-purpose online survey. The survey tool was designed based on the authors' scoping literature review findings [7]. The survey instrument will collect data regarding the duration of TTP arrangements, modality, pedagogy and content taught, assessments, efficiency, and barriers. The survey will remain open until the required sample size is reached, or until all recruitment strategies have been used.

The document analysis tool and survey will collect both qualitative and quantitative data. Qualtrics StatsIQ will be used for descriptive statistical analysis and frequencies for quantitative data. Qualitative data will be analyzed using Braun [14] and Clarke's [15] 6-step guide to thematic analysis. NVivo

(Lumivero) software will be used for data management and coding of qualitative data. The findings from this phase will be used to inform the semistructured interviews for phase 3.

Phase 2: Survey Phase

Phase 2 of the project will use an online survey to address RQ3 (How effective are TTP arrangements in supporting novice perioperative nurses and guiding them throughout the transition period?) by exploring the effectiveness of TPP arrangements within perioperative nursing from the novice nurse perspective. By doing this, the researcher will understand the efficacy of TTP arrangements within perioperative nursing. Understanding transition practices, particularly from the novice nurse experience, is essential as novice nurses are integral to transition arrangements. Transition arrangements should be designed around novice nurses' learning and organizational needs and resources.

Participants, Sample Size, and Recruitment

A convenience sample of novice perioperative nurses who have recently completed a TTP arrangement within perioperative nursing will be sought for this study phase. It is anticipated these participants will be familiar with the transition arrangement they undertook. A 3-year inclusion criterion is set based on Benner's Novice to Expert Theory [16]. Nurses within the perioperative specialty with over 3 years of experience are often considered competent and an expert and no longer novices [16].

Significant missing data were noted when attempting to calculate sample sizes for this phase. An accurate estimate of the current population of novice perioperative nurses in Australia was unable to be achieved without making several assumptions that may lead to inaccurate sample size calculations. As the purpose of this phase is to inform the interview development of the next phase (interview phase), therefore a purposive, convenience sample will be the aim for this survey, where all reasonable recruitment strategies will be undertaken and the survey will remain open for 12 months.

Recruitment will be conducted through social media and snowballing, through professional organizations such as the Australian College of Perioperative Nurses, at conferences, and through university contacts to disseminate to graduate perioperative nursing students.

Data Collection and Analysis

Data will be collected using the revised Casey-Fink Graduate Nurse Experience Survey [17]. The survey tool was modified with the written permission of the survey tool authors. Adjusting the survey allows contextualization to the Australian perioperative nursing setting and enables the inclusion of further questions relating to participants' experiences during the transition. The Casey-Fink Graduate Nurse Experience Survey examines novice nurse transition across 8 domains, these being Role Confidence, Organize and Prioritize Care, Support, Role Satisfaction, Stress and Burnout, Resilience, and Organizational Commitment and Preceptorship [17].

Data will be analyzed using SPSS (IBM Statistics) software [18]. Descriptive and inferential statistics will be completed, including reliability testing (Cronbach α), linear regression, and factor analysis (varimax rotation) [19,20]. The NVivo software [15] and Braun and Clarke's [14] 6 steps of thematic analysis will be used to analyze the open-ended qualitative survey questions. The findings from this phase will be used to inform the semistructured interviews for phase 3.

Phase 3: Interview Phase

In phase 3, semistructured interviews will be conducted to address RQ4 (What support do novice perioperative nurses undertaking TTP arrangements require to become competent and confident clinicians?). These interviews will involve 2 cohorts: novice and perioperative nurse educators. The aim of phase 3 is to comprehensively examine the components of transition arrangements essential for success from the perspective of these 2 sample groups. This approach will also facilitate an exploration of the similarities and differences in the perspectives of the 2 cohorts.

Participants, Sample Size, and Recruitment

A total of 8-12 participants from each cohort will be sought to complete semistructured interviews. Purposive sampling techniques will be used to ensure a suitable breadth of participants. Continuous comparative analysis will be used throughout the interview process to examine data saturation. Participants must meet the eligibility requirements of novice perioperative nurses and perioperative educators, as defined in the above phases, to participate in phase 3.

Recruitment for phase 3 will commence in the previous 2 phases. Both cohorts will have the option to express their interest in participating in follow-up interviews after the completion of their survey. To maintain the confidentiality of participants and their survey responses, participants who choose to enroll for follow-up interviews will be redirected to a separate survey to collect their names, contact details, and cohort group. The study will use social media and snowball if insufficient participants are recruited through this method.

Data Collection and Analysis

A data collection instrument will be developed for phase 3, following the sequential completion of phases 1 and 2. The findings from these earlier phases will inform the development of the interview tool and semistructured interview questions. Before delving into a detailed exploration of TTP arrangements, a comprehensive understanding of the content, methods, and philosophies within TTP arrangements and the experiences of novice perioperative nurses must be obtained.

The interviews will be audio recorded and transcribed verbatim before data analysis is undertaken. NVivo software [15] will be used for thematic analysis using Braun and Clarke's [14] 6-step guide. This process will be applied to both cohorts, and the results will be compared and triangulated to uncover the experiences and perspectives related to TTP arrangements of novice perioperative nurses and experienced perioperative nurse educators. Differences and similarities between the cohorts will be carefully examined and presented.

Phase 4: Meta-Inference and Framework Development

The final phase involves the analysis of data and findings from the previous 3 phases. Data will undergo meta-inference analysis and triangulation to establish the findings directly aligned with the research aims, objectives, and questions. These findings will form the foundation for developing a framework to guide the design, development, and implementation of future perioperative nursing TTP arrangements. This framework will be embedded in the empirical evidence uncovered by this study, existing literature, and adult learning principles. Targeted validity checking will be used to ensure rigor and congruence of the research findings.

Peer Reviews

This study has completed 2 peer reviews. The initial review occurred during the confirmation of candidature milestone for Doctor of Philosophy students. This review encompassed 2 independent reviews from experts in their field. The second review was conducted as part of the approval process by the CQUniversity Human Research Ethics Committee for both phases 1 and 2 of the study.

Ethical Considerations

As this study spans 4 phases, ethics approval will be obtained in 2 applications. The initial ethics application encompasses phases 1 and 2 and has been approved by the CQUniversity Human Ethics Research Committee under approval number 0000024139. The subsequent ethics application will be submitted once data analysis from phases 1 and 2 is completed and a semistructured interview protocol has been developed for phase 3.

Results

This project received approval in June 2023. Following this, Human Research Ethics Committee approval was sought for phases 1 and 2, and recruitment began. As of August 2024, phase 1 has collected 50 responses and phase 2 has collected 69 responses. Data collection for phase 3 is projected to commence in May 2025 once data from phases 1 and 2 have been analyzed. Phase 4 is projected to occur in 2026. Each phase is anticipated to have a results manuscript submitted for publication once data is analyzed and written up.

The results from this study will be disseminated locally and at relevant national and international conferences. The findings from this study will also be disseminated in peer-reviewed nursing journals. Media releases will be undertaken as opportunities arise. In addition, this study will be published and disseminated as a thesis document to meet the requirements of the Doctor of Philosophy program.

Discussion

International Significance

In examining the international implications of this study, it is evident that the findings should hold significant relevance on a global scale, reflecting the shared challenges encountered by novice nurses worldwide as they transition into specialized fields [21].

Identifying and exploring gaps in empirical evidence regarding TTP arrangements within perioperative nursing is not unique to Australia; many countries grapple with similar challenges in standardizing and evaluating TTP programs [7]. By addressing these gaps, this study will offer insights that extend beyond national borders, providing a comparative perspective on the effectiveness of transition practices.

Furthermore, the development of a framework and model based on evidence-based educational, social, and holistic transition arrangements has implications beyond Australian perioperative nurses. Components of the framework could be used to inform the development of TTP arrangements internationally. In addition, aspects of this study can be replicated internationally to identify common trends and differences between countries in TTP arrangement practices. The challenges novice perioperative nurses face are likely shared globally, making a well-informed framework adaptable and applicable in different countries to enhance the quality of transition programs.

Available Evidence

It could be argued that TTP arrangements from other specialty areas could be used within the perioperative nursing realm to support novice nurse assimilation; however, perioperative nursing requires a unique skill set and specialized knowledge that is incomparable to other nursing contexts [3,22]. For this reason, a rigorous literature review was undertaken to establish the existing body of literature related to TTP arrangements within perioperative nursing. The literature review identified a paucity of empirical evidence, with most research on perioperative TTP arrangements consisting of discussion and editorial papers [7]. In addition, most papers described the TTP arrangement they offer rather than provide an evaluation of the TTP arrangements. Papers that evaluated TTP arrangements frequently measured efficacy by participant retention postcompletion [7]. In addition, an Australian national report also identified that TTP arrangements are unregulated and unmonitored [8]. This has led to significant variability between TTP arrangements and their providers.

The lack of empirical evidence and the variability between TTP arrangements provide the rationale and justification of this study. The aims, objectives, and RQs developed are aimed to address these gaps and limitations. It will also provide a guiding framework for TTP arrangement design, development, and implementation within perioperative nursing.

Methodological Discussion

Integration (with or without method integration) is an essential element within mixed methods methodology [10]. This differs from multimethod research, where various methods are used, but data or data analysis are not required to be integrated [10]. Within this study, mixed methods are adopted as the methodology for a multitude of reasons. Mixed methods are frequently used in evaluation research as the research questions are often multifaceted, such as phases 1 and 2 within this study [9]. The third phase of this project requires data collection from multiple sources, as novice perioperative nurses and

perioperative nurse educators are key participants in this topic. The mixed methods methodology is well suited to collecting and mixing multiple data sources from various participant cohorts [9,10].

The mixed methods methodology uses significant formalization approaches to ensure rigor and accuracy of results [10]. Numerous mixed-method designs are available for the researcher to use to provide a pragmatic and appropriate approach to their research. This study uses an exploratory mixed-method, multilevel triangulation design with sequential phase design to achieve the desired research aim and objectives [9,10]. Using this design, the researchers can collect data in distinct phases and sequentially. Each phase of this study requires a differing method due to the lack of perioperative nursing TTP literature. In addition, phase 3 of this study relies on the findings from phases 1 and 2. The findings from phases 1 and 2 are related to the characteristics of TTP arrangements and the experiences and efficacy of these arrangements. Using these findings, an interview tool can be developed for phase 3 to explore TTP arrangements in great depth.

Implementation Challenges and Limitations

The researchers have identified several potential challenges and limitations that may affect this study. The use of online surveys, generalizability, and the methodology will be discussed herein. By identifying these challenges and limitations in the early phases of the study, mitigation strategies can be enacted to prevent or minimize their impact.

The use of online surveys presents a potential implementation challenge. It is estimated that online surveys attract response rates anywhere from 15% to 60% [23]. Regarding this study, it may suggest that the surveys of phases 1 and 2 may not receive the desired number of participants. The implication of this challenge is minimized as sound plans for participant recruitment have been included in the research methods. In addition, the survey will remain available online until an appropriate number of participants is reached. It is also observed within online surveys that some responses may be fraudulent [23]. Fraudulent refers to multiple responses from the same participant, or the tool might be inappropriately and opportunistically used. This may cause misrepresentation in the data collected and affect the findings. This study overcomes this challenge by ensuring that participants must complete a reCAPTCHA before accessing the survey, placing a cookie on participants' browsers to prevent surveys from being completed more than once by the same participant, and preventing search engine indexing [12].

Sample size and generalizability considerations have been incorporated into this study and the methods. However, capturing all potential demographic participants and participant experiences in a study is difficult. Furthermore, it is difficult to ascertain the population sizes of the participant cohorts within this study. The researcher used their own experiences to establish an estimated total population size that was used for sample size calculations. Therefore, the components of this study may not apply to all perioperative novice nurses. Generalizability has been addressed by ensuring accurate sample size calculations for the relevant phases of the study. In addition, it has been addressed by the recruitment strategies and analysis strategies.

Finally, the mixed methods methodology presents some unique challenges. In particular, the length of the study can be greater than a single-method study [10]. This is particularly relevant within this study as phase 3 is sequential from phases 1 and 2; therefore, the project length will be increased. In addition, there is potential difficulty in reconciling and triangulating differences in data. Data sets that may emerge from this research could be noncongruent. However, this will lead to further discussion possibilities [10]. A delimitation of this method is that data sets from each phase can often be cross-validated and confirmed, adding to the validity and trustworthiness of the research.

Acknowledgments

This research project is supported by the Centaur Memorial Fund for Nurses – Higher Research Degree Scholarship. Generative AI was not used in the preparation of this manuscript.

Data Availability

Data sharing is not applicable to this article as no data sets were generated or analyzed during the preparation of this protocol.

Authors' Contributions

NN contributed to the conceptualization, methodology, validation, and writing (original draft). PC, AS, and LJ performed conceptualization, methodology, validation, supervision, and writing (review and editing).

Conflicts of Interest

None declared.

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Abbreviations

RQ: research question
TTP: transition to practice

Edited by T Leung; submitted 01.08.24; peer-reviewed by T Flenady, A Byrne; comments to author 12.11.24; revised version received 18.11.24; accepted 27.11.24; published 23.01.25.

Please cite as:
Nijkamp N, Calleja P, Sahay A, Jack L
Evaluation of the Transition-to-Practice Arrangements for Novice Perioperative Nurses: Protocol for a Mixed Methods Study
JMIR Res Protoc 2025;14:e64970
URL: https://www.researchprotocols.org/2025/1/e64970
doi:10.2196/64970
PMID:39847424

Protocol

Feasibility of a Progesterone-Modified Natural Protocol for Frozen Embryo Transfer: Protocol for a Pilot Cohort Study

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Abstract

Background: With the existence of various frozen embryo transfer (FET) methods currently used in the field of assisted reproductive technologies, the debate surrounding which of these is superior remains. All FET protocols aim to prime the endometrium and time embryo transfer during the window of implantation. Current methods include the true natural cycle FET (tNFET), modified natural cycle FET, artificial cycle FET, and ovulation induction. Each of these harbors, distinct advantages and disadvantages, namely, surrounding the timing of transfer and flexibility conferred through this process. More recently, a newer approach has been used whereby the need to monitor or trigger ovulation is circumvented, with luteal phase support commenced once a certain follicle diameter and endometrial thickness criteria are met but before ovulation. However, the research into this protocol has certain important limitations that our study seeks to address.

Objective: This study aims to assess the feasibility of a progesterone-modified natural cycle protocol for FET. The primary outcome will be the presence of a corpus luteum on ultrasound scans on the day of embryo transfer. The secondary outcomes will include the number of clinic visits required per patient undergoing the protocol, biochemical pregnancy rate, and clinical pregnancy rate.

Methods: We will conduct a prospective cohort study, recruiting 20 women undertaking FET at the Public Fertility Care of The Royal Women's Hospital in Melbourne, Australia. These women will be matched to a control group who have undergone the tNFET protocol within the preceding 12 months of the study start date.

Results: This project received ethics approval on July 17, 2024, with commencement of the study in September 2024, aiming for a duration of completion of 9 months. The completion of the follow-up and submission of the study for publication are anticipated for September 2025.

Conclusions: After this preliminary study, the aim would be to progress to a noninferiority randomized controlled trial to compare the progesterone-modified natural cycle protocol for FET to the tNFET.

International Registered Report Identifier (IRRID): PRR1-10.2196/66579

(JMIR Res Protoc 2025;14:e66579) doi:10.2196/66579

KEYWORDS

frozen embryo transfer; fertility care; reproductive health; infertility; progesterone-modified natural cycle protocol; in vitro fertilization

Introduction

Frozen embryo transfer (FET) has been increasingly used over recent decades in Europe [1,2] and Australia [2]. With advancements in cryopreservation techniques and increasing use of FET, debate still exists around the optimal method of endometrial preparation to achieve the best possible pregnancy rates and improve various maternal and neonatal outcomes. The most widely used protocols for endometrial preparation include the natural cycle FET (NFET), artificial cycle FET (AFET), and ovulation induction methods [3], with the latter two protocols usually reserved for anovulatory women. While the true NFET (tNFET) relies on monitoring for a surge of endogenous luteinizing hormone (LH) and rise in progesterone (P4) as markers of ovulation to time P4 supplementation start and embryo transfer, the AFET protocol involves exogenous hormone (estrogen, followed by P4) administration to mimic the natural cycle and prime the endometrium. Furthermore, while the AFET confers greater flexibility in terms of timing FET precisely, there is evidence to suggest lower overall implantation rates and higher miscarriage rates from this technique [4]. The literature also suggests there may be a higher rate of obstetric complications for both mother and fetus, including pre-eclampsia [5] and fetal macrosomia [6]. Therefore, the advantage of tNFET centers on avoiding excessive exogenous hormone administration and the resulting adverse events (AEs) linked to AFET. However, the inflexibility conferred by the tNFET in terms of the need to closely monitor endometrial thickness, follicle size, and hormone levels may require multiple blood tests and 7-day in-vitro fertilization clinic availability. Further, the ovulation induction protocol involves the expense and invasiveness of using medication without removing the need for a 7-day service or the need for blood tests. Therefore, a protocol that achieves ovulation and gives a degree of flexibility to the timing of embryo transfer would be highly appealing to both patients and in-vitro fertilization clinics.

To address these challenges, some clinics use the modified NFET (mNFET) protocol where exogenous human chorionic gonadotropin (hCG) is administered to trigger ovulation when a dominant follicle of typically 17 mm or more is detected, thereby conferring some flexibility in scheduling FET while still relying on the woman's natural cycle [7]. Retrospective cohort studies have shown favorable outcomes in both the tNFET and mNFET as compared to the AFET [8]. Notably, two recent randomized controlled trials (RCTs) showed similar rates of pregnancy in the mNFET as compared to the tNFET, with higher implantation rates in the mNFET cohort [7,9]. However, at least one study has reported better outcomes with tNFET [10], and the most recent Cochrane systematic review on cycle regimens of FET did not compare tNFET and mNFET [3].

To further explore the potential flexibility conferred by the mNFET method while mitigating the lack of flexibility in scheduling the transfer, a prospective case series proof-of-concept study by Weiss et al [11] has trialed a novel approach whereby timing the FET to the endogenous LH surge is circumvented. Instead, P4 luteal phase support (LPS) via vaginal pessary is commenced once a mature follicle of >12 mm is identified in ultrasound scans and the lining of the endometrium is sufficiently thick at >7 mm, with FET scheduled 2-5 days from this point, depending on the stage of the embryo at the time of cryopreservation. It appears that this P4-modified natural protocol for FET (P4mNFET) provides a simultaneous advantage of both retaining a natural cycle, with authors suggesting ovulation took place regardless, as well as conferring greater flexibility for the scheduling of embryo transfer without compromising clinical pregnancy rates. It should be noted that the authors report a degree of variation in the timing of P4 initiation in relation to the last ultrasound scan without any further blood tests. Importantly, no AEs were reported from this study of 42 participants. A more recent retrospective cohort study comparing this method to AFET demonstrated comparable outcomes in terms of clinical pregnancy, miscarriage, and live birth rates between the methods [12]. A further single-center retrospective cohort study reported similar results when comparing outcomes from patients undergoing FET cycles within the natural and artificial protocols, as compared to a P4mNFET protocol [13]. Taken together, P4mNFET may confer greater flexibility to clinicians and patients in timing FET, negating the requirement to await ovulation, with comparable outcomes.

Overall, this study aims to provide greater flexibility in timing transfer by providing participants with vaginal pessaries of P4 to be used before FET and, subsequently, confirming the absence of elevated endogenous P4 on the day of P4 supplementation start and confirming the presence of a corpus luteum on an ultrasound scan. It is hypothesized that the potential advantages of this P4mNFET protocol, over triggering and manipulating ovulation, may include the increased flexibility in the timing of commencing P4 without the requirement of a large follicle, the elimination of the importance of pinpointing the exact timing of ovulation, and the potential cost-saving to the patient and clinic as a result of these components. It is anticipated that the outcomes of this pilot cohort study may inform the planning and development of a subsequent noninferiority RCT to further reinforce the utility of such a protocol.

Methods

Study Type

The proposed study will adopt a pilot cohort methodology consisting of 12 weeks of intervention and follow-up monitoring of participants for primary and secondary outcomes. Secondary outcomes will be compared with retrospective data from the tNFET control group.

Participants

The study population will consist of 20 women undertaking FET cycles at the Public Fertility Care of The Royal Women's Hospital (RWH), Melbourne, Australia. The recruitment process will commence at this location, whereby clinicians and nursing teams will be invited to screen the patients they interact with for eligibility for the study. These staff members will be trained on appropriate screening according to the study protocol and will be delegated by the principal investigator. Eligible patients will then be approached for study by team members who are not directly involved in potential participants' clinical care and, therefore, will not have had any clinical interactions with the participant. All patients will be provided with a patient informed consent form (Multimedia Appendix 1) to ensure they are familiar with the protocol requirements and understand their rights as participants. Additionally, they will be provided with a patient information document created by the research team (Multimedia Appendix 2) to assist with patient education surrounding the use of the P4 pessary during the study.

Inclusion criteria consist of women with regular cycles defined as 21-35 days, women younger than 40 years at the start of a cycle, and women whose BMI ranges from 18 to 35, inclusively.

The exclusion criteria include anovulatory women, women who are 40 years or older at the start of the cycle, and women who have preexisting contraindications to exogenous P4 supplementation, such as those with liver disease or thromboembolic disease. The exclusion criteria will also include the use of additional LPS (eg, subcutaneous), women with uterine pathology, including congenital malformations of the female reproductive tract, endometrial polyps, intrauterine adhesions, adenomyosis, and leiomyoma. Regarding the retrospective element of the study, patients for whom inclusion criteria information is lacking will not be included in the study.

The control group will consist of retrospective data from 20 women, matched against inclusion and exclusion criteria, within the Public Fertility Services of the RWH data bank. These controls would have undergone tNFET at the service provider within the preceding 12 months of the study start date.

All participant data will be stored securely in the database of the RWH Reproductive Services Unit (RSU), ensuring the security of patients' confidential information. Furthermore, on completion of the study, all patient information will be securely stored within the hospital server with restricted access for a minimum of 15 years, with custodial responsibilities given to the principal investigator.

Outcome Measures

The primary outcome will be the presence of corpus luteum with a characteristic "ring of fire" appearance on the transabdominal ultrasound on the day of embryo transfer.

The secondary outcomes consist of the number of clinic visits required per patient undergoing this protocol, the biochemical pregnancy rate defined as the detection of βhCG in serum or urine [14], and the clinical pregnancy rate defined as the ultrasonographic visualization of one or more gestational sacs [14].

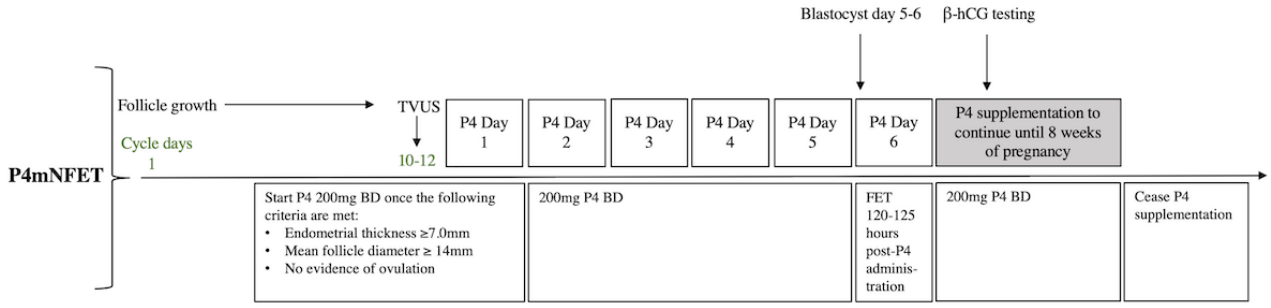
Randomization

This is a pilot prospective cohort study without randomization.

Intervention: P4mNFET Protocol

Participants will undergo active treatment for 2-8 weeks, with a follow-up period of up to 12 weeks or gestation. For a patient with a 28-day menstrual cycle, on days 10-12 (Figure 1), a transvaginal ultrasound will be performed to evaluate for an appropriate endometrial thickness of 7.0 mm and a mean follicle diameter of 14.0 mm. If these ultrasound criteria are met, the patient will undergo blood tests for estrogen, LH, and P4 on the same day; should levels of P4 be under 5 nmol/L, exogenous P4 supplementation via vaginal pessary will then commence on the same day, with FET scheduled 120-125 hours post P4 administration. P4 pessary, ORIPRO (Orion Laboratories Pty Ltd T/A Perrigo Australia, Balcatta, Western Australia), at a dose of 200 mg twice daily, will be the only form of LPS for patients undergoing P4mNFET. Following FET, serum hCG will be taken 10 days later. If positive, LPS via P4 pessary at 200 mg twice daily will continue to 8 weeks' gestation with a pregnancy scan between 6-7 weeks. If negative, the patient will be advised to cease LPS. In the instances where P4 levels are greater than 5 nmol/L, the patient will be removed from the study.

Figure 1. Visual representation of the patient journey with P4mNFET protocol. FET: frozen embryo transfer; hCG: human chorionic gonadotropin; P4: progesterone; P4mNFET: progesterone-modified natural cycle protocol for frozen embryo transfer; TVUS: transvaginal ultrasound.



Control: tNFET Protocol

The control group will consist of patients, matched to the inclusion and exclusion criteria, who would have undergone tNFET at the RWH RSU. Patients undertake an ultrasound on days 10-12 of their cycle for those with a 28-day cycle. Upon detection of a dominant follicle of 18 mm or more and an endometrial thickness of 7 mm or more, serum LH and P4 are taken. An LH surge is defined as >25 IU/L in the context of P4 <5 nmol/L. Ovulation is defined as a P4 >5 nmol/L. LPS, in the form of a vaginal ORIPRO 200 mg pessary (Orion Laboratories Pty Ltd T/A Perrigo, Australia), is commenced on day 1 post ovulation, and embryo transfer is carried out 6 days post LH surge.

Statistical Analysis and Sample Size

Given the qualitative and binary nature of the primary outcome, no statistical testing is proposed for this. Secondary outcomes will undergo *t* tests and Mann-Whitney *U* tests for data that are normally and not normally distributed, respectively. Should there be significant variation in the key baseline variables between the study and the control group, a multivariate analysis will be performed.

Safety Monitoring and Reporting

Safety oversight for the study will be carried out under the direction of the independent safety monitor working within the framework of the Data and Safety Monitoring Board Charter to ensure an objective assessment of the safety and efficacy of the study. AEs deemed secondary to the administration of the pessary will be monitored and reported accordingly by either the investigators or the independent safety monitor, from administration to the end of follow-up. Relevant physical examinations or investigations will then be carried out to ensure the effects of the AE are managed accordingly. The primary investigator will record the AE appropriately into the patient's medical record or study shadow file.

Integration and Dissemination of Findings

On completion of the study, primary and secondary outcomes will be disseminated to investigators, ensuring the confidentiality of patient information. Findings will be synthesized and communicated to colleagues of the RWH RSU and Human Research Ethics Committee, as well as in further peer-reviewed publications related to the RCT that may be conducted following the completion of this cohort study. Additionally, findings will be communicated confidentially in potential presentations at national and international conferences.

Results

This project was conceived in November 2023. It was subsequently approved by the RWH Human Research Ethics Committee on July 17, 2024. Local governance approval was granted on August 28, 2024.

Commencement of the study began in September 2024, aiming for a duration of completion of 9 months, and completion of follow-up and submission of the study for publication in September 2025.

Discussion

Overview

We have designed a pilot cohort nonrandomized study to assess the feasibility of a novel P4mNFET protocol that circumvents the need to monitor for an endogenous LH surge to pinpoint ovulation to schedule FET. This protocol, therefore, may combine the advantages of the tNFET, AFET, and mNFET into one protocol that provides greater flexibility for the timing of transfer with fewer requirements for surveillance and no impact on pregnancy outcomes.

Anticipated Challenges

As with any study of this kind, some challenges are anticipated with patient recruitment. The research team aims to mitigate this via appropriate counseling and use of our patient informed consent form, which is in a question-and-answer format.

The second challenge may be the accuracy of the retrospective data for the control group. This is an inherent issue with all retrospective studies. However, it is anticipated that key secondary outcomes will be accurately reported.

Limitations

As with any study, there are limitations to acknowledge. First, cohort studies lack the same level of rigorous methodology as an RCT. However, based on the results of this pilot, we aim to proceed with a noninferiority RCT to compare this novel protocol to tNFET. Second, the retrospective nature of the control group may be associated with issues related to data entry.

Implications

The implications of this study are that it may inform the future of FET. If primary outcomes are met such that the presence of the corpus luteum is maintained with P4mNFET, then a noninferiority RCT will be carried out to formally compare the two methods. Moving forward, this P4mNFET protocol may provide clinics the opportunity to perform FET with greater scheduling flexibility and comparable outcomes to established methods while potentially leading to cost-saving and increased efficiency.

Acknowledgments

Generative artificial intelligence was not used in the writing or conceptualization of this protocol.

This study is supported by The Royal Women's Hospital, Melbourne, Victoria.

Data Availability

The datasets generated or analyzed during this study are available from the corresponding author upon reasonable request.

Authors' Contributions

AC was involved in the project conceptualization, literature search, and writing of the original draft. EG was involved in the conceptualization, reviewing and editing, project administration, and supervision. VA was involved in the protocol development and study coordination. AP was involved in the study conceptualization and writing of the protocol. WTT was involved in the study conceptualization and writing of the protocol.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Patient informed consent form for recruitment of patients to undergo the progesterone-modified natural cycle protocol for frozen embryo transfer at the Reproductive Services Unit of The Royal Women's Hospital, Melbourne.
[PDF File (Adobe PDF File), 289 KB - resprot_v14i1e66579_app1.pdf]

Multimedia Appendix 2
Participant information sheet for use of progesterone pessary during progesterone-modified natural cycle protocol for frozen embryo transfer.
[PDF File (Adobe PDF File), 95 KB - resprot_v14i1e66579_app2.pdf]

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Abbreviations

AE: adverse event
AFET: artificial cycle frozen embryo transfer
FET: frozen embryo transfer
hCG: human chorionic gonadotropin
LH: luteinizing hormone
LPS: luteal phase support
mNFET: modified natural cycle frozen embryo transfer
NFET: natural cycle frozen embryo transfer
P4: progesterone
P4mNFET: progesterone-modified natural cycle protocol for frozen embryo transfer
RCT: randomized controlled trial
RSU: Reproductive Services Unit
RWH: Royal Women's Hospital
tNFET: true natural cycle frozen embryo transfer

Edited by T Leung; submitted 19.09.24; peer-reviewed by E Horowitz, R Pabuccu; comments to author 27.11.24; revised version received 11.12.24; accepted 25.02.25; published 11.04.25.

Please cite as:
Churchill A, Georgiou E, Abruzzo V, Polyakov A, Teh WT
Feasibility of a Progesterone-Modified Natural Protocol for Frozen Embryo Transfer: Protocol for a Pilot Cohort Study
JMIR Res Protoc 2025;14:e66579
URL: https://www.researchprotocols.org/2025/1/e66579
doi:10.2196/66579
PMID:40215104

Protocol

Early Detection of Type 1 Diabetes in First-Degree Relatives in Saudi Arabia (VISION-T1D): Protocol for a Pilot Implementation Study

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Abstract

Background: Type 1 diabetes (T1D) is a growing global health concern, with a notable rise in incidence in Saudi Arabia. Despite the potential benefits of early detection through screening programs, such initiatives are currently lacking in Saudi Arabia and other Arab countries.

Objective: This study aims to evaluate the feasibility, acceptability, and cost-effectiveness of a T1D-screening program targeting high-risk individuals, specifically children with a first-degree relative diagnosed with T1D.

Methods: The VISION-T1D program is a prospective cohort study focused on the early detection of presymptomatic T1D by screening children aged 2-18 years. The primary screening method involves testing for islet autoantibodies, including insulin autoantibodies, glutamic acid decarboxylase autoantibodies, insulinoma associated-2 autoantibodies, and zinc transporter-8 autoantibodies. Optional genetic testing, including human leukocyte antigen phenotyping and the genetic risk score, is offered. Outcomes include the feasibility of the screening process, prevalence of early-stage T1D, psychological impacts, educational intervention effectiveness, progression rates to stage-3 T1D, and economic viability.

Results: The VISION-T1D program began in May 2024. As of December 2024, a total of 176 families have been enrolled. Data collection will continue until April 2025, with final data analysis projected for mid-2025.

Conclusions: The VISION-T1D study provides a practical approach to T1D screening tailored to the health care landscape of Saudi Arabia. The insights gained from this pilot program will inform the development of a national, population-based screening initiative designed to reduce diabetic ketoacidosis at diagnosis, improve long-term outcomes, and alleviate the economic burden of T1D. The VISION-T1D initiative could also serve as a scalable and sustainable model that can be adopted internationally, contributing to global efforts to manage and prevent T1D.

Trial Registration: ClinicalTrials.gov NCT06513247; https://clinicaltrials.gov/study/NCT06513247

International Registered Report Identifier (IRRID): DERR1-10.2196/70575

(JMIR Res Protoc 2025;14:e70575) doi:10.2196/70575

KEYWORDS

islet autoimmunity; type 1 diabetes mellitus; T1D; screening program; antibody detection by agglutination–polymerase chain reaction; PCR; ADAP; human leukocyte antigen; genetic risk score

Introduction

Background

The incidence of type 1 diabetes (T1D) is rising globally, with Saudi Arabia reporting a surge to 31.4 per 100,000 youths annually, making a nearly 9-fold increase over the past decade [1,2]. This trend is compounded by high rates of diabetic ketoacidosis (DKA) at diagnosis [3], ranging from 40% to 77%, the highest in the Arab region [4,5]. DKA at T1D onset is associated with significant morbidity, mortality, and long-term complications [6-9]. DKA also imposes a substantial economic burden through direct and indirect medical costs [10-12]. Early detection by T1D screening is crucial in reducing DKA incidence and mitigating the health and economic impacts [13,14].

T1D pathogenesis involves a complex interplay of genetic predisposition and environmental factors, resulting in the autoimmune destruction of pancreatic β-cells [15,16]. Individuals with a first-degree relative (FDR) affected with T1D have a 15-fold higher lifetime risk of developing T1D compared to the general population [13]. Screening for islet autoantibodies identifies presymptomatic stages (stages 1 and 2) at least in children, adolescents, and young people, enabling timely interventions that may alter disease progression [13,17-19]. Individuals with multiple positive islet autoantibodies have a 99% lifetime risk of progressing to clinical stage-3 T1D, with 84% developing insulin-dependent diabetes within 15 years of seroconversion [18-20]. Screening programs in several countries have successfully reduced DKA at diagnosis, improved long-term outcomes, and lowered health care costs [13,14].

Despite successful screening initiatives in other countries, Saudi Arabia and neighboring Arab countries lack such programs. Moreover, most prior efforts have been confined to research settings, leaving a gap in knowledge about real-world implementation in health care settings [14,18,20,21]. The VISION-T1D protocol (NCT06513247) aims to bridge this gap by evaluating the feasibility and cost-effectiveness of a pilot, T1D-screening program for FDRs of individuals with T1D in Saudi Arabia. Aligned with Saudi Arabia's National 2030 Vision, which prioritizes health improvement and the reduction of chronic disease burden, the VISION-T1D initiative aims to establish a robust framework for broader, population-based, T1D-screening implementation in Saudi Arabia. Furthermore, it could also serve as a scalable and sustainable model for international adoption, thereby contributing to global efforts to manage and prevent T1D.

Study Objectives

Primary Objectives

The primary objectives are as follows:

- Evaluate the feasibility of implementing a pilot, T1D-screening program for early detection in FDRs of patients with T1D in Saudi Arabia.
- Determine the prevalence of stages-1, -2, and -3 T1D among FDRs of patients with TID in Saudi Arabia.

Secondary Objectives

The secondary objectives are as follows:

- Examine the psychological impacts of T1D screening on caregivers, including changes in anxiety, depression, distress level, and health-related quality of life before and after receiving screening results.
- Evaluate the effect of early detection on reducing DKA incidence at stage-3 T1D onset.
- Analyze the cost-effectiveness of implementing a T1D-screening program in Saudi Arabia.
- Evaluate the natural history of T1D progression in identified presymptomatic individuals, tracking time to clinical onset and changes in health outcomes over time.
- Examine the effectiveness of educational interventions on caregivers' knowledge of T1D screening and early identification.
- Investigate the genetic predisposition to T1D within our population through human leukocyte antigen (HLA) testing and validate the genetic risk score (GRS) 2 in the Saudi population.

Methods

Study Design and Setting

The Vision-T1D study is a prospective cohort designed to screen children aged 2-18 years who have an FDR with T1D (index case). Participants are recruited from the University Diabetes Centre (UDC) at King Saud University Medical City (KSUMC) in Riyadh, Saudi Arabia. The diagnosis of T1D in index cases is based on the American Diabetes Association criteria [22], and T1D classification is determined by a clinical diagnosis from a specialized endocrinologist, with or without confirmatory islet autoantibodies testing. Exclusion criteria included index cases diagnosed with other forms of diabetes and non-Saudi children due to different ethnic and genetic backgrounds.

Ethical Considerations

The study was approved by the Institutional Review Board of King Saud University Ethics Committee (approval: E-248566). The pilot phase began in May 2024, with 1 year dedicated to recruitment and screening. All procedures were conducted in accordance with the ethical standards of the Declaration of Helsinki and national research ethics guidelines.

Informed consent was obtained from all participants or their legal guardians prior to data collection. Privacy and confidentiality were maintained according to GCP standards. Participants identified as at risk or presymptomatic for T1D

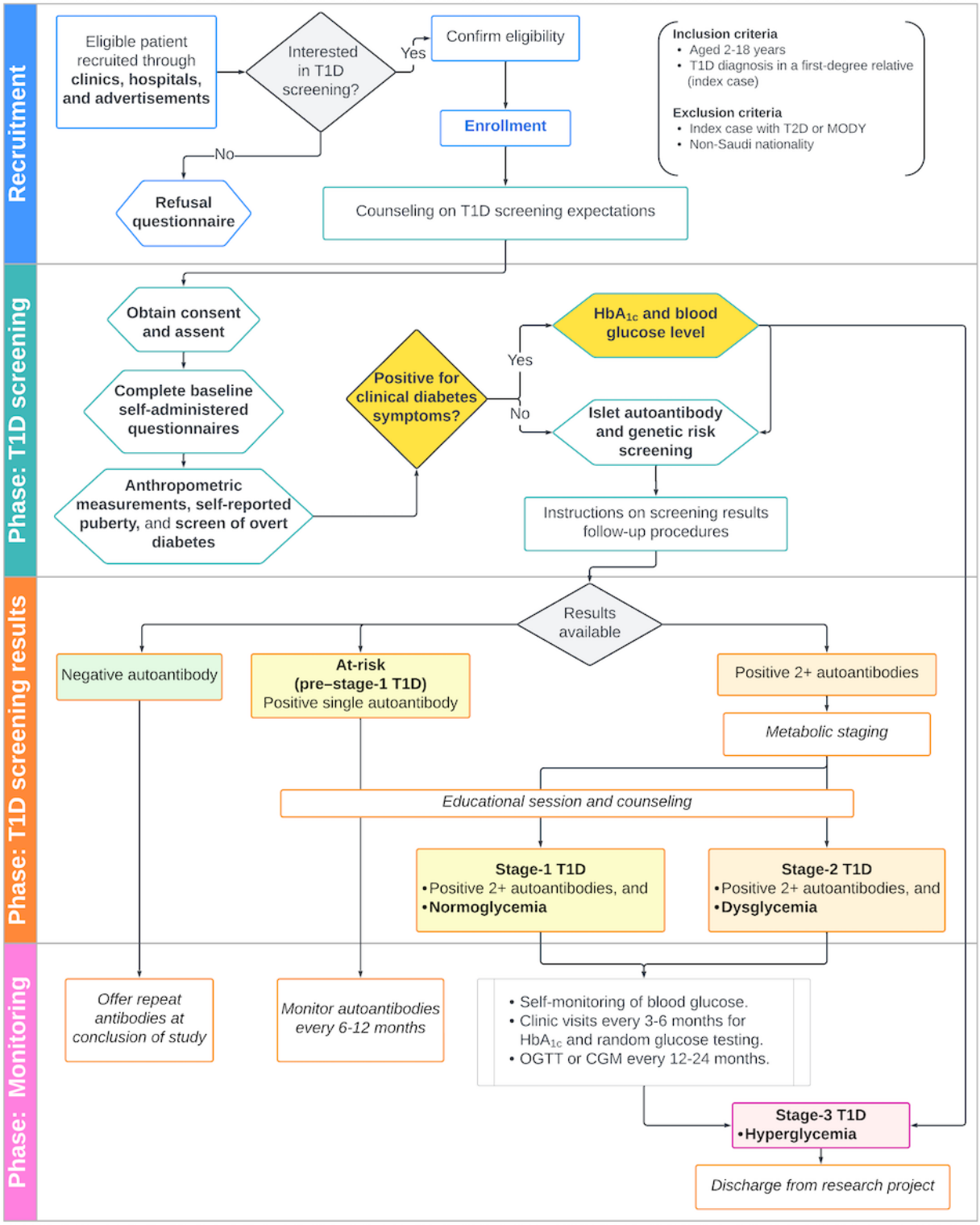
will enter a 4-year clinical follow-up phase, culminating in a total study duration of 5 years.

Participants did not receive financial compensation for participation. However, We have received funding for the project as described in the acknowledgment section.

Study Process and Interventions

The VISION-T1D study consists of 3 well-structured phases: screening, results communication and counseling, and long-term clinical follow-up. Each phase is designed to provide tailored interventions, ensuring appropriate care, monitoring, and education for children and their families (Figure 1).

Figure 1. The study flowchart. CGM: continuous glucose monitoring; HbA_{1c}: hemoglobin A_{1c}; MODY: maturity-onset diabetes of the young; OGTT: oral glucose tolerance test; T1D: type 1 diabetes; T2D: type 2 diabetes.



Phase 1: T1D Screening

Families are recruited and scheduled for an enrollment and screening visit, where they receive comprehensive counseling about participation and education on T1D screening. Upon obtaining informed consent and assent, participants undergo baseline assessments, including completion of questionnaires and the collection of blood samples for islet autoantibody testing. Optional genetic screening for HLA phenotyping and GRS analysis is also offered to evaluate genetic predisposition to T1D. To enhance recruitment, a home testing option is provided, allowing families to conveniently perform finger-prick testing and data collection at home.

Phase 2: Results Communication, Education, and Metabolic Staging

After screening results are available, a research physician reviews the findings. Participants who test positive for islet autoantibodies are invited to a follow-up visit that includes personalized counseling, targeted educational interventions, and additional metabolic staging to determine their T1D stage. Participants with negative islet autoantibody results are notified by the research staff and are invited for repeat autoantibody screening at the conclusion of the long-term follow-up period (approximately 4-5 years later).

Phase 3: Long-Term Clinical Follow-Up

Participants identified as having presymptomatic T1D (stage 1 or 2) or those at risk based on autoantibody markers enter a 4-year clinical follow-up phase. During this period, regular monitoring of disease progression is conducted through metabolic assessments and psychological evaluations. Participants receive continuous support tailored to their risk level and diagnosis.

This systematic, 3-phase approach ensures that participants receive appropriate care, counseling, and monitoring based on their screening outcomes.

Phase 1: T1D-Screening Procedures and Data Collection

Recruitment and Enrollment

Active and passive recruitment strategies are used. Research staff identified potential participants by reviewing patient lists from KSUMC diabetes clinics and pediatric endocrinology inpatient records. Recruitment materials, including advertisements with QR codes, are shared via the UDC and on social media platforms. The QR codes were linked to an introductory video explaining the study and eligibility criteria, along with a contact submission form. Families who decline participation are asked about the reason for refusal.

Informed Consent

Eligible families are scheduled for T1D-screening visits, where informed consent and assent are obtained. A comprehensive educational approach was developed to ensure participants receive standardized information and fully understand the T1D-screening process. This included an animated video and an educational booklet. The video, in Arabic, explains the screening program and key concepts, such as T1D pathophysiology, its stages, and clinical presentation. It emphasizes the benefits of early detection in preventing DKA and improving long-term outcomes; outlines the screening process; and provides an overview of current and emerging T1D treatments, including insulin therapy and disease-modifying interventions. The educational booklet complemented the video, using infographics to illustrate T1D pathophysiology, stages, symptoms, and benefits of screening. It also outlined study expectations and provided key study contact information.

Intervention: T1D Screening

Islet Autoantibodies Screening

The program uses antibody detection by agglutination–polymerase chain reaction (ADAP) assay, a cutting-edge technology developed by Enable Biosciences. The assay measures islet autoantibodies [23-27], including insulin autoantibodies, glutamic acid decarboxylase autoantibodies, IA-2 autoantibodies, and zinc transporter 8 autoantibodies, using dried blood spots on filter paper. The ADAP assay offers notable advantages over other assays for large-scale analysis, such as cost-effectiveness, high sensitivity and specificity, and minimal sample volume requirements. These features make it suitable for large-scale applications, including home testing [25-27].

Genetic Risk Screening

This pilot study integrated optional HLA phenotyping and GRS testing to deepen the understanding of T1D pathogenesis in the Saudi population. Analyses will be conducted by Enable Biosciences, the Barbara Davis Center for Childhood Diabetes, and delegates [28,29]. These tests are used for research purposes only.

HLA Phenotyping

Testing focuses on identifying high-risk HLA genotypes associated with T1D, particularly variants in the HLA region (MHC class II alleles), which account for over 50% of T1D heritability [13]. This approach aims to provide insights into T1D risk associations in the Saudi population, especially in participants with negative islet autoantibodies. HLA typing is performed using oligonucleotide probes for *HLA-DRB1*, *DQA1*, and *DQB1* alleles as previously described [30].

GRS Testing

The GRS aggregates the cumulative contribution of multiple genetic variants into a single score estimating an individual's genetic predisposition to T1D [29,31-33]. This study uses GRS2, an advanced version that incorporates HLA haplotypes, non-HLA loci, and interactions between HLA variants [34]. Testing is conducted using a Kompetitive allele-specific polymerase chain reaction (PCR) assay, as described earlier [35,36]. The Kompetitive allele-specific PCR assay is a cost-effective and efficient alternative to the traditional DNA array and imputation-based methods. It successfully genotypes 60 of the 67 single nucleotide polymorphisms in GRS2, with the remaining single nucleotide polymorphisms excluded due to genotyping challenges. This study represents one of the first applications of GRS2 in FDRs of patients with T1D and the first validation of its use within the Saudi population.

Specimen Collection

Blood samples are collected via fingerstick or venous sampling onto dried blood spot filter paper, based on participant preference. For families opting for home testing, parents collect sample cards and detailed instructions from the clinic, perform the testing at home, and return the samples for processing. All collected samples are stored at –80 °C before being batched and shipped to the United States for analysis.

Measures

Demographics and Clinical Characteristics

Families complete a self-administered questionnaire upon enrollment to collect baseline demographics and clinical characteristics. Information includes the age, sex, medical history, and current medications of the participating child, as well as family demographics such as parental age, marital status, number of siblings, education levels, family income, residential region, and family medical history focused on diabetes or autoimmune diseases among FDR and any self-reported parental comorbidities. For the index case with T1D, the questionnaire captures clinical details, including the relationship to the participant, age at diagnosis, current age, insulin regimen, history of DKA at onset or recurrent DKA, and diabetes-related complications. If multiple FDRs have T1D, similar information is collected for each.

Clinical T1D Screening

Participants are screened for overt diabetes symptoms, such as polyuria, polydipsia, polyphagia, and unexplained weight loss. Research staff conduct point-of-care hemoglobin A_{1c} (HbA_{1c}) and random blood glucose tests if any symptoms are reported. Participants with abnormal blood sugar levels are referred to a research physician for further evaluation, which may include an oral glucose tolerance test (OGTT) and counseling. Those meeting the diagnostic criteria for stage 3 T1D will receive standard medical care and education for new-onset diabetes.

Health Literacy

The Single-Item Literacy Screener tool evaluates parental health literacy using a 5-point Likert scale. A score of 4 or higher indicates adequate health literacy, while a score of 3 or lower suggests limited literacy [37-39].

T1D-Screening Acceptability Assessment Scale

This self-administered tool evaluates caregivers' acceptability of the T1D-screening program through 10 items rated on a 5-point Likert scale. Domains include affective attitude, the ethicality of the screening, perceived effectiveness, self-efficacy, opportunity costs, communication, burden, and general and cultural acceptability. Total scores range from 10 to 50, with higher scores indicating greater acceptability [40].

Psychological Measures

A set of validated Arabic tools assess caregiver stress, anxiety, depression, and quality of life at baseline, after results disclosure, and during long-term follow-up.

Anxiety Symptoms

The Generalized Anxiety Disorder 7-item scale screens for generalized anxiety over the past 2 weeks using a 4-point Likert scale. A score of 8 or more indicates possible generalized anxiety disorder, with 92% sensitivity and 76% specificity [40,41].

Depressive Symptoms

The Patient Health Questionnaire-9 screens for depression. A score of more than 10 suggests possible major depressive disorder, with a sensitivity and specificity of 88% [42-44]. Research staff will screen responses indicating suicidal ideation and prompt immediate referral to emergency care.

Health-Related Quality of Life

The EQ-5D-5L tool from the EuroQol Group measures health across 5 dimensions—mobility, self-care, usual activities, pain or discomfort, and anxiety or depression—each rated on 5 levels. The EuroQol Visual Analogue Scale allows participants to rate their overall health from 0=worst to 100=best [45]. The results are scored using a value set specific to Saudi Arabia, providing a comprehensive quality of life score [46].

Distress

The Subjective Units of Distress Scale measures anxiety and discomfort on a 0-100 scale, with higher scores indicating greater distress. The Subjective Units of Distress Scale is widely used and validated in clinical settings for assessment and monitoring of changes over time [47-49].

Anthropometric Measurements

Baseline assessments will include weight, height, BMI, and self- or parental-reported pubertal status [50].

Phase 2: Result Disclosure, Education, and Metabolic Staging

Results Disclosure

Participants receive written reports explaining the results, estimated risk of progression, long-term follow-up recommendations, and key contact information. The process of sharing results varies based on screening outcomes:

Participants With Negative Results

Families of participants who test negative for islet autoantibodies are contacted by the research staff to receive their results report. They are instructed to contact the research team if T1D develops in the future and are invited for repeat antibody testing at the end of the follow-up phase.

Participants With Positive Results

Families of participants who test positive for multiple islet autoantibodies are invited to a one-to-one counseling visit with a research physician to discuss the result, followed by a group education and metabolic staging to determine their T1D stage.

Participants With Equivocal Results

Families of participants with a single autoantibody are invited for a one-to-one counseling session with a physician to discuss the result. They then join the same group educational session as those with positive results.

Genetic Testing Disclosure

Genetic testing results are shared with families only upon request to avoid unnecessary alarm given the elevated baseline risk among FDRs and the lack of validated Saudi population–based genetic risk estimation. When shared, these results are presented in a dedicated educational session designed to help families understand the complexities of genetic predisposition to T1D.

Educational Curriculum for Participants With Positive or Equivocal Results

The educational curriculum was developed based on a comprehensive robust educational framework and expertise [51]. It is delivered in small group sessions by experienced endocrinologists, diabetes educators, and dietitians. The curriculum covers key topics such as T1D pathophysiology, disease progression stages, and the importance of early detection. Participants learn to identify their specific stage and risk of progression and recognize factors that influence clinical diabetes onset. The curriculum highlights insulin's role as the primary treatment for clinical T1D (stage 3), addressing common concerns and misconceptions. Participants are also trained to monitor their condition by recognizing early T1D symptoms, performing blood glucose checks, interpreting results, and determining when insulin therapy or medical advice is needed.

The program underscores nonpharmacological strategies for reducing the risk of T1D progression through healthy eating and lifestyle modifications and provides an overview of current and future T1D research. The psychological and emotional aspects of receiving T1D screening results are also addressed, and access to support is provided.

Psychological Support

The psychological and emotional impact of T1D risk disclosure is carefully addressed throughout the process. Families experiencing significant psychological burdens are offered counseling sessions and access to professional psychological support. Additionally, all families can self-refer to these services as needed. These measures are designed to alleviate stress, promote resilience, and ensure families feel supported during the follow-up period.

Metabolic Staging

Participants with multiple positive islet autoantibodies undergo metabolic staging to determine their T1D stage. This includes HbA_{1c} measurement, fasting glucose, 2-hour OGTT, or continuous glucose measurement (CGM) if OGTT is not feasible.

OGTT Measurement

Performed after an overnight fast of at least 8 hours. Participants consume a glucose solution dosed at 1.75 g/kg (up to 75 g). Serum glucose levels are measured at fasting baseline and 120 minutes after ingestion.

HbA_{1c} Measurement

Serum samples will be processed in the laboratory per American Diabetes Association–recommended standards.

CGM Measurement

Used as an alternative for participants unable or unwilling to complete an OGTT. CGM glucose profiles over a 2-week period will be reviewed for staging.

Phase 3: Long-Term Monitoring and Clinical Follow-Up

Monitoring for Disease Progression

Participants with positive single or multiple autoantibodies will enter a 4-year follow-up phase. During this period, regular assessments are performed to monitor T1D disease progression, track time to clinical onset, and observe any changes in metabolic staging. Monitoring intervals vary by stage and risk level [18,20]. Participants progressing to stage-3 T1D will transition to standard care.

Self-Monitoring of Blood Glucose

All participants with multiple positive islet autoantibodies results will be instructed to perform self-monitoring of blood glucose testing at home twice over a 2-week period after receiving their results, including one fasting test and one 2-hour postprandial test after a heavy meal. This testing should be repeated every 1-3 months and during any illness. Participants will be provided with contact information and guidance on when to seek medical advice.

Stage-1 Monitoring

Participants categorized as stage-1 T1D (positive autoantibodies with normal glycemia) will have clinic visits every 6 months for HbA_{1c} and random glucose testing. An OGTT or CGM will be performed every 24 months or earlier if there is a 10% or more rise in HbA_{1c} from baseline.

Stage-2 Monitoring

Participants categorized as stage-2 T1D (positive autoantibodies with dysglycemia) will have more frequent clinic visits every 3 months for HbA_{1c} and glucose testing. An OGTT or CGM will be performed annually or sooner if there is a 10% or more rise in HbA_{1c} from baseline.

Monitoring for Single Autoantibody Results

Participants with a single autoantibody undergo metabolic assessment only if symptoms develop. For children younger than the age of 6 years, autoantibody screening will be repeated within 6 months for confirmation, then annually throughout the study. For children aged 6 years or older, annual screening will be conducted for the duration of the study. Autoantibody monitoring will be discontinued if a participant seroconverts to a negative status. No physician visits are required, and families are encouraged to contact the research team if T1D symptoms arise in the future.

Monitoring for Participants With Negative Autoantibodies

All participants who test negative for autoantibodies will undergo follow-up autoantibody testing at the conclusion of the 5-year study period.

Other Monitoring Measures

Clinical Measurements

Weight, height, and BMI are assessed annually for participants with positive autoantibodies.

Psychological Assessment

Parents of children with positive autoantibody results will undergo psychological assessment within one week of receiving screening results. Assessments are repeated during follow-up at 6 and 12 months to track changes over time.

Outcome Definitions and Metrics

Feasibility Metrics

The feasibility of the screening program will be evaluated using the following key metrics.

- - Recruitment rates: The proportion of eligible participants successfully recruited into the study.
  - Screening refusal rates: The percentage of eligible participants who decline participation.
  - Completed screening visit rates: The percentage of participants completing the initial screening visit (phase 1).
  - Completed counseling visit rates: The percentage of participants with positive autoantibody results who complete the counseling session and educational curriculum (phase 2).
  - Completion of long-term follow-up: The percentage of participants with presymptomatic T1D who complete their monitoring visits during the 4-year follow-up period (phase 3). Participants progressing to clinical T1D before the study conclusion will transition to standard clinical care and be considered as having completed follow-up.

Prevalence of Presymptomatic T1D at Screening

Metabolic staging performed during the screening results visit (phase 2) will classify participants into the following stages.

- - Stage-1 T1D: Presence of two or more islet autoantibodies with normal glycemia. Criteria include HbA_{1c} <5.7%, fasting blood glucose <100 mg/dL, and a 2-hour OGTT <140 mg/dL. For CGM users, values >140 mg/dL should be less than 10% of the time over 10 days of continuous wear.
  - Stage-2 T1D: Presence of two or more islet autoantibodies with dysglycemia. Criteria include HbA_{1c} between 5.7% and 6.4%, fasting blood glucose between 100-125 mg/dL, and a 2-hour OGTT between 140-199 mg/dL. For CGM users, values more than 140 mg/dL should be between 10% to less than 20% of the time over 10 days of continuous wear.
  - Stage-3 T1D: Clinical onset of T1D marked by one or more islet autoantibodies and hyperglycemia. Criteria include HbA_{1c} 6.5%, fasting blood glucose levels 126 mg/dL, and a 2-hour OGTT 200 mg/dL. For CGM users, values >140 mg/dL must occur at least 20% of the time over 10 days of continuous wear.
  - At risk (pre–stage-1 T1D): Defined as the presence of a single islet autoantibody with normal glycemia.
  - Isolated genetic predisposition: Defined as the presence of positive genetic risk markers without accompanying islet autoantibodies.

Incidence of DKA

The incidence of DKA at the clinical onset of T1D will be tracked during the long-term follow-up phase (phase 3). DKA occurrences will be captured from clinical records and follow-up visits.

T1D Progression Rate

The annual progression rate to stage-3 T1D will be tracked in participants testing positive during the follow-up phase (phase 3) and categorized based on their initial stage.

Effectiveness of Educational Interventions

The effectiveness of the educational curriculum will be evaluated using pre- and postintervention tests completed by caregivers. These tests are developed to measure changes in knowledge related to the curriculum's objectives, providing a comprehensive assessment of the intervention's effectiveness in preparing caregivers for presymptomatic T1D management.

Health Care Resource Use for Cost-Effectiveness Analysis

Health care resource use will include both program-related and external health care resources. Program-related costs will encompass autoantibody testing, metabolic profiling, results notification visits, and educational or follow-up visits. Non–program-related costs will include diabetes clinic visits (eg, consultations with physicians, educators, nutritionists, or psychologists), emergency department visits for diabetes or DKA, hospitalizations for diabetes, laboratory and imaging studies, and prescription medications for diabetes management either inpatient or outpatient.

Statistical Analyses

Sample Size

The target enrollment is 1300 participants (or 322 families), based on the feasibility of recruiting 70% of eligible families from the UDC clinic cohort. The estimated seropositivity rate for islet autoantibodies among children with an FDR diagnosed with T1D is estimated at 5% to 15%, with a 90% significance level and 80% power. Considering that the UDC serves approximately 450-500 children with T1D, and that the typical Saudi family has 4-6 children younger than the age of 18 years, this sample size is calculated to be sufficient. Recruitment will be expanded to FDRs outside the UDC cohort if the family target is met without reaching the participant's goal.

Statistical Analysis

Descriptive statistics will report continuous data as mean (SD) for normally distributed variables and categorical data as frequency and percentage (N, %). Feasibility metrics and T1D stages will also be summarized as percentages.

To evaluate the psychological effects of T1D screening on caregivers, pre- and postscreening levels of anxiety, depression, and distress will be compared using paired 2-tailed *t* tests or Wilcoxon signed-rank tests, depending on data distribution. The effectiveness of educational counseling will be analyzed similarly, comparing pre- and postintervention test scores. Longitudinal changes in the psychological measures will be evaluated using repeated-measures ANOVA or mixed effects models to track patterns over time.

For participants with presymptomatic T1D, progression rates to stage 3 will be analyzed using Kaplan-Meier survival analysis. Time to event will be calculated from screening age to age at stage-3 T1D diagnosis or last follow-up. Cox proportional hazards models will assess factors associated with disease progression, such as baseline autoantibody titers, genetic risk scores, and demographic variables.

At the 1-year follow-up, cost-effectiveness will be assessed by reporting total costs for all screened participants, cost per child screened, and cost per case detected. The incremental cost-effectiveness ratio calculations will compare outcomes for screened children with controls diagnosed with stage-3 T1D in the general population. The incremental cost-effectiveness ratio will incorporate potential benefits, such as reduced DKA incidence and improved HbA_{1c} levels, while adjusting for control characteristics like age and FDR status.

Results

The VISION-T1D pilot screening program was funded and launched in May 2024, with the initial screening phase scheduled to conclude in April 2025. As of November 2024, a total of 176 eligible families had enrolled, representing approximately 39.1% of the target sample size of 322 families. Final data analysis for the initial screening phase is projected for mid-2025.

Discussion

The VISION-T1D protocol outlines a comprehensive approach to assess the feasibility and impact of a T1D screening among FDRs of individuals with T1D in Saudi Arabia. This model is tailored to address the unique demographic, cultural, and health care characteristics of the Arab region, aiming to deepen understanding of the prevalence and patterns of autoimmunity in at-risk populations. The data generated will provide valuable epidemiological insights to inform future health care policies and targeted interventions.

A key strength of this study is its focus on translating screening programs from the research setting to practical, real-world implementation. It provides a detailed roadmap for integrating T1D screening into health care systems, addressing scientific and operational complexities, particularly within the Arab region. The use of culturally sensitive consent materials, diverse educational methods, and clear protocols ensures that participants and caregivers are well informed, supported, and empowered to manage their health proactively. Additionally, the adoption of the ADAP assay—a cost-effective, sensitive, and low-sample-volume technology—enhances scalability and operational efficiency, making the program accessible for large-scale applications.

This study addresses significant unmet needs in T1D care and research in the Middle East, offering critical insights into genetic predispositions and disease progression in the Saudi population. One of the program's pivotal contributions is the early identification of candidates for T1D prevention therapies. Early detection through screening will facilitate timely intervention with disease-modifying therapies that can delay or prevent the onset of clinical T1D. This proactive approach aligns with global health strategies advocating for prevention and early intervention to mitigate the long-term burden of chronic diseases. Furthermore, this initiative lays the groundwork for the future of prevention trials in Saudi Arabia, contributing to the development of a sustainable infrastructure for T1D research and management.

The study also tackles logistical challenges, such as recruitment, sample analysis, and generalizability, through a combination of recruitment strategies, robust educational tools, and systematic follow-up procedures. While reliance on international laboratories for sample analysis introduces potential delays, the program is designed with long-term sustainability in mind, including plans to establish a centralized laboratory for the ADAP assay in Saudi Arabia.

Despite its strengths, the study has limitations. Focusing on FDRs may restrict generalizability to the broader population, as prior exposure to T1D within the family could influence the acceptability of the screening program. Additionally, cultural and social factors specific to Saudi Arabia may shape perceptions and behaviors related to T1D screening and management, potentially affecting intervention outcomes. Furthermore, the relatively short follow-up period, constrained by funding, limits the ability to assess long-term outcomes and the program's sustainability. Extended follow-up would provide a deeper understanding of the enduring effects of early detection and educational interventions on disease progression and management. Future extensions of this study are based on funding availability or collaborations with national screening programs may allow for prolonged follow-up.

In conclusion, this study represents a critical advancement in addressing the challenges of T1D screening and management of presymptomatic T1D. By integrating innovative screening technology with a robust educational framework and systematic follow-up, this program demonstrates the potential to enhance health outcomes while offering a scalable and sustainable approach to managing presymptomatic T1D. The outcomes garnered from this research will provide a foundation for implementing practical T1D-screening programs and establishing a framework adaptable to similar initiatives in neighboring Arab countries. By addressing both scientific and operational challenges, this study serves as a valuable resource for policy makers, health care providers, and researchers striving to integrate effective T1D management strategies into routine health care practice, ultimately improving the quality of care for at-risk populations.

Acknowledgments

This investigator-initiated study received funding from Sanofi and the University Diabetes Center at King Saud University Medical City for funding this study.

Authors' Contributions

The study was conceptualized by ISA and RAA, who also led the design of the protocol framework, supervised the research process, and provided overall research direction. Methodology, data curation, and formal statistical analysis plans were developed collaboratively by RAA, ISA, and YA, with additional contributions from JS and KA. Data collection plans, strategic guidance, and investigation, including participant recruitment and data collection, were carried out by ISA, MM, KA, MA, SA, AAA, and RAA. DS and CTT were responsible for the provision of laboratory technology and the analysis of blood samples. Funding was secured by RAA, ISA, JS, and MM. ISA and RAA collaborated on the literature review, drafting, revisions, and final submission of the manuscript. All authors reviewed and approved the final version of the manuscript.

Conflicts of Interest

The authors declare that there is no conflict of interest regarding the publication of this paper. DS and CTT were employed by Enable Biosciences. DS and CTT are shareholders of Enable Biosciences. CTT are inventors of the antibody detection by agglutination–polymerase chain reaction (ADAP) patent licensed from the University of California, Berkeley to Enable Biosciences. The ADAP assay used in this study is a product in development. This does not alter our adherence to journal policies on sharing data and materials.

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Abbreviations

ADAP: antibody detection by agglutination–polymerase chain reaction
CGM: continuous glucose monitoring
DKA: diabetic ketoacidosis
FDR: first-degree relative
GRS: genetic risk score
HbA_{1c}: hemoglobin A_{1c}
HLA: human leukocyte antigen
KSUMC: King Saud University Medical City
OGTT: oral glucose tolerance test
PCR: polymerase chain reaction

T1D: type 1 diabetes
UDC: University Diabetes Centre

Edited by A Mavragani; submitted 25.12.24; peer-reviewed by E Bosi, G Solgi; comments to author 31.01.25; revised version received 02.02.25; accepted 05.02.25; published 14.04.25.

Please cite as:
Algadi IS, AlRuthia Y, Mujammami MH, Aburisheh KH, Alotaibi M, Al Issa S, Al-Saif AA, Seftel D, Tsai CT, Al Khalifah RA
Early Detection of Type 1 Diabetes in First-Degree Relatives in Saudi Arabia (VISION-T1D): Protocol for a Pilot Implementation Study
JMIR Res Protoc 2025;14:e70575
URL: https://www.researchprotocols.org/2025/1/e70575
doi:10.2196/70575
PMID:

Original Paper

Effectiveness of The Umbrella Collaboration Versus Traditional Umbrella Reviews for Evidence Synthesis in Health Care: Protocol for a Validation Study

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Abstract

Background: The synthesis of evidence in health care is essential for informed decision-making and policy development. This study aims to validate The Umbrella Collaboration (TU), an innovative, semiautomatic tertiary evidence synthesis methodology, by comparing it with Traditional Umbrella Reviews (TUR), which are currently the gold standard.

Objective: This study aimed to evaluate whether TU, an artificial intelligence—assisted, software-driven system for tertiary evidence synthesis, can achieve comparable effectiveness to TURs, while offering a more timely, efficient, and comprehensive approach. In addition, as a secondary objective, the study aims to assess the accessibility and comprehensibility of TU's outputs to ensure its usability and practical applicability for health care professionals.

Methods: This protocol outlines a comparative study divided into 2 main parts. The first part involves a quantitative comparison of results obtained using TU and TURs in geriatrics. We will evaluate the identification, size effect, direction, statistical significance, and certainty of outcomes, as well as the time and resources required for each methodology. Data for TURs will be sourced from Medline (via PubMed), while TU will use artificial intelligence—assisted informatics to replicate the research questions of the selected TURs. The second part of the study assesses the ease of use and comprehension of TU through an online survey directed at health professionals, using interactive features and detailed data access.

Results: Expected results include the assessment of concordance in identifying outcomes, the size effect, direction and significance of these outcomes, and the certainty of evidence. In addition, we will measure the operational efficiency of each methodology by evaluating the time taken to complete projects. User perceptions of the ease of use and comprehension of TU will be gathered through detailed surveys. The implementation of new methodologies in evidence synthesis requires validation. This study will determine whether TU can match the accuracy and comprehensiveness of TURs while offering benefits in terms of efficiency and user accessibility. The comparative study is designed to address the inherent challenges in validating a new methodology against established standards.

Conclusions: If TU proves as effective as TURs but more time-efficient, accessible, and easily updatable, it could significantly enhance the process of evidence synthesis, facilitating informed decision-making and improving health care. This study represents a step toward integrating innovative technologies into routine evidence synthesis practice, potentially transforming health research.

International Registered Report Identifier (IRRID): PRR1-10.2196/67248

(JMIR Res Protoc 2025;14:e67248) doi:10.2196/67248

KEYWORDS

tertiary evidence synthesis; The Umbrella Collaboration; umbrella reviews; health research methodology; AI-assisted synthesis; AI-assisted; evidence-based decision making; machine learning; ML; artificial intelligence; AI; algorithms; models; analytics; digital health; digital technology; digital interventions

Introduction

Background

The synthesis of evidence in health care is a knowledge-acquisition process designed to transform extensive volumes of data into manageable information to support decision-making based on the best possible evidence. It aims to integrate information from multiple sources on complex topics in a comprehensive, precise, transparent, and easily understandable manner. These principles ensure that synthesized evidence is accessible and useful to all stakeholders, including health care professionals, policy makers, and patients [1].

Evidence synthesis plays a pivotal role in knowledge translation (KT) [2], serving as a bridge between research and health care. Consequently, evidence synthesis is essential for the development of health policies and informed decision-making [3].

The role of all stakeholders in health decision-making underscores the importance of their ability to access, understand, and evaluate health information adequately [4]. A persistent challenge in KT is the low level of statistical and health literacy among the general population and health professionals, which significantly complicates effective health management [5,6]. Therefore, it is crucial to democratize access to high-level health information and to promote active participation of all stakeholders in decisions affecting health care [7].

The evolution of evidence synthesis methodologies has led to the development of tertiary synthesis, designed to condense knowledge from multiple systematic reviews with or without meta-analyses (SR/MA). This synthesis, often referred to as Umbrella Reviews now referred to as Traditional Umbrella Reviews (TUR) to distinguish them from the experimental methodology under study, The Umbrella Collaboration (TU), builds upon the concept of primary studies (individual studies with participant samples) and secondary studies (systematic reviews and analysis of those primary studies). Tertiary synthesis represents a third level, named with other terms such as overviews, meta-epidemiological studies, meta-analyses, meta-synthesis, and meta-reviews also describing this approach [8,9]. Tertiary synthesis has gained prominence in contexts where broad research questions are posed, rapid results are needed, and resources for extensive systematic reviews are limited. TURs follow a structured methodological process that involves several clearly defined stages [9-14]. Although organizations like Cochrane Collaboration [14] and the Joanna Briggs Institute (JBI) [11] have developed and continually updated detailed methodologies for these reviews, there remains considerable divergence in how TUR authors implement these steps in practice. This methodological freedom leads to significant variations among different TURs in terms of rigor and approach.

The urgency for high-quality, timely information during crises like the SARS-CoV-2 pandemic has highlighted the critical need for faster evidence synthesis methods, even if it means accepting certain limitations in comprehensiveness, detail, and precision [15]. This demand has driven the development of innovative approaches such as TU, which leverages artificial intelligence (AI)-assisted software to facilitate tertiary evidence synthesis under human oversight. While AI tools such as PICO (Population, Intervention, Comparison, and Outcome) Portal, DistillerSR, Covidence (Veritas Health Innovation), and Rayyan (Rayyan Systems Inc) have already improved secondary evidence synthesis by streamlining data management and analysis [16], technologies like large language models (LLMs), including ChatGPT, are beginning to demonstrate potential for conducting systematic reviews autonomously, though human supervision remains essential to mitigate risks such as errors and hallucinations [17]. Despite these developments in secondary synthesis, the application of AI and software engineering in tertiary synthesis is still in its early stages, with no dedicated software currently available. TU is at the forefront of this field, pioneering the integration of AI and software engineering with human oversight to ensure accuracy and minimize technology-induced errors. As AI continues to evolve, it is likely that fully automated processes for both secondary and tertiary synthesis will emerge, potentially revolutionizing clinical research and practice. However, building confidence in these technologies will require ongoing development and rigorous validation.

The Umbrella Collaboration (Patent Pending)

TU is primarily a software-driven system engineered to streamline tertiary evidence synthesis, relying on programmed algorithms to automate the majority of its functions. The core of the system is built on a software infrastructure that processes and synthesizes data from SR/MA abstracts stored in MEDLINE. While AI plays a crucial role, particularly through the use of LLMs and machine learning (ML), it is used selectively within the broader software framework to enhance specific tasks.

LLMs are used in generating related search terms, expanding upon human-generated queries to enhance the comprehensiveness of literature searches. Any LLM can be adapted to TU software, up to date we have used ChatGPT 4 [18]. This function is crucial in broadening the scope of the searches while ensuring that the results remain relevant and precise. The AI component is designed to support, not replace, human oversight, ensuring that the final selection of literature is both accurate and comprehensive [19]. To mitigate the risk of AI-generated hallucinations due to insufficient data, TU

primarily operates as a stable, auditable software system. The use of AI is limited to the search term expansion phase, where it suggests synonymous terms for the keywords provided by the human reviewer.

All AI-generated search terms are subject to human validation before being incorporated into the search strategy. The human reviewer evaluates the relevance and appropriateness of each AI-suggested term, ensuring that only those that align with the research objectives are retained. This manual oversight serves as a critical safeguard against inaccuracies or misleading AI-generated suggestions, maintaining the methodological integrity of the evidence synthesis process.

As the TU database grows, ML will be integrated to further refine and optimize the software's performance. Training the system on an expanding dataset is expected to enhance its ability to select, categorize, and analyze relevant research, thereby improving both efficiency and accuracy over time. This approach allows TU to evolve, continuously improving its utility in evidence synthesis through the iterative learning process [20].

Overall, TU represents a hybrid model where traditional software engineering and targeted AI applications work in tandem. This balance ensures that while the software performs most functions automatically, AI enhances specific tasks, such as search term generation and future predictive analysis, under strict human supervision. This strategic integration of AI elements within a primarily software-driven system ensures the reliability and precision of the evidence synthesis process.

The outcomes generated by TU will be presented through an interactive web application designed to enhance accessibility and comprehension for a broad range of stakeholders, including those without advanced statistical expertise. The use of graphical formats and clear language aims to facilitate the interpretation of findings by diverse audiences.

In addition, the platform supports continuous updates, automatically integrating new SR/MA data every 24 hours, thereby ensuring the most current and reliable evidence synthesis. This approach aligns with the concept of Living Systematic Reviews (LSRs) [21], which advocate for frequent updates to maintain relevance in rapidly evolving fields. While Cochrane Collaboration recommends updating LSRs monthly [22], TU is designed to surpass this standard by ensuring updates are incorporated daily, providing near real-time evidence synthesis.

The daily updates provided by TU are expected to enhance its efficiency, allowing for a more dynamic and continuously updated evidence synthesis process. Pilot tests have demonstrated TU's capability to complete tertiary evidence synthesis projects within hours, a significant reduction in time compared to traditional methods (unpublished data). If validated by the upcoming research, this advancement could demonstrate TU's potential to streamline the synthesis process, delivering rapid yet reliable results while upholding the highest standards of accuracy. Should these findings be confirmed, TU may emerge as an invaluable tool for accelerating the pace of evidence-based research.

TU is designed to maximize computational efficiency while maintaining methodological rigor. Unlike TURs, which require extensive manual data extraction and synthesis over months, TU automates critical steps in the tertiary synthesis process, significantly reducing execution time.

In terms of computational complexity, TU does not perform direct statistical meta-analyses but instead extracts and synthesizes pre-existing systematic reviews and meta-analyses. This approach ensures that the computational load remains minimal compared to methodologies that require full-scale meta-analyses or real-time data processing. The most computationally intensive process within TU is the search term expansion using AI, which is constrained to generating synonymous terms based on human-input keywords. This AI function operates on a lightweight model that does not require high-performance computing resources.

A key distinction of TU is that it assists in the entire tertiary review process, rather than being limited to isolated stages. Compared to existing approaches such as DistillerSR, Covidence, and Rayyan, which focus on specific tasks like study screening or data extraction, TU integrates a complete methodology for tertiary evidence synthesis. This includes search term expansion, literature retrieval, synthesis automation, and structured result visualization. While other tools provide assistance in certain steps, TU ensures a fully automated, structured, and reproducible workflow for umbrella reviews.

To our knowledge, there are currently no automated systems specifically designed for tertiary evidence synthesis that comprehensively address and assist in the entire synthesis process. While several tools exist for systematic review automation—such as DistillerSR, Covidence, and Rayyan—these primarily focus on secondary evidence synthesis (ie, systematic reviews) and are not designed to facilitate tertiary synthesis methodologies like umbrella reviews.

In addition, no previous tool has undergone a formal assessment or validation for automated tertiary synthesis, as TU is the first system explicitly developed for this purpose. Unlike existing software, TU does not merely automate isolated steps (such as literature screening or data extraction) but provides a structured, end-to-end approach for tertiary evidence synthesis. This distinction highlights the novelty of TU and underscores the need for this study to formally assess its performance compared to TURs.

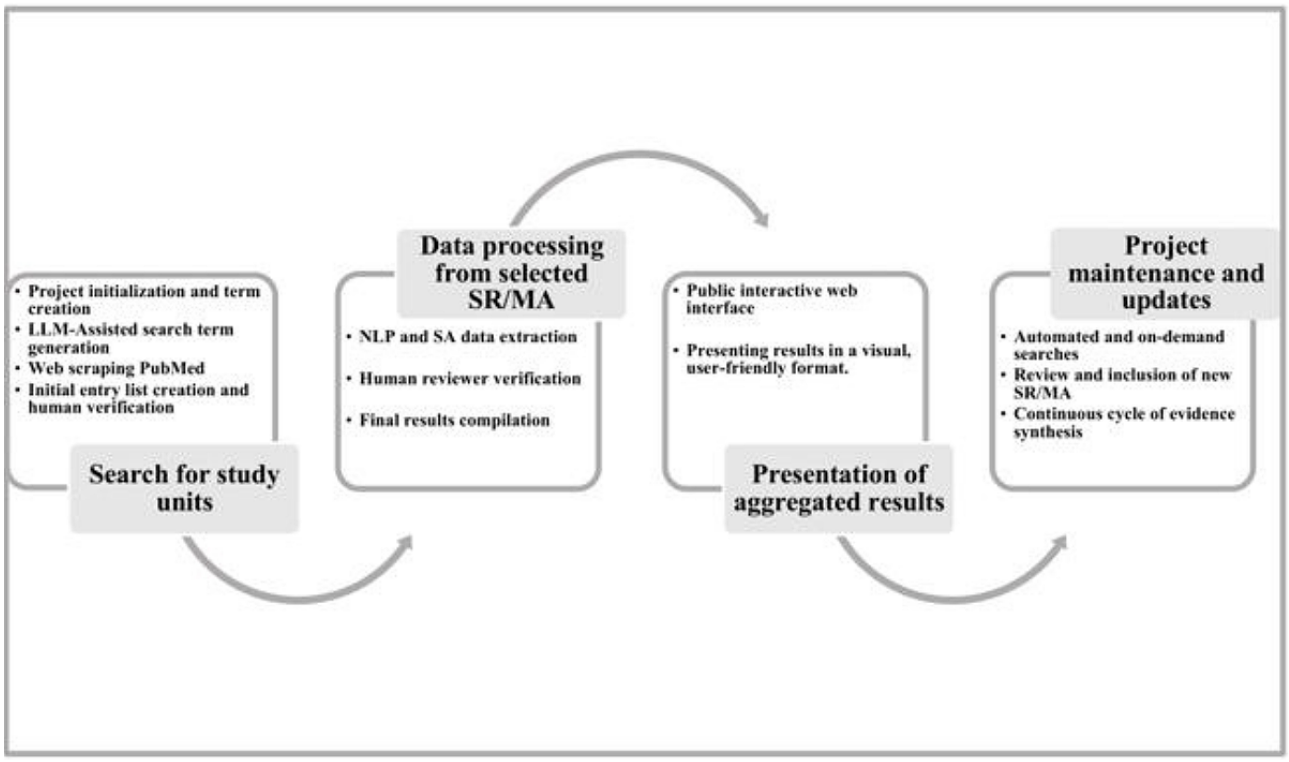
A schematic diagram is provided to clearly illustrate TU's workflow, showing the process from data acquisition to the generation of synthesized results. Abstracts of SR/MA, retrieved from the MEDLINE database via PubMed, form the foundation of the analysis. The decision to use MEDLINE via PubMed as the sole database for literature retrieval in TU is based on its strong coverage of systematic reviews and meta-analyses, as well as the feasibility of leveraging LLMs for search term expansion. Recognizing the potential limitation of relying on a single database, we conducted preliminary assessments to estimate the impact of this decision. Specifically, we evaluated the ability of TU to retrieve references from TURs and analyzed the proportion of systematic review and meta-analysis references found in MEDLINE. Our results showed that TU was able to

retrieve 81.1% (414/511) of TUR references using its AI-assisted search methodology in Medline alone. In addition, an independent assessment of 511 references from 22 TURs found that only 11 references were not indexed in MEDLINE. While some loss of relevant studies is inevitable, these findings suggest that the methodological approach used in TU remains sufficiently comprehensive for tertiary evidence synthesis, balancing feasibility and completeness (unpublished data). The data obtained are processed through a range of techniques, including natural language processing (NLP), sentiment analysis (SA), web scraping (WS), and ML. The expected results comprise synthesized evidence on intervention effectiveness and risk exposures, presented in a graphical and visual format. These results are conveyed in plain language, making them easily understandable by all stakeholders, regardless of their statistical literacy.

The project is continuously updated through automated and on-demand searches, with data from new studies seamlessly integrated into the existing body of evidence. Each inclusion restarts the synthesis process, creating a dynamic, cyclical workflow that ensures the results of the project remain up-to-date (Figure 1).

The implementation of new methodologies in the scientific field requires a comparative validation process with established methods to ensure their reliability and effectiveness. TU, being an innovative methodology still in its theoretical-conceptual stage, must be evaluated against established methodologies. Therefore, the aim of this study is to validate TU by comparing its performance and outcomes with the gold standard, TURs, to establish its credibility and potential superiority.

Figure 1. The Umbrella Collaboration workflow. NLP: natural language processing; LLM: large language models; SA: sentiment analysis; SR/MA: systematic reviews with or without meta-analyses.



Objectives

The primary objective of this study is to assess whether a software-driven AI-assisted system of evidence synthesis, TU, can match the effectiveness of traditional methods of tertiary synthesis, providing a potentially more timely, efficient, and comprehensive approach while remaining open to findings that could demonstrate superior performance. To support the primary objective of evaluating the effectiveness of TU compared to traditional methodologies, this study also aims to assess the accessibility and comprehensibility of TU's outputs as a secondary objective.

Methods

Study Design

Part 1: Quantitative Comparison of Methodologies

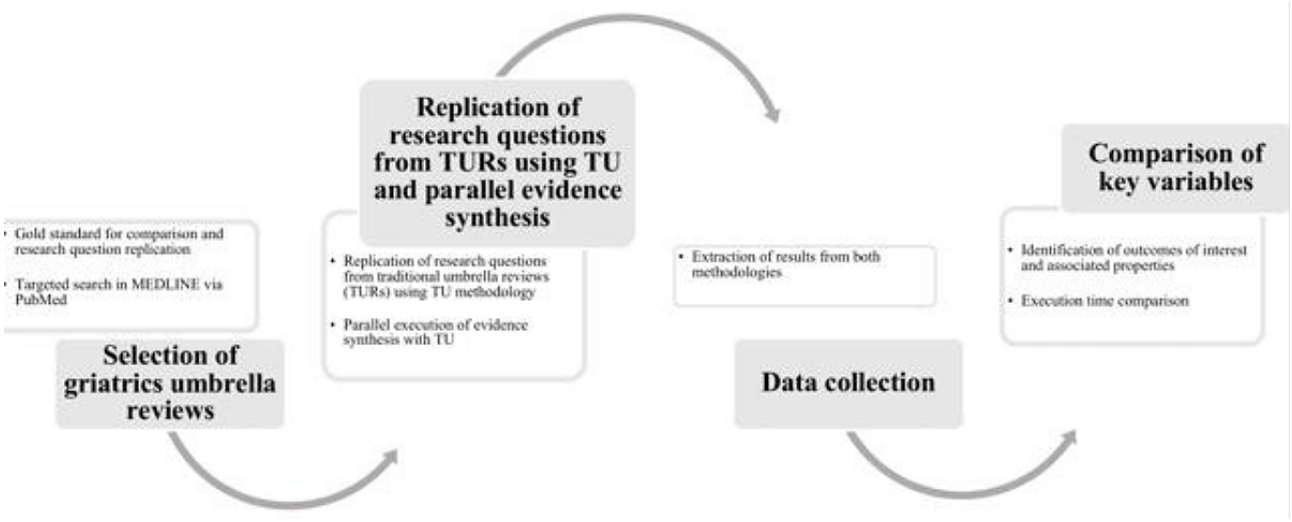
Overview

Figure 2 provides an overview of the study design. The study follows a structured comparative approach in which selected TURs in geriatrics serve as the gold standard for validation. Using the same research questions, projects are conducted in parallel with TU to assess its performance. Data from both methodologies are systematically collected and compared, focusing on key variables such as the identification of outcomes of interest, effect size, effect direction, statistical significance, certainty of evidence, and execution time. The figure illustrates

the step-by-step workflow of the study, from the selection of umbrella reviews in geriatrics as reference models to the comparison of results obtained using TU and TURs.

The first part of this study focuses on a quantitative comparison between the 2 tertiary synthesis methodologies. To facilitate this comparison, a targeted search in PubMed will identify relevant TURs in geriatrics, focusing on representative reviews rather than an exhaustive search. Our approach will involve a focused search in PubMed, using specific terms relevant to geriatrics, to find suitable TURs that serve as a benchmark for this comparative analysis. This targeted search is sufficient for our methodological comparison and does not require the comprehensive search strategy typical of systematic reviews, as our goal is not to cover the entire scope of available literature but to enable a parallel evaluation of synthesis methodologies. Therefore, while the search strategy may appear basic, it is intentionally designed to fulfill the specific needs of our project without aiming for exhaustive literature retrieval, which is beyond the scope of this project.

Figure 2. Study design overview. TU: The Umbrella Collaboration; TUR: Traditional Umbrella Reviews.



Study Variables

In the quantitative comparison, several critical variables will be analyzed. Key among these is the identification and evaluation of outcomes of interest (outcomes). This includes assessing the degree of concordance between the methodologies in identifying outcomes and using a concordance matrix to document and compare the outcomes identified by TU and TURs. In addition, we will analyze the total number of outcomes identified by each methodology, providing a descriptive and statistical comparison. It is essential to define the concept of an "outcome of interest" within the context of tertiary evidence synthesis. An outcome of interest refers to specific aspects identified and evaluated by systematic reviews with meta-analyses that examine the same research question. These outcomes are critical for understanding the overall impact of various interventions on health conditions or the effects of exposure to risks.

A crucial aspect of this analysis involves the comparison of effect sizes for the identified outcomes. TU uses an automated approach for standardizing effect sizes using a custom-designed metric (R_{TU}). This metric transforms all commonly used effect size statistics in evidence synthesis (eg, standardized mean difference [SMD], mean difference [MD], relative risk [RR], odds ratio [OR], hazard ratio [HR], and others) into a single weighted composite measure. The R_{TU} metric enables the aggregation of heterogeneous effect size measures across different systematic reviews supporting a given outcome of interest in tertiary evidence synthesis.

Since this process is fully automated, accuracy is assessed through comparisons with TURs. By replicating research questions from TURs in TU, we compare whether the R_{TU}-derived effect sizes align with those obtained using traditional methodologies. This validation step ensures that the automated transformation process does not introduce systematic distortions and maintains consistency with established effect size estimation methods. Given the diverse metrics used in TURs, such as SMD, MD, RR, OR, and HR, and the unique metric used by TU, we will standardize all effect sizes, used in TURs, to Cohen *d*. This standardization facilitates a direct comparison, ensuring consistency in the interpretation of results.

We will also examine the direction of the effects for each outcome, categorizing them as favorable, unfavorable, or unknown for interventions, and as increasing, decreasing, or unknown for exposures to risks. The statistical significance of the outcomes will be compared by analyzing *P* values and CI, assessing whether the results are statistically significant across both methodologies.

Furthermore, the certainty of the evidence (LoE) associated with each outcome will be evaluated. To assess the LoE within TU, we use sentiment analysis as a NLP technique. This approach allows for the automated classification of certainty indicators extracted from systematic review abstracts. Regarding the concern about the training data for sentiment analysis, at this stage, TU uses a sentiment analysis model initially trained on X (formerly known as Twitter) data. While we acknowledge that this is not highly optimized for medical texts, it provides a cost-effective starting point for sentiment classification without incurring additional expenses. Cloud-based solutions, such as

Azure cognitive services, offer more specialized sentiment analysis models for health care, but these are paid services that exceed our current budget.

We fully recognize the limitations of using general sentiment analysis for LoE, as traditional GRADE (Grading of Recommendations Assessment, Development, and Evaluation)-based approaches consider multiple factors such as study limitations, inconsistency, indirectness, publication bias, and confounders. However, our primary aim is to determine whether a simplified approach, using abstract-level sentiment classification, can yield reasonable agreement with traditional methodologies. TU does not claim to replace the rigor of full-text GRADE assessments but instead seeks to evaluate whether an alternative automated method can provide valuable insights with lower resource demands. We are actively working toward developing our own custom sentiment analysis algorithm tailored to medical literature, trained on validated medical datasets. This will enhance precision and improve TU's ability to evaluate LoE more effectively in the future.

For TURs, this will be done using the GRADE system [23], which categorizes evidence into very low, low, moderate, and high levels. TU applies an SA-based scoring system on a scale from –1 to +1. Both scales will be normalized to a similar quantitative range (0-1) to facilitate comparison. To align the 2 systems, the SA scores are normalized using the following transformation formula: X=(SA score+1)/2. Where X represents the normalized certainty score, ensuring that SA values originally in the range of –1 to 1 are mapped to a 0 to 1 scale. The GRADE ordinal levels are mapped onto the 0-1 scale as follows: very low=0.00-0.25, low=0.26-0.50, moderate=0.51-0.75 and high=0.76-1.00. This process allows TU and TUR certainty ratings to be compared in a standardized manner, enabling statistical concordance analyses between the 2 methodologies.

Finally, the execution time of each methodology will be assessed, with TU providing exact time measurements and TURs relying on an estimated timeframe of 6 to 12 months based on existing literature.

Data Collection and Research Question Replication

Data collection will begin with a targeted search in PubMed to identify TURs in geriatrics, using the search terms "umbrella" AND "geriatric." The identified TURs will serve as benchmarks for our comparative analysis. The research questions from these selected umbrella reviews will be directly replicated in TU without modification, ensuring a precise comparison of outcomes generated by each methodology. TU will be configured to replicate these questions, using automated searches and synthesis through NLP, WS, SA, and ML, with human reviewers verifying and extracting data as necessary. This approach allows us to assess the comparative effectiveness and efficiency of TU relative to traditional methods, particularly in identifying and analyzing outcomes critical to evaluating health interventions and exposure risks. Data from both TURs and TU will be systematically collected and recorded in a database to facilitate precise comparisons of outcomes, effect sizes, and other critical variables, ensuring a thorough evaluation of both methodologies.

The decision to rely solely on abstracts for data extraction in TU was driven by practical and methodological considerations. First, this approach was chosen due to budgetary constraints, as full-text access to all systematic reviews and meta-analyses would require extensive licensing fees or institutional subscriptions, which are beyond the scope of this project. Second, abstracts help mitigate language bias, since all systematic review abstracts indexed in MEDLINE are available in English, regardless of the original language of publication. This ensures a broader and more internationally representative evidence base.

While it is acknowledged that abstracts often contain limited methodological details and may lack comprehensive information on certainty of evidence, outcome effect sizes, or risks of bias, the core objective of TU methodology is to assess whether robust conclusions can still be drawn based on abstracts alone. Recognizing the inherent limitations of abstracts, TU incorporates structured extraction criteria to capture the most relevant information while acknowledging the potential risks of missing key methodological details. The validation process of TU explicitly includes a comparison with full-text TURs to evaluate whether synthesis based on abstracts alone yields comparable conclusions.

Part 2: Evaluation of Ease of Use and Comprehension

Overview

The second part of the study focuses on evaluating and comparing the ease of use and comprehension of the results generated by TU with those from TURs. This evaluation will be conducted through an anonymous and voluntary online survey directed at health professionals, designed to assess their experience with both methodologies.

The survey, developed using Google Surveys for ease of access and data analysis, comprises 16 items. The initial 6 items gather demographic information about the survey respondents, while the subsequent 10 questions directly compare the usefulness and clarity of the results produced by TU and TURs, using a Likert scale ranging from 1 to 5. This scale will measure respondent's perceptions of the clarity, comprehensibility, and ease of use of the results provided by both methodologies (Table 1).

To ensure a thorough evaluation, informational sessions will be held in geriatric departments of university hospitals in Madrid (Spain). During these sessions, the concept of tertiary evidence synthesis and the functionality of TU will be introduced. Health professionals, including those from geriatrics and other rotating specialties, will be given access to the TU platform and guided through its use by an expert. This hands-on experience will be complemented by providing the participants with TUR result tables to facilitate a direct comparison.

Participants will be able to access the survey via a QR code, provided during the sessions, allowing them to complete it either immediately or at their convenience. The survey's responses will be analyzed descriptively, focusing on the overall user experience with TU and its potential advantages in terms of ease of interpretation and presentation compared to traditional methods.

Table 1. Survey questions on the utility of The Umbrella Collaboration.

	Question	Answer Likert scale
1 - 6	Respondent affiliation data	
7	Do you consider that the interactive interface of the "TU"[a] methodology facilitates the understanding of results compared to the static tables of TURs[b]?	• 1: Strongly disagree • 2: • 3: • 4: • 5: Strongly agree
8	Do you believe that the visualization of results using bubble plots in "TU" helps to quickly identify the most relevant outcomes?	• 1: Strongly disagree • 2: • 3: • 4: • 5: Strongly agree
9	Does the graphical representation of the outcomes (illustrated by figures, colors, and sizes) in "TU" enhance your ability to assess the clinical relevance of the results?	• 1: Strongly disagree • 2: • 3: • 4: • 5: Strongly agree
10	Do you find that access to detailed data by clicking on the figures of the outcomes in "TU" interface enhances your evidence analysis experience?	• 1: Strongly disagree • 2: • 3: • 4: • 5: Strongly agree
11	Do you think that "TU" methodology allows for a quicker interpretation of data compared to TUR?	• 1: Strongly disagree • 2: • 3: • 4: • 5: Strongly agree
12	Is the information provided by "TU" useful in your field of work (clinical, research, or educational) for evidence-based decision-making?	• 1: Strongly disagree • 2: • 3: • 4: • 5: Strongly agree
13	Does the ease of use of "TU" interface facilitate greater data exploration compared to traditional methods?	• 1: Strongly disagree • 2: • 3: • 4: • 5: Strongly agree
14	Do you consider the historical evolution of evidence provided by "TU" methodology to be useful?	• 1: Strongly disagree • 2: • 3: • 4: • 5: Strongly agree
15	Does "TU" methodology require less statistical knowledge to interpret the results compared to TUR?	• 1: Strongly disagree • 2: • 3: • 4: • 5: Strongly agree
16	Overall, are you satisfied with "TU" methodology as a tool for tertiary evidence synthesis?	• 1: Strongly disagree • 2: • 3: • 4: • 5: Strongly agree

[a]TU: The Umbrella.

[b]TURs: Traditional Umbrella Reviews.

Statistical Analysis: Data Analysis and Statistical Methods

The quantitative analysis will compare the results obtained by both methodologies. Contingency tables will be constructed to contrast the identification of outcomes, the size effect, the direction of the effect, and the statistical significance, ensuring statistical congruence between the methods. For the evaluation of certainty levels, TU scores will be normalized to a scale comparable to the GRADE levels, which will also be transformed into a numerical scale between 0 and 1.

The chi-square test will be used to determine significant differences between the methodologies. In addition, Pearson and Spearman correlation analyses will be conducted to quantify the relationship between TU certainty levels and GRADE certainty levels of the TURs. Pearson correlation analysis is useful for quantifying the strength and direction of a linear relationship between 2 continuous variables. Moreover, the analysis will be complemented with Spearman correlation analysis due to potential violations of normality assumptions in the data.

Statistical analysis will be performed using IBM SPSS Statistics (version 26), with an alpha level of .05 to determine statistical significance.

Ethical Considerations

This study does not involve human participants, personal data, or animals. All data will be sourced from published materials, and the analyses will be conducted in accordance with established ethical standards for secondary data analysis. In addition, the survey component will be conducted anonymously and on a voluntary basis. Given these considerations, we do not deem it necessary to seek approval from an ethics committee, as the study adheres to standard ethical practices for research of this nature [24].

Results

We will focus on evaluating the effectiveness of the experimental methodology in accurately identifying and analyzing relevant outcomes. Among the results, we will include detailed assessments of effect sizes, the direction of effects, statistical significance, and the certainty of evidence for each outcome. We will compare these findings with those derived from TUR to determine if the experimental approach yields results that are at least equivalent in quality and comprehensiveness.

Finally, the efficiency of the experimental methodology will be evaluated by recording the time taken to complete the synthesis process. While the time required for TUR is estimated to range between 6 and 12 months based on existing literature, we will document the actual time taken by the experimental approach. This will provide a practical measure of the potential time savings offered by the software-driven AI-assisted method, highlighting its feasibility and effectiveness in a real-world context.

To evaluate the ease of use and comprehension of TU within its environment, a detailed survey will be specifically designed. Survey respondents will have access to the TU platform, where they can interact with various interactive screens displaying the results of the synthesis process across different projects completed to date.

Discussion

Principal Findings

The anticipated findings of this study are expected to demonstrate that TU, a semiautomated tertiary evidence synthesis tool, can produce results that are methodologically comparable to TURs while significantly improving efficiency. By leveraging AI-assisted methodologies, TU may streamline the synthesis process, reducing the time and effort required for evidence aggregation. In addition, the study aims to assess whether tertiary evidence synthesis can be effectively conducted using only systematic review abstracts, balancing feasibility with methodological rigor. If successful, these findings could support the broader adoption of AI-driven approaches in tertiary synthesis, potentially transforming the landscape of evidence-based decision-making in health care.

The primary objective of this study is to evaluate whether TU, a software-driven system designed to facilitate tertiary evidence synthesis with AI-assisted methodologies, can match the effectiveness of TURs. TU integrates with its software development advanced technologies such as NLP, SA, WS, and ML to enhance the efficiency of evidence synthesis.

The semiautomated processes implemented by TU could signify a significant advancement in making evidence synthesis more accessible and timely, with the potential for continuous updates as new data becomes available. The study's findings could pave the way for broader adoption of AI-driven methodologies in evidence synthesis, potentially reducing the time and resources needed for comprehensive reviews. TU's integration of software engineering projects and AI with traditional methods could streamline the review process, enabling faster aggregation and interpretation of data across various research domains.

Several software tools assist in systematic and umbrella review processes, such as DistillerSR, Covidence, and Rayyan. These platforms improve efficiency in evidence synthesis by automating tasks such as study screening, data extraction, and literature management. However, they do not offer a fully structured and automated methodology for tertiary evidence synthesis, which remains a predominantly manual process. In contrast, TU is designed to support the entire tertiary synthesis workflow, rather than focusing on isolated stages. TU integrates (1) AI-assisted search term expansion, which enhances literature retrieval by suggesting synonymous terms for human validation; (2) automated data extraction from systematic review abstracts, allowing for a structured and efficient synthesis process; (3) a dedicated framework for tertiary synthesis, unlike other tools that primarily assist in secondary synthesis (systematic reviews); and (4) interactive and visual result presentation, providing stakeholders with an accessible interpretation of findings, rather than traditional tabular outputs.

Ongoing Project Status

Once created, projects in TU remain active indefinitely, preventing obsolescence. This continuous updating of evidence

synthesis is a key feature that differentiates TU from static review methodologies. The system conducts literature searches every 24 hours or on demand by the human reviewer responsible for the project. This allows for real-time incorporation of newly published studies, ensuring that the synthesis remains current and reflective of the latest scientific evidence. While TUR requires manual updates, often years apart, TU transforms the synthesis process into a living evidence system, ensuring that the latest research is incorporated seamlessly. This eliminates the need for reinitiating entire projects and allows researchers to work with continuously updated data.

One similarity between TU and existing platforms is the incorporation of automation to enhance efficiency. However, TU distinguishes itself by providing a fully integrated tertiary synthesis methodology with a self-updating mechanism, ensuring both methodological rigor and computational efficiency in umbrella reviews.

By offering a platform that supports real-time updates and provides accessible synthesis outputs, TU has the potential to enhance the utility of tertiary synthesis for a wide range of stakeholders, including those with limited statistical expertise. However, a key limitation of TU is its reliance on a single database (MEDLINE via PubMed), which might not capture all relevant studies. This study will examine whether this limitation can be mitigated by the system's other capabilities. Ultimately, the timely and comprehensible evidence synthesis provided by TU could facilitate more informed decision-making in clinical settings, particularly in rapidly evolving areas of medical research.

Future research will be essential to further validate and refine TU. Planned next steps include expanding the sample size of included TURs to increase representativeness, conducting blinded validation studies to minimize potential biases, and testing the tool across different reviewer profiles to assess usability beyond expert users. In addition, TU's methodology should be applied to other medical and nonmedical disciplines to evaluate its versatility. A critical aspect of future validation will also involve independent expert review, ensuring that TU's findings align with established methodological standards. Finally, economic feasibility studies comparing TU with traditional synthesis approaches will be necessary to assess its cost-effectiveness and scalability in real-world implementation.

Limitations

The decision to use only one database, MEDLINE via PubMed, in TU is both a recognized limitation and a deliberate choice shaped by resource constraints and technical considerations. While systematic reviews typically require searching multiple databases to capture all relevant literature [25], our approach focuses on testing whether TU can achieve outcomes comparable to TURs despite these limitations. While the pilot study provided preliminary evidence of PubMed's strong coverage, further validation through TU is necessary to confirm its applicability across different domains.

Furthermore, while searching multiple databases is often recommended to avoid language and indexing biases, especially those related to non-English literature [26,27]. TU mitigates some of these biases by focusing on abstracts in English, as all PubMed abstracts are provided in this language regardless of the original publication's language. However, the absence of Chinese databases in our approach is a notable limitation, given that only a small proportion of Chinese journals are indexed in MEDLINE.

The decision to rely exclusively on abstracts rather than full texts in TU is a deliberate methodological choice aligned with the core objective of this study: to evaluate whether tertiary evidence synthesis can be conducted efficiently, with fewer resources, and without requiring extensive methodological expertise from the reviewer, while still producing results comparable to TURs.

We acknowledge that abstracts may lack key methodological details, including certainty of evidence assessments, effect size calculations, and risk of bias evaluations. However, the fundamental hypothesis of TU is that an automated, structured approach to abstract-based synthesis may still yield clinically useful conclusions, particularly when applied under standardized and reproducible conditions. Moreover, relying on abstracts offers two key advantages: (1) minimization of language bias: all systematic review abstracts in MEDLINE are available in English, regardless of the original publication language, which ensures that non-English studies are not automatically excluded due to language barriers, a common issue in traditional systematic reviews; and (2) feasibility and accessibility: full-text access to all systematic reviews requires extensive licensing fees and institutional subscriptions, which may not always be feasible. Abstracts provide a universally accessible data source, allowing for broader implementation of evidence synthesis methodologies.

While TU does not claim to replace the depth of full-text review, this study aims to evaluate whether a structured synthesis based solely on abstracts can yield results that are sufficiently coherent and robust to serve as a complementary or alternative approach. If validated, this methodology could provide an efficient solution for synthesizing evidence in settings where full-text access is restricted or when rapid evidence synthesis is needed.

While we acknowledge the potential benefits of testing TU across multiple medical domains, this study is a pilot study designed to assess the feasibility of our methodology in a single, well-defined field, geriatrics. At this stage, limiting the scope to geriatrics is a strategic choice, ensuring that the study maintains clarity, feasibility, and methodological rigor in its initial validation phase. This focused approach allows for a controlled evaluation of TU against TURs, ensuring that the initial validation is conducted under clearly defined conditions. If the results demonstrate that TU can produce findings comparable to TURs, future studies will expand its application to other medical fields, such as cardiovascular medicine and psychiatry, as well as nonmedical domains, including education, sociology, and other disciplines with abundant systematic reviews. This stepwise approach ensures a methodologically sound progression, allowing TU to be tested and refined incrementally before broader implementation.

In this initial phase of the study, we have prioritized clinical health professionals as the primary participants for the ease of

use and comprehension surveys. This decision is based on the primary objective of TU, which is to facilitate evidence synthesis for clinicians and health care professionals who may not have extensive expertise in systematic review methodologies. Given that TU is designed to enhance the accessibility and usability of tertiary evidence synthesis in clinical practice, it is essential to first evaluate its clinical utility and interpretability among end-users.

We fully acknowledge the importance of a rigorous methodological review by epidemiologists and research methodologists, as well as the need to assess the validity of results produced by TU. However, this will be addressed in a subsequent phase of research, where surveys will be extended to other key stakeholders, including epidemiologists and research methodologists, to evaluate the methodological robustness of TU. Health care policy makers and hospital administrators, assess TU's potential role in decision-making. Patients and caregivers, to explore how synthesized evidence can be communicated effectively to the general population. This stepwise approach ensures that TU is first assessed from a clinical perspective before expanding to other critical stakeholders in future validation studies.

Another limitation of this study is the potential for response bias in the ease-of-use and comprehension survey. Given that most participants will complete the survey immediately after structured demonstrations of TU, their responses could be influenced by the context of the presentation. This could lead to a more favorable assessment of TU than what might be observed in an independent evaluation setting. This halo effect can impact the perceived usability and effectiveness of TU. Future studies should aim to validate these findings through independent assessments in settings where TU is used without direct guidance from the research team.

Conclusion

This study aims to validate TU as a tool for tertiary evidence synthesis in health. If this methodology proves to be as effective as TURs, but more efficient in terms of project execution time and more accessible in terms of ease of use and comprehension, it could significantly enhance the way evidence synthesis is conducted, facilitating informed decision-making, and improving health outcomes. The results of this study may represent a step toward the integration of innovative technologies into the routine practice of evidence synthesis, with the potential to transform the field of health research.

Acknowledgments

This project has received a research grant from the Fundación Alfonso X el Sabio.

Conflicts of Interest

The authors BC, MR-C, JP-M, AP-L, and BC-R were involved in the development of The Umbrella Collaboration (TU) software. In addition, BC and MR-C are owners of the software and may have financial or intellectual property interests in its future applications. While this study was conducted with the aim of validating TU as an evidence synthesis tool, the authors have taken all necessary precautions to ensure that the study design, data analysis, and interpretation of results remain as objective and methodologically rigorous as possible. To mitigate potential biases, comparisons were conducted against gold-standard Traditional Umbrella Reviews (TURs), and statistical methodologies were used to ensure transparency and replicability of findings. Furthermore, the affiliations of the authors did not influence the study design, execution, data analysis, or interpretation of results. All research activities were conducted following rigorous methodological standards to ensure impartiality and scientific integrity.

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Abbreviations

AI: artificial intelligence
GRADE: Grading of Recommendations Assessment, Development and Evaluation

HR: hazard ratio
JBI: Joanna Briggs Institute
KT: knowledge translation
LLM: large language model
LoE: certainty of the evidence
LSR: Living Systematic Review
MD: mean difference
ML: machine learning
NLP: natural language processing
OR: odds ratio
PICO: Population, Intervention, Comparison, and Outcome
RR: relative risk
RTU: custom-designed metric
SA: sentiment analysis
SMD: standardized mean difference
SR/MA: systematic reviews with or without meta-analyses
TU: The Umbrella Collaboration
TUR: Traditional Umbrella Reviews
WS: web scraping

Edited by A Schwartz, J Sarvestan; submitted 06.10.24; peer-reviewed by PH Liao, R Mpofu; comments to author 31.01.25; revised version received 16.02.25; accepted 09.03.25; published 14.04.25.

Please cite as:
Carrillo B, Rubinos-Cuadrado M, Parellada-Martin J, Palacios-López A, Carrillo-Rubinos B, Canillas-Del Rey F, Baztán-Cortes JJ, Gómez-Pavon J
Effectiveness of The Umbrella Collaboration Versus Traditional Umbrella Reviews for Evidence Synthesis in Health Care: Protocol for a Validation Study
JMIR Res Protoc 2025;14:e67248
URL: https://www.researchprotocols.org/2025/1/e67248
doi:10.2196/67248
PMID:40057944

Protocol

Resource-Oriented Case Management to Implement Recommendations for Patients With Chronic Pain and Frequent Use of Analgesics in General Practices (Project RELIEF): Protocol for a Single-Arm Exploratory Feasibility Study

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Abstract

Background: Chronic noncancer pain (CNCP) is a frequent reason for counseling in general practice. Current German guidelines emphasize its biopsychosocial etiology and the importance of self-care and nonpharmacological treatment strategies such as education, physical and social activity, and psychological approaches. Comprehensive assessments are necessary to individualize treatment maximally and monitor appropriate use of pain medication. General practitioners face many challenges in implementing holistic pain management, which considers biological, psychological, and social aspects. In project RELIEF (resource-oriented case management to implement recommendations for patients with chronic pain and frequent use of analgesics in general practices), a case management program was developed to facilitate implementation of guideline recommendations on pain management regarding medical assessment and monitoring, patient and practice team education, promotion of self-care strategies, and rational pharmacotherapy.

Objective: We evaluated the feasibility of the intervention and study procedures before applying them in a larger cluster randomized controlled trial. Our secondary objective is to estimate potential effects of the complex intervention.

Methods: A single-arm trial with general practices and patients with CNCP and analgesics use will be conducted, accompanied by a mixed methods process evaluation. The intervention comprises 5 components, including software-supported medical pain history, 3 scheduled structured appointments, e-learning on CNCP for general practitioners and medical assistants, educational material for patients, toolbox with information on (regional) resources for patients and practice teams. Participating practices will be located in the federal state of Baden-Württemberg, Germany, and will recruit eligible patients (adults with CNCP for more than 3 months, with at least moderate pain-related disability, permanent or on-demand use of analgesics or co-analgesics in the previous 4 weeks, and practice team assessed ability to participate actively in the trial). A questionnaire given to the first 150 adult patients entering the practice in February 2025 will help screen eligible patients. The primary objective will be measured

by a set of predefined indicators. The key secondary outcome is pain-related disability measured by the Pain Disability Index German version. All participants will be asked to participate in the process evaluation. Outcome evaluation data will be gathered by paper-based and digitally provided questionnaires to be completed by participants. Process evaluation data will be gathered in surveys and a qualitative study. Descriptive analyses will be performed.

Results: Recruitment occurred between October and December 2024. Targeted sample size was 6 practices and 50 patients. The intervention period will be February-June 2025. It is expected that eligible patients will benefit from the intervention and that improved medication management and intensified use of nonpharmacological treatment strategies will reduce pain-related disabilities and other patient-reported outcomes.

Conclusions: This study will provide valuable information regarding feasibility and potential effects before testing the intervention in a confirmatory cluster randomized controlled trial.

Trial Registration: German Clinical Trials Register DRKS00034831; https://www.drks.de/search/de/trial/DRKS00034831

International Registered Report Identifier (IRRID): PRR1-10.2196/66335

(JMIR Res Protoc 2025;14:e66335) doi:10.2196/66335

KEYWORDS

chronic noncancer pain; case management; primary care; general practice resource-oriented; chronic pain; analgesics; pharmacological treatment; pain medications; holistic approach; feasibility; single-arm; exploratory; pilot study; screening; questionnaire; survey; protocol

Introduction

Background

About 20% of the patients in German general practices are affected by chronic pain [1], defined as pain that persists for more than 3 months or reoccurs [2]. Classification systems distinguish between chronic primary pain which cannot be explained by a detectable tissue damage (eg, fibromyalgia, unspecific low back, and psychosomatic pain disorders) and chronic secondary pain which is likely to have been caused at least initially by an organ or tissue damage (eg, degenerative or inflammatory diseases of the joints or spine and nerve damages) [2]. While cancer-related pain has characteristics of continuous or intermittent pain [3], chronic noncancer pain (CNCP) comprises any painful condition not associated with malignant disease and persisting for at least 3 months [4]. It interferes with activities of daily life and has a negative impact on quality of life and physical function [5]. CNCP is considered to be a major public health problem and one of the most common reasons why patients seek medical care [6,7]. The understanding of chronic pain pathogenesis has become more differentiated in recent years and there is consensus that chronic pain is always maintained or influenced by an interaction of biological, psychological, and social factors. Furthermore, psychological comorbidities such as depression, anxiety, or posttraumatic stress disorder are frequently associated with chronic pain [8]. Depending on which factors or comorbidities prevail, different treatment strategies are effective. Thus, comprehensive medical pain assessment is necessary in order to individualize treatment as best as possible.

Guidelines emphasize the importance of holistic pain management and nonpharmacological and noninvasive treatment strategies such as education, physical activity, social activity and support, relaxation techniques, or cognitive behavioral therapy. Analgesics should only be used temporarily and supportively until nonmedical treatments show an effect [9]. However, about two thirds of patients with chronic pain take analgesics [10] which may have severe adverse effects. Particularly alarming is the high percentage of patients taking nonsteroidal anti-inflammatory drugs (NSAID) which are also available as over-the-counter drugs. In a large telephone survey, 72% of German respondents with chronic pain stated using nonprescribed NSAID [10]. If taken on a long-term basis, NSAID may lead to renal insufficiency, gastrointestinal damages and cardiovascular events. Furthermore, the rise of opioid prescriptions for CNCP is observed with concern in Germany, even though there are no signs for an opioid epidemic [11]. The majority of opioid prescriptions are issued for CNCP, although it is well known that opioids are frequently not or little effective in this indication and associated with a high risk for adverse events such as obstipation, falls, cognitive impairments, or addiction [12]. If analgesics are applied, it is vital to perform thorough medication management and to adhere to monitoring recommendations. The German guideline for long-term use of opioids in chronic noncancer pain (LONTS) gives clear recommendations for safe opioid management [13]. However, adherence to guidelines might be impacted by factors such as personal attitudes, preferences, and experiences [14] and General practitioners (GP) might be less likely than other specialists to follow a guideline since they favor their own experience [15,16], or might not be aware of guidelines. Suboptimal pain management does not only result in unnecessary suffering of the affected patients but also in high costs for the health care system: patients with pain-related disabilities have a 6-fold higher rate of sick leaves and 4.5-fold higher rate of physician visits [17].

In Germany, patients with CNCP are mainly treated in ambulatory care by GPs and specialists such as orthopedists, neurologists, or rheumatologists. Only 10% have ever seen a pain specialist or received multimodal pain therapy [18]. GPs frequently know their patients and the patient's family for many years. They often act as coordinators of care and are frequently the main prescribers of all medications. Therefore, they play a crucial role in the care of patients with chronic pain. In spite of these good preconditions, it remains challenging for GPs to

implement structured and holistic pain management in their daily practice [9].

Within the project RELIEF (Resource-oriented case management to implement recommendations for patients with chronic pain and frequent use of analgesics in general practices), a case management program was developed to support GP in implementing guideline-based pain management. The program focusses on patients with CNCP and 4 essential areas of pain management: medical assessment and monitoring, practice team and patient education, self-care, and rational pharmacotherapy.

Overall Aim of the Study

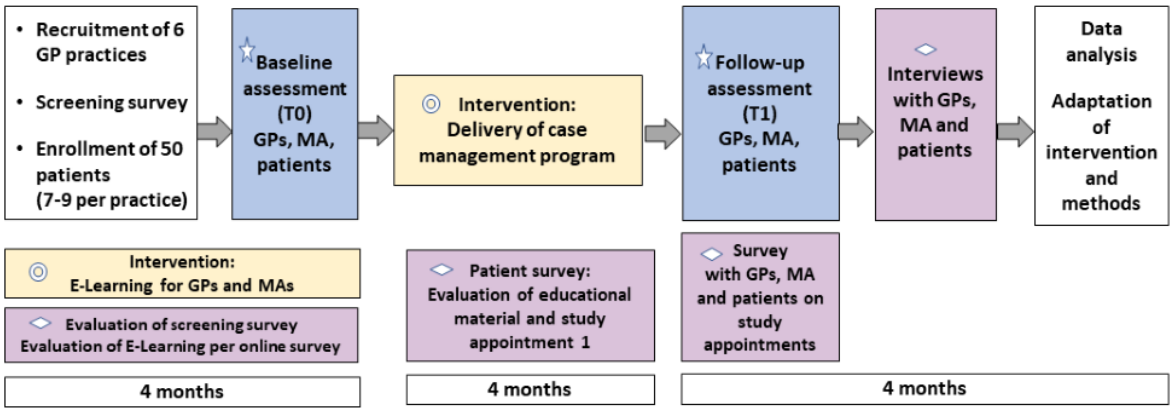
The main objective of this pilot study is to test the developed program in a small number of practices with a small number of patients to assess the feasibility of the developed intervention components (eg, assessment and e-learning) and methods used for recruitment (eg, screening process) and data collection. Thus, a control group (no intervention) will not be involved. The evaluation of the program's potential effectiveness and data generation on the prevalence of the programs' target group in German general practices are secondary objectives. Based on findings of this study, the program and evaluation concept will be adapted where applicable and applied in a subsequent confirmatory cluster randomized controlled trial (not described in this protocol).

Methods

Study Design

A single-arm, exploratory pilot study with accompanying process evaluation will be conducted to pilot the case management program. Conducting a pilot study provides a good opportunity to assess feasibility of a full-scale study and can be considered an essential prerequisite to enhancing likelihood of success of the main study. Pilot studies should be well designed with clear feasibility objectives, and explicit criteria for determining feasibility [19]. Figure 1 details the design for the RELIEF pilot study.

Figure 1. The design of the pilot study in RELIEF. Yellow box (circles): intervention components; blue box (star): outcome evaluation; purple box (diamond): process evaluation. GP: general practitioner; MA: medical assistant; RELIEF: resource-oriented case management to implement recommendations for patients with chronic pain and frequent use of analgesics in general practices.



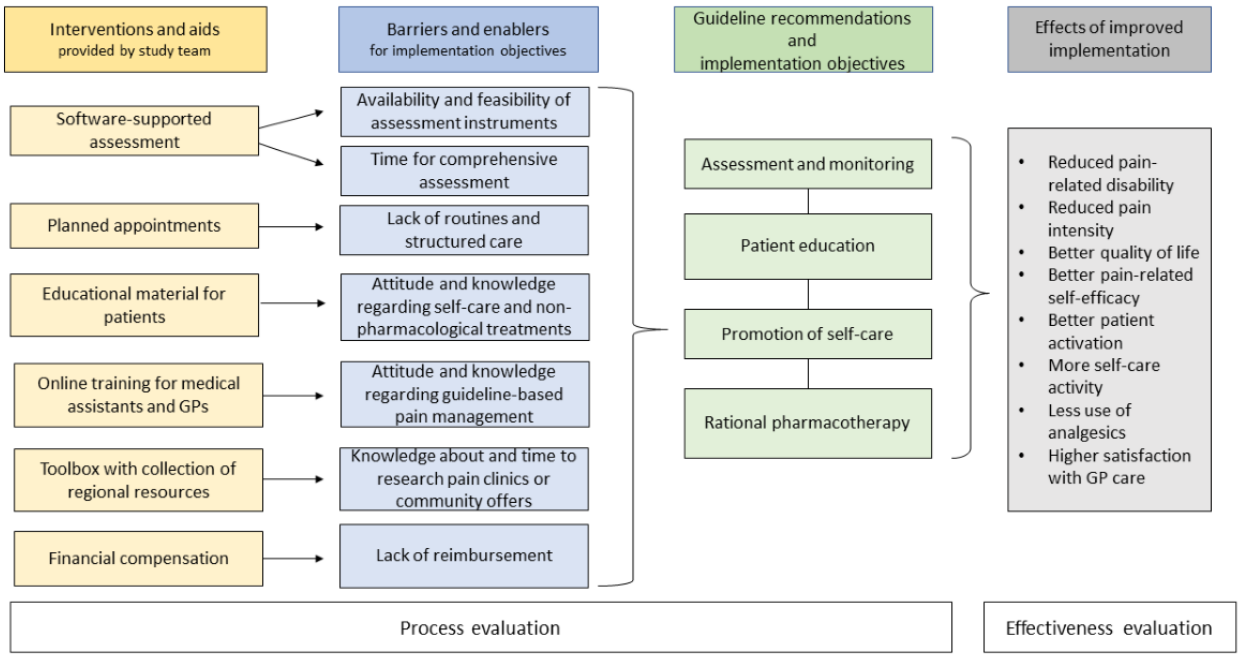
Intervention

The RELIEF intervention consists of five key components: (1) medical pain assessment and monitoring using a module specifically developed for the RELIEF intervention to be applied within an established case management software (CareCockpit) [20], (2) 3 scheduled structured appointments with GPs and medical assistants (MA), (3) e-learning on chronic pain management for GPs and MA, (4) educational video- and paper-based material for patients, and (5) a toolbox with a collection of resources for pain management for patients and practice teams. GP and MA will receive financial compensation for their additional efforts related to participation in the study (€200 [approximately US $216] per GP, €400 [approximately US $432] per MA) and number of included patients (€80 [approximately US $86] per included patient). GPs can apply for a total of 8 continuing medical education points upon completing the e-learning modules.

It is expected that patients participating in the case management program will benefit from the intervention. It is hypothesized that improved medication management and intensified use of nonpharmacological treatment strategies will result in a reduction in pain-intensity and pain-related disabilities, improved patient activation, more self-care activity and less use of analgesics. Figure 2 describes the assumed effect mechanism of the developed intervention.

It is assumed that adherence to guideline recommendations for CNCP by practice teams (green boxes) will improve if the intervention components (yellow boxes) effectively reduce identified barriers or make use of identified enablers respectively (blue boxes). Improved adherence to guideline recommendations will result in improved health outcomes or health behavior, respectively (gray box). Primary and secondary outcomes (gray box) focus on the effects of improved guideline adherence while adherence as well as assumed linkages between interventions and barriers are assessed within the scope of a comprehensive process evaluation.

Figure 2. The assumed effect mechanism of the intervention. GP: general practitioner.



After enrolling in the pilot study, patients will complete a pain assessment through a browser-based proprietary app available to study participants only (TeleVital app linked to CareCockpit) at home on their own digital device (smartphone, tablet, computer, etc). The assessment focusses on various aspects of pain and mental comorbidities. Within 2 weeks, patients will have a scheduled structured appointment (study appointment 1) with their GP during which the patients' specifications in the assessment will be discussed and complemented by an open pain history taking. For this purpose, GPs or medical assistants will perform a manual import of the assessment data into the software CareCockpit, an established case management software currently used by about 800 general practices in Baden-Württemberg, Germany, for the case management program PraCMan [20]. This is a care model for patients with multimorbidity insured by the statutory health insurance AOK Baden-Württemberg. The data import will only be started when the patient is present in the practice to ensure that GPs are able to react immediately on critical information such as severe depression. Practice teams will receive the data in 2 versions: the original version with all items and patients' responses and, in addition, a summary of the assessment with automatically calculated scores.

At the end of study appointment 1, educational material on chronic pain (a booklet and links to educational videos tailored to patient's self-efficacy, to be used as often as patients want, and at their own speed) will be handed out to patients and the date for study appointment 2 will be set for about 2-4 weeks later. During study appointment 2, patients and GPs or patients and medical assistants will reflect on the educational material provided and agree on treatment goals related to daily activities (eg, to be able to do some gardening) and self-care activities (eg, physical activity or relaxation techniques). If necessary, medication is prescribed and therapies outside the general practice are initiated (eg, physiotherapy, multimodal pain therapy, psychotherapy, and rehabilitation), and monitoring activities (diagnostics, amendments to therapy plan, discussion of possible adverse effects, pain management, medication, self-care, etc) are planned. A treatment plan containing all this information will be issued by the responsible GP through the CareCockpit software and the date for study appointment 3 will be set for 4-6 weeks later. During study appointment 3, practice teams will check whether activities could be applied as planned. If necessary, the treatment plan will be adapted. The activities performed during study appointments 1-3 will briefly be documented by the practice teams through a checklist in the CareCockpit module. The intervention period will end with a follow-up assessment 4 weeks after study appointment 3.

A webinar will be offered by the study team to go over study organization and measures with all participating practice teams. Participating GPs and MAs will complete an e-learning on chronic pain management with 4 modules covering the pathogenesis of chronic pain, self-care activities (relaxation technics, physical activity, and topical applications), analgesics and interprofessional and interdisciplinary pain therapy. The e-learning is expected to be completed before the first patient receives study appointment 1. A website with a toolbox containing useful links and information on chronic pain as well as a collection of regional resources (eg, hospitals providing multimodal pain therapy and counseling centers etc.) will be provided by the study team. Table 1 summarizes the planned course of the RELIEF case management program.

Table 1. The course of the case management program in the RELIEF[a] pilot study.

Who	Where	What
Week 0		
MA[b]	Practice	• Enrollment into study
Patient	At home	• Structured pain assessment through TeleVital appT0 baseline assessment through a paper-based questionnaire
Week 2		

GP[c]	Practice	• Study appointment 1:
		  • Discussion of the results of the structured pain assessment
		  • Open pain history taking
		  • Patient receives educational material

Patient	At home	• Reading educational material or watching educational videos, respectively
Week 5 to 6		

• MA
• MA or patient
• GP
	Practice	• Study appointment 2:
		  • Reflection on educational material
		  • Agreement on treatment goals and self-care activities
		  • Treatment plan is issued

Patient	At home	• Applies treatment plan
Weeks 10 to 12		
• MA • GP	Practice	• Study appointment 3: • Monitoring if treatment plan and self-care could be applied as planned; if necessary, adaption of the treatment plan
Patient	At home	• Applies (adapted) treatment plan
Week 16		
Patient	At home	• T1 follow-up assessment; end of pilot study

[a]RELIEF: resource-oriented case management to implement recommendations for patients with chronic pain and frequent use of analgesics in general practices.

[b]MA: medical assistant.

[c]GP: general practitioner.

Recruitment

General practices will be recruited through known contacts such as the established practice network of about 800 practices that use a particular case management system for chronically ill patients (PraCMan) [21] and a network of teaching and research practices affiliated with the Department of Primary care and Health Services Research, University Hospital Heidelberg. The target is to include 6 practices. Based on previous experiences, it can be assumed that about 10% of the practices approached are interested in participating in research projects. Therefore, 60 practices in a predefined region will be randomly drawn and an invitation to participate in the pilot study will be sent to them by postal or electronic mail together with a declaration of interest form. Practices that declare interest in participation will receive written information about study aims and procedures. In case the recruitment target is not met, another random sample will be drawn.

To identify eligible patients and to gather information on the prevalence of the target group in primary care, a screening survey will be conducted (see Data Collection and Outcomes section below). Eligible for participation will be adult patients with CNCP for more than 3 months, with at least moderate pain-related disability (minimum 4 points on a scale from 0-10), permanent or on-demand use of analgesics and co-analgesics in the previous 4 weeks, and practice team assessed ability to participate actively in the pilot study (sufficient cognitive abilities and internet access). Patients with cancer pain or in palliative care will be excluded. Recruitment target for each practice is 7-9 patients. If more than 9 patients agree to participate in the piloting, the practice team will select 7-9 patients who are according to their assessment likely to benefit from the program. Specific reasons for their choices will be explored in the process evaluation.

Data Collection and Outcomes

For the screening survey, each participating practice will hand out a screening questionnaire to the first 150 adult patients entering the practice from a defined date on. The practice team will collect the questionnaires, check eligibility with a provided template and invite all patients meeting the inclusion criteria to participate in the pilot study by handing out the study information material. The practice team will add information regarding reasons for nonparticipation, known CNCP diagnosis, known use of analgesics, and prescription of analgesics during the last month on the screening questionnaires of all patients meeting the inclusion criteria (regardless of whether they agree to participate in the study or not) by checking the patient file. The practice team will deidentify all questionnaires (also of patients without chronic pain) by cutting the lines for name and birthdate and send them to the study center for evaluation purposes regarding prevalence of patients in a primary care setting who meet the inclusion criteria.

Data collection related to medical pain history (used by practice teams only, not by researchers) comprises the following steps: patients receive a weblink from their GP practice leading to a browser-based app called TeleVital and complete the assessment through the app on their own digital device. TeleVital is a proprietary development of the Department of Primary Care and Health Services Research, University Hospital Heidelberg, and facilitates structured data collection in studies which use the CareCockpit. Data generated in the TeleVital app data will be stored on a secure server located at the University Hospital Heidelberg, Germany until it is transferred to the CareCockpit software installed in the GP practice. Data import will be initiated manually by the practice team at the next patient contact. Thus, practice teams will receive the assessment data only when the patient is present in the practice. Practice teams will use the assessment data for the purpose of diagnostics and treatment. It contains information on pain history, pain characteristics, use of analgesics, use on nonpharmacological measures, treatment targets, and items from validated screening questionnaires such as the Pain Detect questionnaire on neuropathic pain [22] and on mental comorbidities such as posttraumatic stress disorder [23].

Data collection for the outcome evaluation comprises the following steps: primary objective of this pilot study is to assess the case management's feasibility, measured by a set of predefined feasibility indicators. Regarding the intervention components, feasibility indicators refer to the software-supported medical pain history, study appointments, educational material for patients, and e-learning for GPs and MA. Feasibility of study procedures will be measured for the patient recruitment and enrollment process, completion of T0 and T1 questionnaires and drop-out rate. To facilitate this assessment, transfer of partial documentation from the CareCockpit to the study center will be used either electronically or paper-based, depending on preference and available resources in the participating practices. Table 2 describes the feasibility indicators in relation to the intervention components, and Table 3 details the feasibility indicators for study procedures.

Table 2. The feasibility indicators for intervention components in the pilot study.

Interventions	Data source	Indicator	Rating
Software-supported medical pain history	CareCockpit data process evaluation	Percentage of patients with pain assessment transferred to practice computer	• ≥80%: feasibility given • <80%, but reasons solvable by modification: feasibility likely • <80% and reasons not solvable by modification: feasibility not given
Planned appointments	CareCockpit data	Percentage of patients who received all 3 study appointments	• ≥80%: feasibility given • <80%, but reasons solvable by modification: feasibility likely • <80% and reasons not solvable by modification: feasibility not given
Educational material for patients	Evaluation questionnaire and patient interviews	Percentage of patients who perceived the provided content relevant and comprehensible	• ≥80%: feasibility given • <80%, but reasons solvable by modification: feasibility likely • 80% and reasons not solvable by modification: feasibility not given
E-Learning for GPs and medical assistants	Evaluation questionnaire and general practitioner and medical assistant interviews	Percentage of health care professional who perceived the e-learning relevant and comprehensible.	• ≥ 80%: feasibility given • <80%, but reasons solvable by modification: feasibility likely • 80% and reasons not solvable by modification: feasibility not given
Toolbox	Survey and general practitioner, medical assistant, and patient interviews	Percentage of participants who perceived the toolbox as relevant	• ≥80%: Feasibility given • <80%, but reasons solvable by modification: feasibility likely • 80% and reasons not solvable by modification: feasibility not given

Table 3. The feasibility indicators for study procedures in the pilot study.

Study procedure and data source	Indicator	Rating
Patient recruitment		
Screening questionnaire	Percentage of patients who agreed to participate in the screening survey	• >80%: feasibility given • <80%, reasons solvable by modification: feasibility likely • <80% and reasons not solvable by modification: feasibility not given
Screening questionnaire	Percentage of patients in screening survey meeting all inclusion criteria	• >10%: feasibility given • <10%, but reasons solvable by modification: feasibility likely • <10% and reasons not solvable by modification: feasibility not given
Screening questionnaire	Percentage of practices that enrolled 7-9 patients	• >80%: feasibility given • <80%, reasons solvable by modification: feasibility likely • <80% and reasons not solvable by modification: feasibility not given
Outcome evaluation		
T0 and T1 questionnaires	Percentage of patients who completed T0 and T1 questionnaires	• >80%: feasibility given • <80%, reasons solvable by modification: feasibility likely • 80% and reasons not solvable by modification: feasibility not given
General practitioner report	Patient drop-out rate	• <20%: feasibility given • >20%, but reasons solvable by modification: feasibility likely • >20% and reasons not solvable by modification: feasibility not given

A range of secondary outcomes will be determined to gather information on potential effects of the program. All secondary outcomes are participant-reported and will be collected before (T0) and after (T1) the intervention by paper-based questionnaires which participants will complete at home and send directly to the study center.

Outcome measures on patient level comprise the German versions of the following validated instruments: Pain Disability Index German version (PDI-G) [24] (key secondary outcome), Patient Activation Measure [25], Short Form 12 Health Survey scale for health related quality of life [26], De-Jong-Gierveld loneliness scale [27], Pain Self-Efficacy Questionnaire German version [28], Avoidance-Endurance Fast Screening instrument [29], Pain-Catastrophising Scale [30], selected items of the European Project on Patient Evaluation of General Practice Care (EUROPEP) questionnaire on evaluation of GP care [31,32], and pain intensity (numeric analogue scale). Further study-specific items will be used to assess the use of self-care such as physical activity (3 items), relaxation techniques (1 item) and use of topical applications (1 item) and patients will be asked to document their pain medication (over-the-counter and prescribed). Secondary outcomes on GP and MA level refer to quality indicators for ambulatory pain management developed in the RELIEF project. Data for the process evaluation will be collected at various points in time as detailed in Figure 1.

During patient recruitment, practice teams will be asked to send the deidentified patient screening questionnaires to the study center for evaluation purposes. The e-learning for GPs and MA will be hosted on the platform Moodle on the server of the aQua Institute, Göttingen. After completion of the e-learning GPs and MA will be asked to fill in a short digitally provided survey to evaluate the training regarding aspects such as subjective knowledge increase, appropriateness of required time, appropriateness of didactical methods, and usability of the platform. The survey will be conducted through the survey tool Lime Survey hosted at a server of the University Hospital Heidelberg. Survey data will be linked through a pseudonym to the following meta-data gathered by the e-learning platform (e-learning completed or not completed, time needed to complete the e-learning (minutes), and number of logins necessary to complete the e-learning).

Patients will complete a paper-based pseudonymized questionnaire focusing on use and perceived usefulness of the provided educational material and experiences with study appointment 1. Patients will complete the questionnaire after going through the content provided and within 4 weeks after study appointment 1. At the end of the intervention period, patients will be asked to fill in a second questionnaire focusing on their experiences with study appointment 2 and 3 as part of the T1 follow-up survey.

All participating GPs and medical assistants will be invited to report their experiences during the pilot in a telephone interview. All patients will be invited to an interview after completing study visit 3. Depending on the response rate, a purposive sample of patients will be drawn. Written informed consent to participate will be obtained using separate information documents and agreement forms. Key questions on the interview guides will refer to intervention feasibility with regards to specified feasibility indicators, usefulness of provided material and tools, perceived effectiveness of the case and care management program, and suggestions for modifications from the perspective of health care providers and patients. Interviews will be recorded and transcribed verbatim. Transcripts will be pseudonymized and stored on secure servers at the Department of Primary Care, University Hospital Heidelberg. All audio files will be deleted after completion of data analysis.

Data Analysis

A plan for the primary analysis will be finalized before data bank closure. All analysis will be performed in R (version 4.2.0 or higher; R Foundation for Statistical Computing) or in SPSS (version 28.0.1.0; IBM Corp) in a validated environment. The final analysis will be done as soon as the database has been declared to be complete and accurate and has been locked. Descriptive statistics will be provided to summarize demographics and baseline characteristics. In general, continuous variables will be described using number of observations, mean, SD, median, Q1, Q3, minimum, maximum, 95% CIs and, if existing, number of missing values at T0, T1 and for T0-T1 if appropriate. For categorical variables, absolute and relative frequencies will be given with missing values being reported as a separate category at T0 and T1. A CONSORT (Consolidated Standards of Reporting Trials) flow diagram will be created to display the progress of all participants through the trial. This includes the number of patients assessed for eligibility and the number of patients excluded because they did not meet inclusion criteria, declined to participate, or any other reason.

Primary Outcome Analysis

For each objective of the intervention components and study procedures, a descriptive analysis will be performed to assess feasibility. For each objective, 95% CIs will be given based on the Wilson Score interval for binary measures [33]. Reasons for not fulfilling an indicator will be categorized and evaluated descriptively.

Secondary Outcomes Analysis

As one of the aims of the study is to estimate the effect size, the 95% CI (2-sided) of the PDI-G percent change from baseline to T1 (T0-T1), which is planned to be the primary outcome in a subsequent cluster randomized trial and therefore of major interest in this pilot study, will be given. Only questionnaires with at least 6 out of 7 answered items will be considered. Missing items will not be imputed. Questionnaires with less than 6 answered items will not be considered.

As a sensitivity analysis, missing values of the PDI-G will be replaced on item level using multiple imputation based on predictive mean matching using the variables age, sex, center, and pain intensity at baseline as potential predictors. Missing scores and differences can then be calculated using the imputed items. Furthermore, a best- and worst-case scenario will be looked at, where missing values will be imputed by the highest and lowest observed value for T0 and T1 in the best case scenario and vice versa in the worst case scenario (lowest and highest observed value for T0 and T1, respectively). As another sensitivity analysis, a mixed linear regression model for the dependent variable PDI-G score at T1 will be performed including age, sex, and PDI-G at T0 as fixed effects and center as random effect. Descriptive analysis at item level and for the total number of pain-related patients at T0 and T1 will be done. Descriptive analysis of the item and score level will be done for all remaining secondary outcomes. For differences in scores between baseline and follow-up, 95% CIs will be reported. Missing values for secondary outcomes will not be imputed.

No sample size calculation was performed, as the main purpose of the pilot study is to investigate feasibility of the applied interventions and study procedures. Considering the exploratory nature of the pilot study, and based on experiences from previously conducted research, a total of 50 patients is considered sufficient to provide an initial estimate of the potential effect of the intervention measured by the PDI-G percent change from baseline to T1 (T0-T1), which is the key secondary endpoint. Assuming a SD of 13.7 and 15.4 score points [34] corresponding to a SD of 19.6% and 22% score points respectively, a sample size of 50 patients and a 2-sided 95% CI would yield the following: assumed SD 19.6: [x-5.6, x+5.6]; assumed SD 22: [x-6.3, x+6.3], where x is the point estimate of the PDI-G percent change from baseline to T1 (T0-T1).

Analysis of Process Evaluation Data

Analysis of the qualitative data collected in the process evaluation will use an inductive approach based on the themes covered in the interview guide (including unintended effects). Data management will be done in MAXQDA (Verbi Software). Written surveys will be conducted digitally through the survey tool Lime Survey hosted on secure servers of the Heidelberg University. All quantitative survey data and data from free text fields will be analyzed descriptively using SPSS and visualized in Excel (Microsoft). In addition, data entered by the practice teams into the CareCockpit software to document activities performed during the study appointments will be transferred to the study center and analyzed within the scope of the process evaluation. All data will be deidentified before analysis. All data generated in the process evaluation will be triangulated for classification of intervention and program feasibility. Final assessment of feasibility will be performed by 2 researchers in a consensus process.

Ethical Considerations

The pilot study in RELIEF received ethics approval from the Ethics Committee of the Medical Faculty at University Heidelberg, Germany (S-329/2024; June 05, 2024) and the state medical association of Baden-Württemberg (B-F-2024-057; July 02, 2024). The study will be conducted in accordance with the Declaration of Helsinki. All participants will give written consent before participation.

Results

The recruitment for this pilot study started in October 2024 and was open until end of December 2024. The targeted sample size was 6 practices and 50 patients. The intervention period began in February 2025 and will run until June 2025. Findings are expected to provide an indication of potential patient benefits as well as feasibility of the interventions and study procedures. First evaluation results regarding potentially necessary adaptations of intervention components and study procedures are expected to be available in July 2025. Publication of findings and necessary adaptations are expected for the second and third quarters in 2025.

Discussion

Principal Findings

Findings in this exploratory pilot study will provide a clear indication regarding intervention feasibility and applied study procedures. It is expected that eligible patients will benefit from the intervention and that improved medication management and intensified use of nonpharmacological treatment strategies will result in a reduction of pain-related disabilities and other patient-reported outcomes. Potentially necessary adaptations of intervention components and study procedures will be finalized before testing the intervention in a randomized controlled trial which is planned to begin late in 2025. The evidence base regarding the chosen combination of intervention measures for patients with CNCP in German primary care is still limited. The expected effects appear to be plausible; however, they are not certain, so this pilot study can provide an important contribution.

The common belief that pain is a normal part of aging may explain why chronic pain is often underestimated and underreported [35]. Studies found that older adults tend to adopt a stoic attitude toward experiencing pain and prefer to use self-reliance–based coping strategies, though these may not always be effective [35,36]. A study in Italy explored coping strategies used by older adults to manage chronic pain and found that frequently coping self-statements, resting, task persistence, and guarding were described, while the least used strategies were relaxation and exercise or stretching [37]. The latter are clearly recommended in German guidelines [9]. Other studies also explored life experiences and needs of older adults with chronic pain and strategies they use to cope with and manage pain [38,39] or aimed to promote effective and tailored pain self-management interventions [36,40]. The RELIEF case management program contains innovative elements: GPs, MAs, and patients may benefit from the more structured care processes and patient activation which in turn can provide room and time for open discussion with patients on their needs. Meticulously obtained pain history for example, provides important information for pain assessment regarding onset and course, pain episodes, quality, intensity, activity impairment, and any stress factors in a patient's personal life [41]. Some elements of the innovative program can be assigned to medical assistants, for example reflecting on the educational material or setting individual treatment targets with patients. Thus, MA will be more involved in CNCP care than usual, which may increase their competences, strengthen their role in the care process, and support sharing of the workload in team-based care [42].

Educational components will be used as an explicit treatment strategy anchored directly in the general practice setting. Care programs for disease management usually offer patient education outside of the GP practice which has the disadvantage of GPs being unfamiliar with the presented content which makes it difficult to refer to and pick it up in the course of treatment [9]. Combining therapies with delivering content remotely through the internet or mobile devices is increasingly used to promote and improve self-management of chronic conditions. And complement face-to-face pain treatments [43]. On the other hand, some elements of the RELIEF program may cause additional burden: patients will be asked to provide detailed information about their pain history, mental condition and personal goals and receive comprehensive information about chronic pain. This may provoke adverse effects such as negative, stressful emotions, yet also has the potential for reflection about perhaps still unused self-care potential and possible behavior adaptation. Participation in the case management program will require additional appointments and therefore be associated with an additional time burden for patients and practice teams alike. This pilot study will assess thoroughly whether the assumed effect mechanisms are plausible and whether the potential benefits outweigh potential harms.

Strengths and Limitations

This study is a single-arm exploratory pilot study which leaves room for bias. Primary and secondary outcomes are based on self-reported data. In the multifaceted program, the potential impact of the various components might be difficult to separate. Strong aspects will be the program's closeness to daily practice and the exploration of implementation outcomes in the accompanying process evaluation which adds value to this study. The analysis of components of the complex implementation program using predefined feasibility indicators contributes to the transparency of the implementation program.

Dissemination Plan

After completing this feasibility study, findings will be disseminated through oral and poster presentations at scientific conferences as well as in a scientific article in a peer-reviewed journal.

Conclusion

This study will provide valuable information regarding potentially necessary adaptations before applying the intervention in a confirmatory cluster randomized controlled trial.

Acknowledgments

Project RELIEF (resource-oriented case management to implement recommendations for patients with chronic pain and frequent use of analgesics in general practices) is exclusively funded by the German Federal Ministry of Education and Research (01GY2106). The funder had no role in design and conception of this study. For the publication fee, the authors acknowledge financial support by Heidelberg University.

Data Availability

In line with the obtained ethics approval, all data sets that will be generated and analyzed during this pilot study and the process evaluation will not be publicly available due to data protection laws. They will be stored on secure servers at the Department of Primary Care and Health Services Research, University Hospital Heidelberg. Deidentified sets of these data can be made available by the corresponding author on reasonable request.

Authors' Contributions

RPD, CS, and SB designed this pilot study and the intervention components and drafted and revised this study protocol. AB provided expertise on statistical analysis and critically revised the manuscript. CS and RPD shared the project management. All authors provided input and critical feedback and approved the final version of the manuscript.

Conflicts of Interest

The principal investigator CS is member of the guideline commission of the German Society of General Practice and Family Medicine (DEGAM). SB is a doctoral candidate in RELIEF. All authors declare no conflict of interest.

Multimedia Appendix 1
SPIRIT checklist.
[PDF File (Adobe PDF File), 190 KB - resprot_v14i1e66335_app1.pdf]

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Abbreviations

CNCP: chronic noncancer pain
CONSORT: Consolidated Standards of Reporting Trials
EUROPEP: European Project on Patient Evaluation of General Practice Care
GP: general practitioner
LONTS: German guideline for long-term use of opioids in chronic noncancer pain
MA: medical assistant
NSAID: nonsteroidal anti-inflammatory drug
PDI-G: Pain Disability Index German version
RELIEF: resource-oriented case management to implement recommendations for patients with chronic pain and frequent use of analgesics in general practices

Edited by A Schwartz; submitted 10.09.24; peer-reviewed by E Ross; comments to author 09.12.24; revised version received 20.12.24; accepted 03.03.25; published 15.04.25.

Please cite as:
Poß-Doering R, Brinkmöller S, Balzer A, Wurmbach VS, Paul C, Stolz R, Zugaj MR, Tesarz J, Wensing M, Straßner C
Resource-Oriented Case Management to Implement Recommendations for Patients With Chronic Pain and Frequent Use of Analgesics in General Practices (Project RELIEF): Protocol for a Single-Arm Exploratory Feasibility Study
JMIR Res Protoc 2025;14:e66335
URL: https://www.researchprotocols.org/2025/1/e66335
doi:10.2196/66335
PMID:

Protocol

Student Acceptance of Digital Entrustable Professional Activities: Protocol for a Cohort Study

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Abstract

Background: Integrating digital entrustable professional activities (EPAs) and simulations in medical education represents a substantial shift toward competency-based learning. This approach focuses on developing specific skills through manageable units and enhancing proficiency in high-stakes environments. The technology acceptance model provides a framework to evaluate the adoption of these educational technologies, emphasizing the roles of perceived usefulness and ease of use.

Objective: This cohort study aims to investigate the acceptance of digital EPAs among medical students within simulated training environments. It seeks to understand how perceived usefulness and ease of use influence this acceptance, guided by the principles of the technology acceptance model.

Methods: The cohort study will involve medical students in the clinical phase of their education at Ludwig Maximilians University Munich. The survey, distributed through the Module-6 distributor, will capture their perceptions of digital EPAs. The data will be analyzed using regression analysis.

Results: Data collection is anticipated to be complete by April 2025, with analysis concluded by May 2025. The results will provide insights into students' attitudes toward digital EPAs and their willingness to integrate these tools into their learning.

Conclusions: This study will contribute to the understanding of digital EPAs' role in medical education, potentially guiding future design and implementation of these tools. While highlighting the importance of perceived usefulness and ease of use, the study also acknowledges limitations in sample size and recruitment methodology, indicating the need for further research with more diverse and larger groups. This research is poised to shape future medical training programs, aligning with the evolving landscape of medical education.

International Registered Report Identifier (IRRID): PRR1-10.2196/59326

(JMIR Res Protoc 2025;14:e59326) doi:10.2196/59326

KEYWORDS

medical education; entrustable professional activities; EPAs; digital EPAs; technology acceptance model

Introduction

Background

The concept of entrustable professional activities (EPAs) has changed the approach to medical education, shifting the focus toward competency-based learning. They cover core functions like educational theory, curriculum design, and assessment while also addressing emerging areas such as self-development and technology use in health care education [1]. EPAs are designed to break down complex medical skills into manageable units, allowing learners to gain proficiency in specific tasks progressively [1]. This methodology has been instrumental in ensuring that medical trainees are adequately prepared for the responsibilities they will face in their professional lives while empowering teaching staff to maximize the learning outcomes of their students [2].

Complementing EPAs, the use of simulations in medical training has become increasingly important. These simulations provide realistic, interactive environments where students can practice and hone their skills without the risks associated with real-life clinical settings. As highlighted by Chernikova et al [3] and Smetana and Bell [4], computer-based simulations, in particular, offer dynamic representations of real-world medical scenarios. These tools are invaluable for developing both the cognitive decision-making and motor skills essential in the medical field.

However, despite the advancements in and the separate explorations of EPAs and simulations, the combination of these two into a digital format, more specifically digital EPAs, remains largely unexplored. While both EPAs and simulations have been part of extensive research efforts individually, their integration into a digital EPA format offers a new development for these two teaching methods [1,3,4]. Yet digital EPAs and their acceptance among learners and educators remains largely unexamined [5].

In understanding the adoption and effectiveness of these educational technologies, the technology acceptance model (TAM) offers valuable insights. Introduced by Davies [6] and further explored by Marangunić and Granić [5], the TAM posits that perceived ease of use and usefulness are critical factors influencing the acceptance and integration of new technologies in learning environments. This model has been widely applied in various contexts to understand how users come to accept and use technological tools in their work.

The aim of this study is therefore to identify how well students perceive the usefulness of digital EPAs as well as their ease of use. In addition, we will investigate whether this perception influences students' intention of using digital EPAs in their studies.

EPAs in Medical Education

EPAs, as a didactic concept, focus on competency-based curricula to help students acquire specific competencies, potentially contributing to a more flexible duration of training [1]. They are characterized by a gradual reduction of supervision until learners can perform tasks completely independently [7]. This development occurs over five stages, starting with mere presence and observation to the independent guidance of younger learners [1,8]. EPAs represent specific professional activities distinguishing them from conventional learning objectives [2]. A competency-oriented teaching method could reduce the training duration for faster-learning medical students without compromising the quality of education [9]. Such a system could benefit not only medical students but also the teaching staff, program developers, and medical institutions, as well as other employees, by clearly defining which tasks can be performed with what degree of autonomy [1,2,10].

Digital EPAs

Simulations, as interactive representations of real-world scenarios, play a crucial role in the acquisition of complex skills. Simulation-based learning, as demonstrated by Chernikova et al [3] in their 2020 meta-analysis, is a highly effective approach to designing learning environments in higher education and can be beneficial from the beginning of study programs for students at all levels. Simulations provide an effective medium for developing complex skills, such as those required in surgery, combining theoretical knowledge with practical expertise, such as seen in spinal surgery [11]. In combination with the concept of EPAs, as gradually increasing levels of clearly defined competencies, this suggests complementing real-life training with training in simulations. These simulations would need to precede real-life training by allowing students to practice the same competencies (digital EPAs). Systematic use of these digital EPAs could potentially substantially increase the quality of and reduce the time required for real-life training, which is often cost-intensive or requires rare and critical situations (eg, high-stakes operations).

However, such a shift in education would need to be accepted by all stakeholders (ie, medical educators, medical students, and patients).

The TAM

The TAM has significantly influenced the understanding of technology adoption and use [5]. This model's foundation was built on two critical factors: perceived usefulness and perceived ease of use [5]. These factors are pivotal in shaping users' attitudes and intentions toward adopting technology. Davies' [6] original model proposed that users' motivation to use a system is influenced by these two beliefs [5]. Perceived usefulness reflects the degree to which a person believes that using a specific system would enhance their job performance [12]. Perceived ease of use refers to the belief that using a particular system would be effortless [12]. The interaction between these two beliefs plays a critical role in determining the user's attitude toward the system and, consequently, their actual use behavior [6].

The significance of the TAM extends beyond traditional technologies and has proven to be indispensable, especially in designing user-friendly and effective technology-based learning systems. In a world where digital technologies are increasingly coming to the forefront, TAM remains a critical framework for researchers and practitioners to predict and understand user behavior toward new technological advancements.

This Study

In this cohort study, we will focus on medical students, investigating how well they perceive the usefulness of digital EPAs as well as their ease of use in medical education. In addition, we will investigate whether this perception influences students' intention of using digital EPAs in their studies. Since this teaching concept is largely unfamiliar to students, they are first presented with a written EPA, followed by a digital version, which the questionnaire will refer to. The example EPA, as well as the digital EPA, can be accessed via Open Science Framework (OSF) [13].

Methods

Recruitment Plans and Study Population

The study population for this cohort study will consist of medical students in the clinical phase of their studies. This cohort is optimally suited for the application of digital EPAs,

as these are aimed at learning specific skills, which is the core of the clinical phase of medical studies. The plan is to distribute the survey link through the major study distribution lists of Ludwig Maximilians University Munich, such as the Module-6 distributor. This would ensure that only students in the clinical phase participate in the survey. In addition, students would have the flexibility to complete the questionnaire at their convenience.

Inclusion Criteria

Medical students must be at least in their third year of medical training. This ensures that the preclinical foundational subjects, such as macroscopic and microscopic anatomy, physiology, biochemistry, and medical psychology, have already been completed. In addition, they must have passed their first medical state examination.

Exclusion Criteria

Reasonable command of the German language is required to participate in this study.

Data Analysis Plans

A regression analysis will be performed assuming a moderate effect size. Furthermore, an α level, common in social sciences, of .05 was chosen. The statistical power of the study was set standardly at P=.80. To calculate the necessary sample size for these specific parameters, the software G*Power 3.1 [14] was used. This calculation indicated that a sample size of 68 participants is required to meet the above criteria. To provide additional security and account for possible dropouts, a margin of 10% will be added to the calculated sample size. This means that a total of 75 participants should be recruited for the study. Assuming a response rate of approximately 25% (based on previous experiences), we will contact 300 students (about 25% of all viable students at Ludwig Maximilians University Munich) via email.

Questionnaire and Hypotheses

Overview

The basis for the conception of the questionnaire is the research work by Abdul Ghani et al [15], which used the TAM as a foundation for evaluating digital game-based learning. The questionnaire was only adapted to the context of digital EPAs. The entire questionnaire can be found on OSF [13]. Both the German translation shown to the participants and an English version of the questionnaire can be found there. The hypotheses below were formulated based on the TAM and are to be explored through the questionnaire.

Construct: Perceived Usefulness

Operational Definition

Perceived usefulness [6] reflects students' perception of whether the use of digital EPAs in a simulated environment will enhance their performance (independent variable).

Hypothesis

The more useful medical students find digital EPAs in medical simulations, the higher their behavioral intention to use this technology as part of their studies will be.

Construct: Perceived Ease of Use

Operational Definition

Perceived ease of use [6] refers to a student's perception that using digital EPAs for learning skills during their medical studies will require minimal effort (independent variable).

Hypothesis

The easier medical students find the operation of digital EPAs in medical simulations to be, the greater their behavioral intention to use this technology will be.

Construct: Attitude

Operational Definition

Attitude [6] refers to student's judgment on whether the use of digital EPAs is beneficial to them (independent variable).

Hypothesis

The more positive the attitude of medical students toward digital EPAs in medical simulations is, the higher their behavioral intention to use this technology will be.

Construct: Behavioral Intention (Operational Definition)

Behavioral intention [6] refers to a student's intention to theoretically use digital EPAs for their studies during the clinical phase of medical school if they were to be offered.

Due to the construct of the TAM, "Behavioral Intention" is highly influenced by "Perceived Usefulness" and "Perceived Ease of Use," making it the dependent variable.

Digital EPAs

Due to the unfamiliar teaching concept of EPAs for students, as well as the digital EPAs, a formulated EPA and its digital counterpart were created based on a paper by Ten Cate and Taylor [1]. The digital EPA merely represents a theoretical implementation of the previously formulated EPA for students in the future. It cannot yet be tested digitally in this form and can, therefore, only be presented to students conceptually in the form of continuous text. The complete description of the EPA and the digital EPA can be found on OSF [13]. Additionally, there is both a German and an English version for the same reasons as with the above questionnaire.

Ethical Considerations

Ethics approval by the host university is pending. The study will only be conducted once it is granted.

Results

The data collection of this study is expected to be completed by the end of April 2025. Following this, data analysis is to take place, which is to be completed by May 2025, following the reporting standards of the *Journal of Medical Internet Research* for statistics.

All data, in anonymized form, and the code for analysis will be uploaded to the project's OSF repository.

Discussion

This study hypothesized that the higher students' PU and PEU are, the higher their behavioral intention to use will be and that this relationship would lead to higher actual system use [6].

The basis for our study is, on the one hand, the increasing emergence of EPAs in medical curricula as well as in specialist training and continuing education and, on the other hand, the widespread use of digital simulations [1,3,4]. The merging of both concepts remains relatively unexplored and can only be considered a successful development of traditional EPAs if this concept is also accepted by the learners themselves. Using the tried and tested TAM model, a meaningful evaluation of this situation will be made [5]. Since digital EPAs can increasingly contribute to medical training improvement, our findings are to be considered as a starting point for the design and implementation of these didactic tools so that more effective implementation and more engaged use among learners can be promoted in the future.

Nevertheless, our study must be viewed in light of some limitations. The sample size and the methodology of recruitment could limit the generalizability of the results. Future studies should involve larger and more diverse groups of medical students to gain a more comprehensive understanding of acceptance factors. In addition, investigating the long-term effects of digital EPAs on learning outcomes could provide valuable insights.

In summary, this study should serve as a starting point for more extensive research projects so that factors influencing the acceptance of digital teaching technologies in medicine, particularly digital EPAs, can be comprehensively investigated. By emphasizing the importance of usefulness and ease of use for the acceptance and use of digital EPAs, our study opens new perspectives for the design of effective and engaging medical training programs that meet both the needs of the students and the requirements of a constantly changing medical training landscape.

Acknowledgments

MD has received funding during the research for this paper from the "Promotionsstipendium" of the medical faculty of the Ludwig Maximilians University Munich.

Data Availability

All data will be made available in anonymized form on the Open Science Framework repository after completion of the study.

Authors' Contributions

MD was responsible for the visualizations and writing of the initial draft, including substantive translation. CR and MS extensively contributed to the writing process by reviewing and editing the initial draft. Further, MS had the role of supervisor for the project as well as project administration. All authors read and approved the final manuscript.

In preparing this manuscript, a generative artificial intelligence (AI) tool (ChatGPT-4o, version February 2024, OpenAI) was used solely for language enhancement and stylistic refinement. No content generation, data analysis, or research-related functions were performed by AI. The authors retain full responsibility for the originality, accuracy, and integrity of the scientific content presented in this paper. All intellectual contributions and findings are the result of the authors' independent work.

Conflicts of Interest

None declared.

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Abbreviations

EPA: entrustable professional activity
OSF: Open Science Framework
TAM: technology acceptance model

Edited by T Leung; submitted 09.04.24; peer-reviewed by AS Al-Adwan, Y Holzhausen, S Jung; comments to author 16.07.24; revised version received 17.10.24; accepted 29.01.25; published 25.03.25.

Please cite as:
Domann M, Richters C, Stadler M
Student Acceptance of Digital Entrustable Professional Activities: Protocol for a Cohort Study
JMIR Res Protoc 2025;14:e59326
URL: https://www.researchprotocols.org/2025/1/e59326
doi:10.2196/59326
PMID:

Corrigenda and Addenda

Correction: Disaster Preparedness Intervention for Older Adults (Seniors' Positive Involvement in Community Emergencies): Protocol for a Quasi-Experimental Study

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Related Article:

Correction of: https://www.researchprotocols.org/2024/1/e58895

(JMIR Res Protoc 2025;14:e71160) doi:10.2196/71160

In "Disaster Preparedness Intervention for Older Adults (Seniors' Positive Involvement in Community Emergencies): Protocol for a Quasi-Experimental Study" JMIR Res Protoc 2024;13:e58895) the authors made one correction.

The last name of author JC, "Crowely", has been revised to "Crowley".

The correction will appear in the online version of the paper on the JMIR Publications website on January 16, 2025 together with the publication of this correction notice. Because this was made after submission to PubMed, PubMed Central, and other full-text repositories, the corrected article has also been resubmitted to those repositories.

Submitted 10.01.25; this is a non–peer-reviewed article;accepted 10.01.25; published 16.01.25.

Please cite as:
White-Lewis S, Lightner J, Crowley J, Grimes A, Spears K, Chesnut S
Correction: Disaster Preparedness Intervention for Older Adults (Seniors' Positive Involvement in Community Emergencies): Protocol for a Quasi-Experimental Study
JMIR Res Protoc 2025;14:e71160
URL: https://www.researchprotocols.org/2025/1/e71160
doi:10.2196/71160
PMID:

Corrigenda and Addenda

Correction: Methodology for the Positive Voices 2022 Survey of People With HIV Accessing Care in England, Wales, and Scotland: Cross-Sectional Questionnaire Study

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Related Article:

Correction of: https://www.researchprotocols.org/2025/1/e58531

(JMIR Res Protoc 2025;14:e72512) doi:10.2196/72512

The paper "Methodology for the Positive Voices 2022 Survey of People With HIV Accessing Care in England, Wales, and Scotland: Cross-Sectional Questionnaire Study" published in JMIR Res Protoc 2025;14:e58531) had a few errors. Hence, the following edits have been made (changes italicized).

In the **Abstract,** the following subsections had a few sentences modified, as follows:

- Objectives: "This paper aimed to describe the methodology, recruitment strategies, and *key demographic* features of participants…"
- Methods: "…At the start of 2023, due to under-recruitment mainly due to the impact of the monkeypox (Mpox) outbreak, a separate sequential recruitment strategy was initiated in *14 of the largest clinics* to increase participant numbers."
- Results: "…The median age of participants was 52 years, 3428 of participants were men, 2991 were *White*, and 1121 were *Black*."

In the **Introduction** section, the following paragraphs have been revised, as follows:

- "High levels of perceived and internalized stigma associated with *HIV status are experienced* by people with HIV, impacting their mental health…
- PV is a cross-sectional *questionnaire study of people with HIV who receive HIV specialist care in England, Wales, and Scotland, which is carried out every 3-5 years.*…
- Our paper aims to describe the methodology and study design of the second round of the *study: Positive Voices 2022 (PV2022).*"

In **Methods** section, the first column of ***Table 1*** has been edited to improve readability and clarity.

The following incorrect values were updated in ***Table 2***:

- The number of Positive Voices 2022 participants was changed from *4620* to *4622*.
- "Age group (years)" category: The percentage of participants in the 55-64 subcategory was changed from *30.2* to *30.3*.

- "Gender" category: The number and percentage of participants in the "Prefer not to say *and unknown*" subcategory was changed from *34 (0.7)* to *36 (0.8)*.
- "Ethnic group" category: The number and percentage of participants in the "Other (including prefer not to say and unknown)" subcategory was changed from *176 (3.8)* to *178 (3.9)*.
- "Year of diagnosis" category: The number of participants in the "2019-2023" subcategory was changed from *213* to *214*.
- "Year of diagnosis" category: The number of participants in the "2014-2018" subcategory was changed from *800* to *801*.
- Footnote "a" was assigned to the "Age group (years)" category and was updated from *Missing sociodemographic information for 2 participants* to *Age was missing for 2 participants.*

A few abbreviations have been introduced for better readability. These have also been added to the abbreviations list at the end of the article.

A few additional changes have been listed below:

- Under Study Design:
  "The questionnaire data were linked to clinical data on antiretroviral therapy (ART), HIV viral load, and CD4 *lymphocyte* count from the HIV and AIDS reporting system (HARS)…"
- Under Setting:
  "178 HIV clinics in the country, returned an expression of interest, *98* % of whom were in England (99/101)…"
- Under Sample Size:
  "HARS was used as a sampling frame to *provide a representative*, random sample of people with *HIV within each participating clinic, who* could be approached to participate in the PV2022 survey. HARS is a surveillance database held at the UKHSA that consists of pseudonymized data on the demographic, clinical, and *treatment characteristics* of people with HIV that is reported each quarter year by all HIV service providers in England…
  …Therefore, considering this, a sample list of 17,121 patients was created *with the assumption* that approximately 14,400 would be recruitable. …the PV2022 response rate was expected to be between 30% and 50%, resulting in 4320 *to* 7200 participants being recruited. … ±1.4% and ±1.1% *(with 95% confidence)* for the response rates of 30% and 50%, respectively."
- Under Study Management:
  "PV2022 was a collaboration between the University College London (UCL) NICHE *team, the UKHSA HIV national surveillance team, and a NICHE Patient and Public Involvement representative. "A Person-Centered Needs Informed Model of Care for People with HIV" (NICHE)* is a National Institute for Health Research (NIHR) funded program..."
- Under Questionnaire Development:
  "…These included demographic and socioeconomic factors, HIV related factors, comorbidities, met and unmet health, social and welfare *service* needs, quality of life measured by EQ-5D-5L, *height and weight*, smoking and alcohol status *by the Alcohol Use Disorders Identification Test-Consumption (AUDIT-C)*, recreational drug use and general practice (GP), and HIV clinic satisfaction, enabling assessment of trends over time in these factors…
  …New items included in the PV2022 questionnaire included… a modified version of the *Duke-UNC (University of North Carolina)* Functional Social Support Questionnaire…
  Questions on stigma and discrimination were expanded to take account of internalized *and other* stigma and included an adapted validated stigma scale [27]. In addition, participants *who* completed the study online in PV2022 were able to opt-in to complete "Positive Outcomes," an HIV Patient Reported Outcome Measure (PO-PROM), a tool designed for use in clinical settings to assess *the needs and concerns of* people with HIV…"
- Under Study Documents:
  "...a password-protected study log that listed each clinic's sample list of *randomly selected* participants. ... and unique identifier displayed on the outside, as well as the patient information leaflet, *questionnaire*, a freepost..."
- Under Linkage:
  "Data on ART *use*, the most recent CD4 lymphocyte count,..."
- Under Ethical Considerations:
  "All participants received a digital gift voucher for 5 GBP (*equivalent to* US $6.50)..."

In the **Results** section, the following sentences have been edited:

- Under Response Rate:
  "...the original preselected participant recruitment strategy (*49*%, Figure 1). Of the 930 sequentially recruited participants, 906 were able to be matched to HARS: 222 (*25*%) of these had initially been preselected to take part in the survey.
  Men had a higher response rate (60%) (3428 completed out of 5715 accepted or declined) compared with women (1124/2580, 44%) and *White people* had a higher response rate (2991/4724, 63%) compared with *Black African people* (983/2380, 41%) *or those of* other ethnicities (648/1158, 56%)."
- Under Age, Gender, *and Ethnic* Distribution of PV2022 Participants:
  "The median age of PV2022 participants (n=4620) was *52 (IQR 43-60) years, and about* 3 quarters of participants had been diagnosed with HIV more than 10 years ago (Table 2). Nearly a quarter of participants were women (24%) and over a fifth (21%) of participants were *Black African people* (Table 2).
  A total of *67* PV2022 participants identified as transgender or gender diverse...
  Compared with the national population of people accessing HIV care, *Black African individuals were underrepresented in the PV2022 sample (10% lower)*, and *White* participants were overrepresented (13% higher; Figure 2)...

Participants from the sequential recruitment route were younger compared to the preselected random recruitment strategy (median age 49 (IQR 39-57) years versus 53 (IQR 45-60) years, for sequential versus random recruitment respectively), overrepresented men (85% vs 72%) and White people (67% vs 64%) and underrepresented Black African people (14% vs 23%).

A higher proportion of *participants who completed the online questionnaire were White compared to participants who completed the paper questionnaire (67% online vs 63% paper*; Figure 1 and Multimedia Appendix 2)."

In the **Discussion** section, the following edits were made:

- Under Principal Findings:
  "…The pandemic exacerbated inequalities in health and access to health care, particularly amongst those living in economic hardship [38] and for *Black African individuals and those of other* minority ethnic groups [39], and the HIV population consists of a high proportion of these groups.

  Strengths of PV2022 include the large sample size, the inclusion of a broadly representative sample of 1 in 20 people with HIV in *England, Scotland and Wales* (as evidenced by comparison with the national HARS database) and the linkage of participant self-reported questionnaire data to HIV clinical data from HARS.

  ..., whose mental and physical health, and experiences of *health* care, may be different and valuable for informing and improving HIV specialist services.

  Findings from PV2022 informed the development of the intervention for the "Psycho-Social Intervention for People With HIV–Evidence From a Randomised Evaluation" *(SPHERE)* trial, which commenced in United Kingdom HIV clinics in August 2024."

The correction will appear in the online version of the paper on the JMIR Publications website on February 27, 2025, together with the publication of this correction notice. Because this was made after submission to PubMed, PubMed Central, and other full-text repositories, the corrected article has also been resubmitted to those repositories.

Submitted 11.02.25; this is a non–peer-reviewed article;accepted 11.02.25; published 27.02.25.

Please cite as:
Sewell J, Kelly C, Aghaizu A, Kitt H, Pelchen-Matthews A, Martin V, Farah A, Smith C, Brown A, Humphreys C, Sparrowhawk A, Delpech V, Rodger A, Lampe F, Kall M
Correction: Methodology for the Positive Voices 2022 Survey of People With HIV Accessing Care in England, Wales, and Scotland: Cross-Sectional Questionnaire Study
JMIR Res Protoc 2025;14:e72512
URL: https://www.researchprotocols.org/2025/1/e72512
doi:10.2196/72512
PMID:40053800

Protocol

Validation of the Nociception Level Index for the Detection of Nociception and Pain in Critically Ill Adults: Protocol for an Observational Study

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Abstract

Background: In the intensive care unit (ICU), many patients are unable to communicate their pain through self-reporting or behaviors due to their critical care condition, mechanical ventilation, and medication (eg, heavily sedated or chemically paralyzed). Therefore, alternative pain assessment methods are urgently needed for this vulnerable patient population. The Nociception Level (NOL) index is a multiparameter technology initially developed for the monitoring of nociception and related pain in anesthetized patients, and its use in the ICU is new.

Objective: This study aims to validate the NOL for the assessment of nociception and related pain in critically ill adults in the ICU. Specific objectives are to examine the ability of the NOL to: (1) detect pain using standard criteria (ie, self-report and behavioral measures), (2) discriminate between nociceptive and nonnociceptive procedures, and (3) generate consistent values when patients are at rest.

Methods: The NOL will be monitored in three ICU patient groups: (1) Group A, participants able to self-report their pain (the reference standard criterion using the 0-10 Faces Pain Thermometer) and express behaviors; (2) Group B, participants unable to self-report but able to express behaviors (the alternative standard criterion using the Critical-Care Pain Observation Tool); and (3) Group C, participants unable to self-report and express behaviors. The NOL will be tested before, during, and after two types of standard care procedures: (1) nonnociceptive (eg, cuff inflation to measure blood pressure, soft touch) and (2) nociceptive (eg, tube or drain removal, endotracheal or tracheal suctioning). Receiver operating characteristic curve analysis of the NOL will be performed for Groups A and B using pain standard measures as reference criteria. Mixed linear models for repeated measures

will be used to compare time points, procedures, and their interaction in each group (A, B, and C). Based on power analyses and considering an attrition rate of 25%, a total sample size of 146 patients (68 in Group A, 62 in Group B, and 16 in Group C) is targeted.

Results: This study was funded in April 2020 but could not be launched until 2022 due to the COVID-19 pandemic. Recruitment and data collection began at the primary site in July 2022 and has been implemented at the secondary sites in 2023 and 2024 and is planned to continue until 2026.

Conclusions: The primary strength of this study protocol is that it is based on rigorous validation strategies with the use of pain standard criteria (ie, self-report and behavioral measures). If found to be valid, the NOL could be used as an alternative physiologic measure of pain in critically ill adults for whom no other pain assessment methods are available.

Trial Registration: ClinicalTrials.gov NCT05339737; https://clinicaltrials.gov/study/NCT05339737

International Registered Report Identifier (IRRID): DERR1-10.2196/60672

(JMIR Res Protoc 2025;14:e60672) doi:10.2196/60672

KEYWORDS

validation; NOL; Nociception Level; nociception; pain; intensive care unit; ICU; critical care; protocol

Introduction

Background

Patients in the intensive care unit (ICU) are exposed to many noxious stimuli as part of standard care, which may involve nociception and pain. Although nociception and pain are interrelated, they are distinct concepts. Nociception involves the neural processes of encoding noxious stimuli that lead to autonomic (eg, increased vital signs) and behavioral responses, which may or may not imply the sensation of pain [1,2]. Pain is a personal and multidimensional phenomenon influenced by biological, psychological, and social factors [1-3]. Appropriate detection of nociception and pain is key to providing adequate analgesia during critical illness in order to reduce the risk of adverse outcomes such as prolonged mechanical ventilation, longer ICU stay, and chronic pain development [4,5].

Many ICU patients experience pain at rest, and this pain is significantly increased during nociceptive procedures as part of standard care (eg, drain or tube removal, endotracheal suctioning, line insertion, wound care, and turning) [6-9]. Behavioral responses such as grimacing and muscle rigidity are commonly observed in ICU patients during standard care procedures and have been associated with their self-reported pain [10]. While the patient's self-report (the reference standard) is the preferred method of pain assessment, it is unsuitable for patients unable to rate their pain due to a combination of several factors affecting their capacity to communicate, such as mechanical ventilation (>33% of Canadian ICU patients) [11], sedation, or an altered level of consciousness. In such situations, behavioral assessment tools such as the Behavioral Pain Scale (BPS) [12] and the Critical-Care Pain Observation Tool (CPOT) [13] are alternative standard measures of pain in patients unable to self-report with minimal motor function to exhibit behavioral responses [14]. However, these behavioral assessment tools cannot be used in heavily sedated patients or those receiving neuromuscular blocking agents as they become unresponsive to stimulation [15].

Alternative methods for pain assessment are necessary when none of the pain standard criteria (ie, self-report or behavioral measures) can be used. Although individual vital signs (eg, heart rate, blood pressure) are easily accessible through continuous bedside monitoring, they are not valid for ICU pain assessment due to inconsistent findings across studies and clinically insignificant variation in their values (<20%) [14,16]. However, research in the field of pain and anesthesia has shown that the combination of physiologic parameters is superior to their individual values [17]. Inspired by initial data from healthy subjects exposed to tonic heat stimuli inducing different pain levels [18], the Nociception Level (NOL) index (Medasense Biometrics Ltd) is a multiparameter technology, which was further developed for nociception monitoring and related pain in anesthetized patients [19-21]. In our recent review [22] of 6 studies in anesthetized patients, the NOL index outperformed single physiologic parameters for the detection of nociception during standard care procedures and experimental stimuli [17,20,23-25].

Although the validity of the NOL is supported in anesthesia, its use in the ICU is new. To our knowledge, we are the first research team to have pilot-tested the use of the NOL for nociception and pain assessment in the ICU. We conducted 2 pilot studies in 15 mechanically ventilated [26] and 54 cardiac surgery ICU patients [27] able to self-report their pain. In both studies, discriminative validation of the NOL was supported with higher index values during nociceptive procedures (ie, chest tube removal, endotracheal suctioning) compared with rest and a nonnociceptive procedure (ie, noninvasive blood pressure [NIBP] using cuff inflation). The NOL values were positively associated with self-reported pain and CPOT scores during nociceptive procedures, providing initial evidence of criterion validation with pain standard criteria [26,27]. Also, a NOL cutoff >25 was found to adequately classify patients with moderate to severe self-reported pain intensity (>4/10) [27]. However, these pilot validation studies of the NOL were limited to 2 nociceptive procedures as part of standard care and were solely conducted in ICU patients who were able to self-report. Further validation of the NOL during various standard care procedures in critically ill adults with different levels of consciousness or sedation and in response to analgesic treatment is necessary to confirm its validity for the assessment of nociception and related pain in the ICU.

Study Rationale, Goal, Objectives, and Research Hypotheses

An instrument can only be shown as valid for a specific purpose in a given population and context [28]. The NOL index was initially developed and validated for nociception monitoring and related pain in anesthetized patients [17,19-25]. Therefore, validating its use for nociception (primary purpose) and pain assessment (related purpose) in critically ill adults admitted to the ICU (different population and context of care) is necessary. Inspired by our pilot work, strategies for this larger validation study include: (1) criterion validation (ie, NOL's ability to detect pain according to pain standard criteria) and (2) discriminative validation (ie, NOL's ability to discriminate between nonnociceptive and nociceptive procedures) [28]. Considering that reliability is a necessary condition for validity [28], test-retest reliability of the NOL's ability to generate consistent values in similar conditions (eg, at rest) will also be examined.

Research Question: Is the NOL a valid method for the assessment of nociception and pain in critically ill adults in the ICU context?

In order to answer this research question, specific validation objectives are to examine the NOL's ability to:

1. Detect pain in ICU patients able or not to self-report using appropriate pain standard criteria (ie, criterion validation);
2. Discriminate between nonnociceptive and nociceptive procedures part of standard care as well as before and after the administration of a breakthrough opioid dose (ie, discriminative validation);
3. Generate consistent values in similar conditions (ie, pre- and post-nonnociceptive and nociceptive procedures) when ICU patients are at rest.

Our research hypotheses to be tested include:

H1. The NOL index adequately classifies ICU patients with pain based on either their self-reported pain intensity or CPOT scores.

H2. The NOL index produces higher values during nociceptive procedures compared to nonnociceptive procedures and lower values post- versus preopioid administration.

H3. The NOL index generates consistent values pre- and post-nonnociceptive and nociceptive procedures when ICU patients are at rest.

Methods

Study Design

A prospective observational design was selected as it is appropriate for validation purposes using ICU standard care procedures in critically ill adults. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: Guidelines for Reporting Observational Studies is used for the description and reporting of the study [29].

Settings

This study is conducted in the ICUs of 3 tertiary-level university-affiliated health centers in Montréal, Québec, Canada. These ICUs have a total capacity ranging from 16-59 beds, and each ICU admits, on average, 1000-2750 patients annually.

Participants

A consecutive sampling method is used to approach all eligible patients or their representatives during the study period. This sampling method aims to capture a representative sample of ICU patients able or not to self-report. Eligible ICU patients (Textbox 1) are assigned to one of the following groups:

1. Group A can communicate their self-report of pain and can exhibit behaviors (conscious and alert with Glasgow Coma Scale [GCS] [30] score of 13 to 15 or Richmond Agitation Sedation Scale [RASS] [31] score of 0);
2. Group B cannot communicate their self-report but can exhibit behaviors (altered level of consciousness with GCS score of 6 to 12 with a score ≥4 on the motor subscale or RASS score of –1 to –3); and
3. Group C cannot communicate their self-report or exhibit behaviors (unconscious with GCS score of 3 to 5 with a score ≤3 on the motor subscale or RASS score –4 or –5 or receiving neuromuscular blocking agents).

Exclusion criteria were selected to control for potentially confounding variables that may affect the NOL signal or pain standard measures. Patients assigned to Group A who screen positive for delirium are excluded as this condition is likely to affect the reliability of their self-report of pain [32]. Patients with conditions that may seriously influence perfusion of the hands, heart rate, heart rate variability, blood pressure, repetitive or high movements due to agitation or behavioral responses (eg, agitation, cognitive, or psychiatric conditions) are also excluded, thereby strengthening the internal validity of the study. Finally, patients with *Clostridium difficile* must be excluded because the required disinfection product (ie, sodium hypochlorite 5000-6000 ppm) could damage the NOL device, according to the manufacturer.

Textbox 1. Eligibility criteria of intensive care unit (ICU) patients.

Inclusion criteria:

- Admitted to the ICU >24 hours
- Aged >18 years
- English or French speaking

Exclusion criteria:

- Delirium (Group A only)
- Lack an available finger
- Severe peripheral vascular disease affecting the upper limbs
- Uncontrolled cardiac arrhythmia (eg, atrial fibrillation)
- Pacemaker with paced rhythm
- Severe edema in upper limbs
- Hypoperfusion state or shock and receiving norepinephrine (>14 mcg/min) or equivalent vasopressors to maintain a systolic blood pressure >90 mmHg or a mean arterial pressure >65 mmHg
- Agitated (Richmond Agitation Sedation Scale +1 to +4)
- Psychosis
- Cognitive deficits (eg, Alzheimer)
- Positive for Clostridium difficile
- Pregnancy

Recruitment and Consent Procedures

ICU patients are screened for eligibility by the research staff in collaboration with the medical and nursing team. Potentially eligible ICU patients able to self-report and consent, if they agree to participate, are assigned to Group A. Other potentially eligible ICU patients unable to self-report and consent are assigned to either Group B or C. According to Article 21 of the Quebec Civil Code for minimal risk studies, a significant person qualified to consent to care required by the state of health of the person of full age is asked to provide consent on their behalf for the research study.

Group A: Potentially eligible ICU patients able to self-report are approached for participation by their responsible nurse or physician. If interested, the research staff provides information about the study to the patient and obtain written informed consent.

Group B and Group C: For potentially eligible ICU patients unable to self-report, the person qualified to consent on their behalf is approached by their responsible nurse or physician. If interested, the research staff provides information about the study to the significant person and obtain written informed consent. If a patient participant who was previously unable to consent regains the ability to consent at any time, the research staff provides them with the informed consent form, allowing them to decide on their continued participation in the study. If a patient participant decides to withdraw from the study and requests their research data be removed, all collected information will be deleted.

Study Procedures

Before starting data collection, the group assignment of the participant is confirmed by the research staff. Then, the research staff sets up the NOL device at the bedside, places the finger probe on the participant's finger, and proceeds with calibration (requires less than 5 minutes). The screen of the NOL device is faced away from the patient and family members present in the room to reduce potential bias. Research staff also installs a video camera on a tripod at the foot of the bed to capture the face and the upper body in order to allow for interrater reliability examination of CPOT scores with another trained research staff not present at the bedside.

Participants are assessed at rest before, during, and 15 minutes after nonnociceptive and nociceptive procedures that are part of ICU routine care. Whenever possible, 15 minutes postprocedure are respected to allow for the resolution of the release, reaction, and elimination of stress hormones (ie, epinephrine and norepinephrine) and stress-activated responses that may be present following noxious stimulation [33]. The nonnociceptive procedures are ideally performed prior to nociceptive procedures and include soft touch (ie, research staff touching the patient's arm for 1 minute) and cuff inflation for blood pressure measurement (NIBP), which were empirically shown to be painless in previous studies [34], including our pilot NOL studies [26,27]. In the sequence of nonnociceptive procedures, soft touch is performed first and cuff inflation last. Then, the goal is to observe up to two nociceptive procedures per participant (Textbox 2). Nociceptive procedures are selected according to the standard care required by the patient's condition. These procedures do not involve mobilizing the patient out of bed, as important movements may introduce

artifacts in the NOL data. When possible and as required by the patient's condition, participants are also assessed before and 15 minutes postadministration of a breakthrough dose of an opioid such as fentanyl, morphine, or hydromorphone through a parenteral route (mainly through intravenous or subcutaneous routes) to capture onset or peak of action. The decision to administer an opioid is made as per local practice and based on an assessment performed by the ICU nurse or physician. Within a window of 48 hours after obtaining informed consent, a total of 10 to 12 time points of data collection is completed with each participant during their ICU stay (Table 1).

The NOL index is continuously monitored during the data collection time period, and values are extracted in a standardized manner as done in previous clinical studies for NOL data analysis purposes [24-27]. CPOT assessments (one-minute observation or duration of the procedure) are performed on participants from Groups A and B by research staff, and then conscious patients able to self-report (Group A) are asked to provide their self-report of pain intensity at each time point. Video recording is stopped before participants provide their self-report to avoid possible bias by the research staff, who will view the videos for CPOT scoring at a later time. Finally, demographic and clinical information is extracted from the participants' medical files. At the end of data collection, the study equipment (ie, video camera, tripod, NOL device, and keyboard) is disinfected according to the prevention control infection procedures of each institution before being used for another patient.

Textbox 2. List of nociceptive and nonnociceptive standard care procedures in the intensive care unit.

Nociceptive procedures

- Chest tube removal
- Drain removal
- Mouth, endotracheal, or tracheal suctioning
- Arterial line insertion
- Peripheral intravenous line insertion
- Subcutaneous injection
- Wound care
- Bed turning or repositioning

Nonnociceptive procedures

- Soft touch of the patient's arm
- Noninvasive blood pressure cuff inflation (NIBP)

Table 1. Assessment time points and pain variables to be measured in each group (A, B, and C).

Measure	Nonnociceptive procedures				Nociceptive procedure 1			Nociceptive procedure 2			Analgesic[a]	
	Pre	Soft touch	Cuff inflation	Post	Pre	During	Post	Pre	During	Post	Pre	Post
NOL[b]	A[c], B[d], C[e]	A, B, C	A, B, C	A, B, C	A, B, C	A, B, C	A, B, C	A, B, C	A, B, C	A, B, C	A, B, C	A, B, C
Behaviors	A, B	A, B	A, B	A, B, C	A, B	A, B	A, B	A, B	A, B	A, B	A, B	A, B
Pain level	A	A	A	A	A	A	A	A	A	A	A	A

[a]Administration of an analgesic as required by the patient's condition.

[b]NOL: Nociception Level Index.

[c]Group A: Patients are able to communicate their self-report of pain and can exhibit behaviors.

[d]Group B: Patients are unable to communicate their self-report of pain but can exhibit behaviors.

[e]Group C: Patients who cannot communicate their self-report of pain or exhibit behaviors.

Variables and Measurement Tools

Primary Measure: The Nociception Level (NOL) Index–All Groups (A, B, and C)

The Pain Monitoring Device-200 (PMD-200; Medasense Biometrics Ltd; Figure 1) is used in this study. PMD-200 offers the multiparametric NOL index (0-100) and was approved by Health Canada for clinical use in September 2017. The NOL captures several physiological parameters simultaneously through a finger probe and disposable sensor, which includes 4 small sensors, sampled 50-500 Hz: (1) accelerometer, (2) photoplethysmograph, (3) galvanic skin response, and (4) peripheral temperature. From these 4 sensors, the following physiological parameters are extracted: heart rate, heart rate

variability, photoplethysmography pulse wave amplitude, skin conductance level, number of skin conductance fluctuations, skin temperature, and their time derivatives. All these parameters are integrated and analyzed simultaneously using a Random Forest machine learning model approach to provide the NOL index, which can range from 0 to 100 [17]. A NOL cutoff value >25 for the detection of self-reported pain was found in our pilot study with ICU cardiac surgery patients [27].

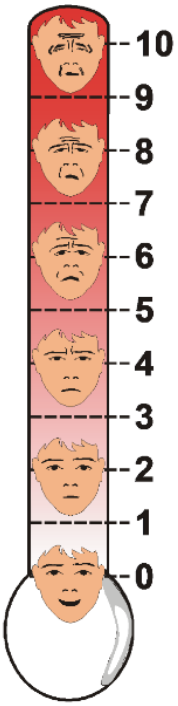
Figure 1. Nociception Level (NOL) index.

The PMD-200 device allows the documentation of each event (ie, beginning and end time of rest and procedure assessment) or any contextual information (eg, interruption during a procedure), which is facilitated with the use of a wireless keypad. All NOL data are electronically collected every 5 seconds by the PMD-200 monitor.

Reference Standard Measure of Pain–Group A

The Faces Pain Thermometer (FPT) was selected to measure pain intensity as it can accommodate adult patients of various ages. It consists of an enlarged visual thermometer including 6 faces with a numeric rating scale scoring from 0="no pain" to 10="worst possible pain" (Figure 2). The validity and reliability (test-retest) of the tool were established in ICU patients [35]. The FPT was used in many previous validation studies led by the primary investigator [13,34,36] and pilot NOL studies [26,27].

Figure 2. The 0-10 Faces Pain Thermometer (FPT)[35].



Alternative Reference Standard Measure of Pain–Groups A and B

The Critical-Care Pain Observation Tool (CPOT) [13] was selected for behavioral pain assessment in critically ill adults. The CPOT was used in our NOL pilot studies [26,27], and it is 1 of the 2 behavioral scales suggested as alternative reference standard measures of pain by the Society of Critical Care Medicine [14] and has been implemented in clinical practice in the 3 study ICUs. The CPOT includes 4 behavioral items: (1) facial expressions, (2) body movements, (3) muscle tension, and (4) compliance with the ventilator (for mechanically ventilated patients) or vocalization (for nonintubated patients). Each item is scored from 0-2, and the total score can range from 0-8. The CPOT has been validated in 47 studies with more than 3900 ICU patients with surgical, trauma, and medical diagnoses from various countries [34]. Consistent findings of good interrater reliability (interclass correlation coefficient [ICC] >0.60 between research staff and ICU nurses) and ability to discriminate between various nociceptive and nonnociceptive procedures were found across studies. Criterion validation of the CPOT was also supported by positive correlations (r>0.40) with ICU patients' self-reported pain intensity [34]. A CPOT score >2 was found to adequately identify patients with self-reported pain (AUC>0.80) [34,36].

The research staff of all sites have been trained to use the CPOT using a standardized training session previously described [37]. Briefly, this 60-minute training session covers the description of the CPOT content and its scoring process. Patient videos are viewed to practice scoring with the tool with the goal of reaching consistent CPOT scores between raters within a total score difference of no more than 1 point.

Demographic and Clinical Information for ICU Patient Participants

Demographic information (eg, age, sex, gender, and ethnicity) is collected from the patient or their representative. Information related to the patient's clinical condition (ie, ICU admission diagnosis, mechanical ventilation, the severity of illness [Acute Physiology and Chronic Health Evaluation; APACHE II] [38], level of consciousness [GCS] [30], sedation level [RASS] [31], delirium screening with the Confusion Assessment Method-ICU [39] or Intensive Care Delirium Screening Checklist [40], according to the respective tool used at each site), as well as medication information (ie, morphine equivalent doses [41] received within 4 hours before and during the entire data collection, sedative agents, vasopressors, and use of opioids before ICU admission) is extracted from the medical records by the research staff. The following clinical information is collected at the time of obtaining consent and performing data collection: mechanical ventilation status, GCS score, RASS score, and delirium screening.

Sample Size Calculation

The primary objective is to validate the NOL using pain standard criteria (ie, self-report and CPOT scores). Therefore, ROC is considered our primary analysis and guides the sample size calculation for Group A and Group B. Power calculations were based on our pilot findings [26,27] and results from previous ICU studies considering a clinically acceptable AUC of 0.75 [42] (using a null hypothesis of AUC=0.50) with a power of 80% and an adjusted α of .025 (2 ROC curves for each procedure in each group). For Group A in whom the self-report of pain is obtained and using a ratio of 2:1 in pain:no pain cases according to self-reported pain intensity scores of <4 and >4, a sample of 54 patients is required. For Group B in whom only the CPOT scores are available and using a ratio of 1.5:1 in pain:no pain cases according to CPOT scores of <2 (no pain) and >2 (pain), a sample of 50 patients is necessary. For Group C (unable to self-report and express behaviors), we will not be able to use any pain standard criterion. Therefore, our main objective is to test whether the NOL can discriminate between a nociceptive procedure and a nonnociceptive procedure. In order to detect a minimal mean increase of 10 in the NOL value during the nociceptive procedure (with a standard deviation of 10 as found in our pilot findings), a minimal sample size of 13 patients is required to run paired t tests with a power of 80% and an α of .01 (to account for multiple test comparisons). Considering an attrition rate of 25% (data collection was completed in 73% of consenting patients in our pilot work), recruitment targets include 68 patients in Group A, 62 patients in Group B, and 16 in Group C for a total of 146 ICU patients. Power calculations were performed by a statistician using Power and Precision 4 (Biostat Inc).

Data Analysis

SPSS software (version 29; IBM) and SAS (version 9.4; SAS Institute) will be used for data analysis. Descriptive statistics will be computed to characterize the study samples and outcomes. The NOL signal quality will be checked for all enrolled patients to ensure the accuracy of the data. As done in previous studies, NOL values will be averaged within 15 seconds before and after the peak value obtained after the start of each nonnociceptive procedure (7 NOL values total around the peak for soft touch and NIBP) and nociceptive procedure. In addition, NOL values will be averaged over a 1-minute period at rest before and after the procedure. CPOT scores will be obtained independently by 2 trained raters, one at the bedside and one who will view the patient videos at a later time. Intraclass correlation coefficients (ICC) will be calculated between the CPOT scores of both raters during procedures. ICC>0.80 will confirm excellent interrater reliability [28].

For objective 1 (criterion validation), the receiver operating characteristic (ROC) curve [43] will be performed to examine the ability of the NOL to adequately classify patients with pain. In patients able to self-report (Group A), an established pain intensity score >4 based on participants' self-reports as the reference standard criterion indicating moderate to severe pain will be used [10,44]. This criterion is also commonly used in practice to support clinical decisions in the administration of opioids. A ROC curve will be obtained for each nociceptive procedure (a total of 2 procedures per patient). In patients unable to self-report but in whom behaviors can be observed (Group B), we will use the determined CPOT score >2 as the alternative reference criterion, which is associated with the presence of moderate to severe pain [44]. Again, for Group B, a ROC curve will be obtained for each nociceptive procedure (total of 2 procedures per patient) [45]. As a supplementary analysis, we

will perform ROC curves for repeated-measures design in each group (A and B) and compare them [46]. In addition, considering that the CPOT will be available in Group A and Group B, ROC curves will be performed in each group separately to compare the AUC of independent curves for each of the 2 procedures [45]. The NOL cutoff value that will optimize both sensitivity and specificity will be determined.

Discriminative validation (objective 2) is our main objective to test in Group C, and paired *t* tests comparing the NOL values of each nociceptive procedure with the nonnociceptive procedure will be obtained. Generalized linear mixed model for repeated measures will allow us to compare the NOL index values across time points (pre, during, and post), procedures (nonnociceptive vs nociceptive), and their interaction in each group (A, B, and C). The generalized linear mixed model technique incorporates the full-information maximum likelihood procedure, which allows parameter estimation for missing data [47]. NOL values are expected to be significantly higher during nociceptive procedures in all 3 groups. Covariates (eg, sex, gender, morphine equivalent doses, opioid use before ICU admission) may be added if appropriate. Finally, NOL data obtained at pre- and postadministration of an opioid dose will be tested separately using paired *t* tests as not all patients will be candidates for these assessments.

For test-retest reliability (objective 3), paired *t* tests will be performed between pre and post-nonnociceptive and nociceptive procedures in all 3 groups. Nonsignificant paired *t* tests are expected to support the stability of NOL values when the patients are at rest.

Ethical Considerations

Ethical approval was submitted in February 2022 and approved by the Medical and Biomedical Research Ethics Committee of the primary site in June 2022 (project # MP-05-2022-2988). A first amendment of the research protocol (version 2) was approved in June 2023 regarding the addition of pacemaker as an exclusion criterion as it affects the generation of the NOL signal. A second amendment of the research protocol (version 3) was approved in September 2024 for the addition of a third study site and revision of the sample size. According to our pilot studies [26,27], participating in this study is not associated with any known risks; however, participants will be informed that if they find the finger probe uncomfortable, they can choose to switch fingers or hands or have it removed to stop data collection. Participation in this research project is completely voluntary. Participants or their representatives have the freedom to decline or withdraw from the study at any time without providing a reason, with no consequences. Opting not to participate or withdrawing will not affect the quality of care and services they are entitled to receive. Participants or their representatives can also choose not to answer specific questions or decline video recording if they prefer.

The confidentiality of collected data, video recordings, and contact information will be maintained. Electronic folders will be saved on the secure server of the institution and their access will be restricted to only the research team members with their own username and password. Mechanisms to ensure confidentiality will include the assignment of numeric codes and the removal of personal identifiers. The code key linking the participants to their research file will be kept in a file protected by a unique password, stored separately from the coded research data, and only accessed by the research team. Informed consent forms will also be stored separately from the coded research data. The REDCap (Research Electronic Data Capture; Vanderbilt University) [48] web application licensed by the primary site will be used to create the data collection forms and to facilitate data storage and management between the study sites.

For monitoring control, safety and security, the research files may be examined by a person mandated by Canadian or international regulatory authorities, such as Health Canada, as well as authorized representatives of the study sponsor (the institution) or the research ethics board. The data will be permanently destroyed after 15 years. All participants have the right to access their study files at any time to verify and correct the information if necessary. They are informed and consented to the fact that summarized deidentified data will be presented in scientific conferences and publications.

Results

This study was funded in April 2020 (see the funding report in Multimedia Appendix 1) but could not be launched until 2022 due to the COVID-19 pandemic. It was registered to ClinicalTrials.gov (NCT05339737) in April 2022. Recruitment and data collection began at the primary site in July 2022 and has been implemented at the secondary sites in 2023 and 2024. Recruitment and data collection will be ongoing until 2026.

Discussion

In alignment with our pilot findings [26,27], we anticipate that the NOL will be able to detect pain according to pain standard criteria and to discriminate between nociceptive and nonnociceptive procedures. The enrollment of critically ill adults with various clinical conditions and the capacity to communicate will allow us to better generalize our validation findings to the ICU population.

Methodological Strengths

The selection of rigorous validation strategies according to methodological guidelines in health measurement is the main strength of this study. With the participation of conscious ICU patients able to self-report, we can use the reference standard of pain, that is, self-reporting, for criterion validation. Furthermore, this validation strategy is reinforced by using the alternative reference standard, that is, the CPOT. Regarding discriminative validation, 2 strategies were selected, that is, discrimination between nonnociceptive and nociceptive procedures as well as before and after opioid administration. Test-retest reliability pre- and post-nonnociceptive and nociceptive procedures will allow us to examine the stability of the NOL values when patients are at rest. Both reliability and validation strategies are necessary to confirm the validity of an instrument [28].

In order to reduce potential bias related to pain scoring, Group A participants who are able to self-report will be blinded to the

NOL values screen during the procedures. CPOT scoring will be completed by research staff before obtaining the patient's self-report (ie, Group A participants) so raters are not influenced by self-reported pain intensity scores. Interrater reliability of CPOT scores will also be examined.

Our study lies in its foundation built upon the robust pilot work of the NOL conducted in the ICU setting. Our previous pilot studies have provided valuable insights and preliminary data to inform and support the research hypotheses and methodological decisions made in this study protocol. By expanding a rigorous validation process of the NOL to patients who are representative of the broader ICU population, the knowledge gained could contribute to identifying an alternative measure of pain in the most vulnerable critically ill adults.

Potential Limitations and Mitigation Strategies

Recruiting ICU patients or obtaining written consent from the persons qualified to consent for them is challenging. This requires daily screening of eligible patients and close follow-up. Support from the nursing staff and physicians is key to identifying eligible patients and approaching those qualified to consent for them. Our research team has developed efficacious recruitment procedures, trained competent research staff, and established close collaboration with ICU care teams in all sites, which facilitate the implementation of this study. The feasibility of recruitment was also demonstrated in our pilot work. A screening log will be completed at each site to compile eligibility criteria and reasons for refusals, losses, or withdrawals. In our pilot studies [26,27], we were unsuccessful in obtaining data from some participants mainly due to missing the procedure, either because temporary fellows forgot to inform the research team or the procedure occurred after ICU discharge. Chest tube removal and endotracheal suctioning were the sole nociceptive procedures included in our pilot studies. Broadening the selection of nociceptive procedures may reduce the number of missed observations of these events. However, we may still miss some procedures due to urgent situations. Also, data collection will be planned as soon as possible after obtaining written consent to minimize losses. In addition, we will document any challenges related to the use of NOL (eg, absence or loss of signal) and troubleshooting strategies. Finally, CPOT raters cannot be blinded to the procedures they will view on the videos. As a result, they may anticipate patients' behavioral responses to the procedure, which may influence their ratings. The examination of interrater reliability of CPOT scores involving trained research staff from different settings and using 2 methods of rating (bedside and video) may help minimize this potential bias.

Conclusion

The validity of the NOL has been supported in anesthetized patients, but its use in the ICU context is still new. Its validation in the ICU is relevant as many critically ill adults may be unable to self-report or express pain behaviors. As part of the validation process, it is key to validate the NOL with patient groups in whom pain standard criteria can be used as well as during nociceptive and nonnociceptive procedures in order to support its validity for both nociception and related pain assessment in the ICU. If found to be valid, the NOL could be used as an alternative measure to detect nociception and pain and to guide pain management decisions in the most vulnerable, critically ill adults.

Acknowledgments

We thank the ICU team and the dedicated research staff for making this study possible. Doctoral support funding to the graduate research trainee (SST) was provided by FRQS (Fonds de Recherche du Québec – Santé), MES-Universités (Ministère de l'Enseignement Supérieur-McGill University), and RRISIQ (Réseau de Recherche en Interventions en Sciences Infirmières du Québec).

This study is primarily funded by the Canadian Institutes of Health Research (CIHR Project Grant #168983) led by CG (principal investigator) and PR (coprincipal investigator) with coinvestigators. SST is a graduate research trainee on this major grant and obtained a research stipend.

Medasense Biometrics Ltd has not been involved in any part of this NOL validation protocol.

Data Availability

The dataset generated during and analyzed during this study is not publicly available due to ethical agreement but may be available from the corresponding author on reasonable request.

Authors' Contributions

CG, PR, SST, DL, MCG, and HTW contributed to conceptualization. CG, PR, SST, DL, MCG, and HTW handled funding acquisition. CG, PR, SST, DL, MCG, HTW, and WO contributed to the methodology. CG and PR performed supervision. CG, SST, and PR contributed to writing the original draft. CG, PR, SST, DL, MCG, HTW, and WO contributed to writing–review and editing.

Conflicts of Interest

None declared.

Multimedia Appendix 1 [PDF File (Adobe PDF File), 75 KB - resprot_v14i1e60672_app1.pdf]

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Abbreviations

APACHE: Acute Physiology and Chronic Health Evaluation
BPS: Behavioral Pain Scale
CPOT: Critical-Care Pain Observation Tool
FPT: Faces Pain Thermometer
GCS: Glasgow Coma Scale
ICC: interclass correlation coefficient
ICU: intensive care unit
NIBP: noninvasive blood pressure
NOL: Nociception Level
NRS: Numeric Rating Scale
RASS: Richmond Agitation Sedation Scale
REDCap: Research Electronic Data Capture
ROC: receiver operating characteristic
STROBE: Strengthening the Reporting of Observational Studies in Epidemiology

Edited by T Leung, D Khajeei; submitted 28.05.24; this is a non–peer-reviewed article;accepted 26.10.24; published 28.02.25.

Please cite as:
Gélinas C, Shahiri T S, Wang HT, Gallani MC, Oulehri W, Laporta D, Richebé P
Validation of the Nociception Level Index for the Detection of Nociception and Pain in Critically Ill Adults: Protocol for an Observational Study
JMIR Res Protoc 2025;14:e60672
URL: https://www.researchprotocols.org/2025/1/e60672
doi:10.2196/60672
PMID:40053798

Proposal

Development of a Framework for Youth- and Family-Specific Engagement in Research: Proposal for a Scoping Review and Qualitative Descriptive Study

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Abstract

Background: Youth and families play an indispensable role in health research, given their unique lived experiences and expertise. Aligning research with patients' needs, values, and preferences can significantly enhance its relevance and impact; however, recent research has highlighted various challenges and risks associated with youth and family engagement in health research. These challenges encompass the perils of tokenism, power imbalances and dynamics, questioning the motives behind engagement, and limited accessibility to patient-friendly training for patient partners, as well as inadequate training on patient engagement for researchers and the absence of equitable engagement tools. To address these risks and challenges, different patient engagement models, theories, frameworks, and guiding principles have been developed and adopted; to date, however, their transferability to youth- and family-specific engagement in research has been limited.

Objective: The objectives of this project are (1) to determine the extent of the literature on the application of patient engagement models, theories, frameworks, and guiding principles in the context of youth-specific research; and (2) to determine how meaningful the key components and constructs of these models, theories, frameworks, and guiding principles are to youth and their family members.

Methods: This project will use an integrated knowledge translation approach and consists of 2 phases: (1) a scoping review to identify patient engagement models, theories, frameworks and guiding principles in youth research; and (2) a qualitative descriptive study using one-on-one semistructured interviews with youth and family members to understand their conceptualization of meaningful engagement in health research. For phase 1, the following databases were searched: Medline, CINAHL, EMBASE, PsycINFO, and the Cochrane Central Register of Controlled Trials. Literature from 2013 to August 28, 2024, was captured. Primary studies using a patient engagement in research model, theory, or framework, or guiding principles, in youth will be included. The risk of bias of included studies will not be assessed. Extracted data will be quantitatively summarized using numerical counts and qualitatively using content analysis. For phase 2, we will recruit 9 to 17 youth and 9 to 17 family members. Transcripts will be analyzed using an inductive approach outlined by Braun and Clarke.

Results: The project has received funding from the Canadian Institutes of Health Research. A 9-member integrated knowledge translation panel consisting of 6 youth and 3 family members has been established.

Conclusions: The findings from this study will identify what is currently known about the application of patient engagement models, theories, frameworks, and guiding principles in youth-specific research and the important components of these models, theories, frameworks, and guiding principles from the perspective of youth and their families. These findings will be instrumental to developing a youth- and family-specific engagement in research framework called the UNITE framework and subsequently, a validated measure.

International Registered Report Identifier (IRRID): PRR1-10.2196/65733

(JMIR Res Protoc 2025;14:e65733) doi:10.2196/65733

KEYWORDS

youth and family engagement; frameworks; implementation science; scoping review; qualitative

Introduction

Background

Patients play an essential role in health research, given their unique lived experiences and expertise, which can significantly enhance the quality, relevance, and impact of research by aligning it with patient needs, values, and preferences [1,2]. The overarching objective of patient engagement in health research is to generate research that contributes to improved health care service delivery, clinical outcomes, and population health [3]. Recent research has highlighted the myriad benefits and positive outcomes associated with patient engagement for patient partners, investigators, and research endeavors [4-8]. For example, engaging patients has influenced initial research priorities, study designs, interpretation of findings, health care interventions, and knowledge mobilization strategies, resulting in outcomes that more closely align with patient perspectives [7,9]. When patient engagement is characterized as meaningful and authentic, it provides a rewarding experience for patients and researchers alike [10].

However, other recent research has highlighted various challenges and risks associated with patient engagement in health research. These challenges, which include tokenism [11-14], power imbalances/dynamics [12,15], limited accessibility to patient-friendly training for patient partners [16], and the absence of equitable engagement tools [17], can have lasting effects on patient partners, including mental and physical exhaustion, deteriorating health, doubts about the value of

engagement, and a sense of having personally failed both the team and the broader patient community [18]. A recent article by patient partners led by Richards et al [18] on how patient engagement can falter highlighted key themes, including "patient partners as a checkmark," "unconscious bias towards patient partners," "lack of support to fully include patient partners," and "lack of recognizing the vulnerability of patient partners" [18].

To address these challenges and risks, various patient engagement models, theories, frameworks, and guiding principles (eg, the strategy for patient-oriented research [SPOR], the patient engagement in research [PEIR] framework, and "ways community members can participate in the stages of research" from the Ontario Brain Institute) have been developed and adopted within the research community [10,19,20]. For example, the PEIR framework [10] includes eight key components, which collectively contribute to meaningful patient engagement in research: (1) procedural requirements, (2) convenience, (3) contributions, (4) support, (5) team interaction, (6) research environment, (7) feeling valued, and (8) benefits. A subsequent measure of meaningful patient engagement in research from the patient perspective has been developed, the Patient Engagement in Research Scale (PEIRS-22) [21,22]. This measure is designed to be completed by adult patients and family caregivers who partner with researchers on projects.

It is important to acknowledge that existing frameworks often predominantly emphasize the benefits of patient partners to the research project and team, sometimes overlooking the reciprocal benefits that may occur between the research team and patient partners, especially youth partners [23]. This skewed approach fails to fully consider the potentially extractive nature of research collaboration, as aptly described by Metz and Damschroder [23], where the research process can unintentionally exploit the knowledge and contributions of youth without adequately reciprocating in terms of personal and professional development opportunities. This issue takes on particular significance when crafting an engagement framework tailored for youth, as research teams have the potential to foster skill development, positively impact their life and career trajectories, and contribute to their holistic growth [23].

Despite the significant contribution of the PEIR framework [10] and the PEIRS-22 [21,22], they lack the incorporation of a comprehensive review of the evidence on existing frameworks, and their development was based on participants with limited diversity in terms of gender, race, education, primary diagnosis (all had arthritis), and age [10,21,22]. These limitations impede the transferability of this framework and measure to youth- and family-specific engagement in health research.

Furthermore, there is a model of engagement specifically designed for use with youth called the McCain model of youth engagement [24]. However, it was developed solely in the context of youth mental health systems research for youth and young adults aged 15 to 29 years [24], limiting transferability (ie, across different contexts and family members) and highlighting the need to develop a broader framework. Accordingly, our research seeks to directly address these specific gaps in existing engagement models, theories, and frameworks by developing a youth and family-specific engagement in research framework, the UNITE framework.

Research Objectives

This proposal has two objectives: (1) to determine the extent of literature on the application of patient engagement models, theories, frameworks, and guiding principles in the context of youth- and family-specific research; and (2) to understand how meaningful the key components and constructs of these models, theories, frameworks, and guiding principles are to youth and their family members. Collectively, these findings will be foundational to the development of the UNITE framework and a subsequent validated measure.

Methods

Study Design

This study will be conducted in 2 phases, with phase 1 consisting of a scoping review and phase 2 consisting of a qualitative descriptive study.

Integrated Knowledge Translation Approach

Integrated knowledge translation (iKT) is defined as a collaborative relationship between researchers and relevant knowledge users as partners that facilitates mutually beneficial decision-making related to a study or research program [25]. Youth aged 10 to 24 years in Canada and their family members who have engaged in health research (ie, as patient partners) in the last 3 years were recruited as iKT panel members via Holland Bloorview Kids Rehabilitation Hospital's Youth Advisory Council and Family Leader Program, professional networks, social media pages, and email lists. A sample of diverse youth advisors who have participated in our previous research on best practices in youth engagement were also approached, including youth with disabilities or developmental differences [26]. A total of 6 youths and 3 family members were recruited to be part of the iKT panels. The lead youth representative will lead the iKT panels. The lead youth representative and research team decided to hold separate iKT panels (ie, having a youth panel and a family panel with the opportunity to mix panels when needed). This approach will ensure that both groups feel comfortable and can freely express their unique perspectives. Activities of the panels have included planning study activities, and may include participant recruitment, data collection and analyses, and knowledge mobilization. Panel discussions will be conducted in a manner that respects diverse perspectives and experiences. A reflective exercise on equity, diversity and inclusion developed by the Strategy for Patient-Oriented Research Evidence Alliance will be conducted with iKT panel members to encourage dialogue and understanding around equity, diversity and inclusion [27].

Phase 1: Scoping Review on Patient Engagement Models, Theories, Frameworks, and Guidance in Youth Health Research

The methodology for the scoping review will follow the methodological frameworks of the Joanna Briggs Institute (JBI) [28] and Khalil et al [29]. The scoping review protocol has been registered on the Open Science Framework Registries [30] and

was guided by and reported according to the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) [31]. The completed PRISMA-P checklist can be found in Multimedia Appendix 1. The results of the scoping review will be reported using the Preferred Reporting Items for Systematic Reviews and Meta-Analysis extension for Scoping Reviews (PRISMA-ScR) checklist [32].

Stage 1: Developing a Search Strategy

The population, concept, and context (PCC) framework was used to guide the search strategy (population: World Health Organization [WHO] definition of "young people" as those aged 10-24 years [33]; concept: patient engagement in research; context: models, theories, frameworks, and guiding principles). With the assistance of a research librarian, literature search strategies using Medical Subject Headings and text words related to patient engagement and models, theories, frameworks, and guidance or guiding principles were developed. The search strategy combined structured database-specific subject headings (as available) and keywords or synonyms. An information specialist with expertise in conducting searches for systematic and scoping reviews drafted the search strategy using OVID Medline (Multimedia Appendix 2) and worked with the research team to refine and finalize the search. The final search strategy also underwent peer review using the Peer Review of Electronic Search Strategies (PRESS) statement checklist with another librarian/information specialist [34].

The following databases were searched: Medline, CINAHL, EMBASE, PsycINFO and Cochrane Central Register of Controlled Trials. Searches were limited to English. Literature from 2013 to August 28, 2024 was captured, consistent with when the term "patient engagement" became frequently used [35]. We will also search the gray literature in specialized databases like OpenGrey, Grey Literature Report, and GreyNet International, platforms like arXiv, bioRxiv, and SSRN, and databases such as ProQuest Dissertations and Theses.

Stage 2: Evidence Screening and Selection

All primary studies using a model, theory, or framework for patient engagement in research among young people will be eligible for inclusion. Studies with a model, theory, or framework may have also reported on guiding principles. We define young people as those aged 10 to 24 years, consistent with the WHO definition [33]. We define a model as the essential elements or variables of a phenomenon or a specific aspect of a phenomenon; a theory as "a set of analytical principles or statements designed to structure our observation, understanding and explanation of the world"; and a framework as an explanation of a phenomenon by organizing it into a collection of descriptive categories and the relationships between them [36]. Systematic reviews, meta-analyses, editorials, commentaries, and nonspecific conference proceedings will be excluded to focus on including primary results and not preliminary findings or ongoing research; however, the reference lists of such articles will be hand-searched for relevant articles.

Removal of duplicates as well as level 1 and level 2 screening will be managed through Covidence. To increase reliability, the level 1 screening form will be piloted on a random sample of approximately 50 articles. Eligibility criteria descriptions will be revised if deemed necessary by the team, or if low agreement (ie, <70%) [37] is observed, to improve the consistent application of the selection criteria. Agreement will be measured using Cohen κ [38]. A pilot test of the level 2 screening will also be performed on approximately 25% of the articles, similar to the process for level 1 screening. For studies that are excluded at level 2, the reason for exclusion will be recorded. All screening will occur in duplicate and independently. When necessary, another reviewer will be sought to resolve conflicts.

Stage 3: Data Extraction

A standardized data extraction form will be developed by the research team and iKT panels based on the *JBI Manual* data extraction recommendations [28] and those recommended for the extraction, analysis, and presentation of results in scoping reviews [28,39]. Extracted data will include study characteristics (eg, study design, year of publication, geographic location), youth and family participant characteristics (eg, age of the youth), and details of the engagement models, theories, frameworks, and guiding principles (eg, components or values and principles and how they were enabled or enacted in the study), as well as study results. Additional categories for data extraction identified through discussions with the research team and iKT panels will be added to the final data extraction template as applicable. The data extraction template will be piloted for 2 to 3 articles to ensure all relevant results are extracted. All data will then be extracted in duplicate by 2 independent reviewers. Discrepancies in the extracted data will be discussed and resolved by the 2 reviewers. Quality and risk of bias will not be assessed, as this is not required in scoping reviews [32].

Stage 4: Data Analysis

The extracted data will be quantitatively summarized using numerical counts and qualitatively summarized using content analysis [40]. The data will be grouped by the main components of the model, theories, frameworks, guiding principles (and how they were enabled or enacted), study designs, and associated methods (eg, one-on-one interviews). We will also synthesize data on how youth and family members were engaged throughout the research process, the types of outcomes collected, and results. Depending on the available data, subgroup analyses may be conducted by health condition, sex, gender-related variables, and other PROGRESS-Plus characteristics (PROGRESS-Plus is a term meaning "place of residence, race/ethnicity/culture/language, occupation, gender/sex, religion, education, socioeconomic status, social capital") [41]. If feasible, we will contact the study authors of the included studies to confirm that all the data collected were included in the published article (ie, nothing was excluded due to word count limitations of a journal).

Phase 2: Qualitative Study to Understand Key Components and Constructs for Development of a

Framework for Youth- and Family-Specific Engagement in Research

Study Design

Phase 2 will adopt a qualitative descriptive approach [42,43]. Findings from the scoping review will inform the development of the interview guide for phase 2, such as identifying what aspects of the included models, theories, frameworks, and guiding principles resonate with youth and family members and which do not.

Recruitment

We will recruit Canadian youth (aged 10-24 years) and their family members who have had experience in youth engagement in health research (eg, as partners of a research project) within the last 3 years. Participants will be recruited via our professional networks, including those of the iKT panel members (eg, the Kids Brain Health Network, the Bloorview Research Institute Family Engagement Office, and the SickKids Patient and Family Engagement Office), social media pages, and email lists. We will also enlist the help of a diverse group of youth advisors who have participated in our research team's previous research for recruitment [26,44,45]. We aim to recruit 9 to 17 youth and 9 to 17 family members; this is consistent with the sample size in qualitative studies to reach thematic saturation [46].

Data Collection

Youth and family participants will take part in separate, one-on-one, semistructured telephone or online interviews with a member of the research team with expertise in qualitative research methods [47,48]. All interviews will be digitally recorded and transcribed verbatim for data analysis. The interview guides will consist of questions focused on youth and family members' conceptualization of meaningful engagement in health research. The interview guide will be pilot-tested with various members of the research team and iKT panel. We will use probes or recursive questioning during interviews to explore issues in greater depth and verify the interviewer's understanding of the collected information [49,50].

Data Analysis

We will use inductive thematic analysis, as described by Braun and Clarke [51,52], which is consistent with the pragmatic orientation of this research [53]. Codes and themes will be refined through discussion with the larger research team. The software program NVivo (version 14; Lumivero) will be used during the analysis of the transcripts to help organize the codes. Multiple aspects of trustworthiness will be used [54]. For example, we will demonstrate credibility via peer debriefing with various members of the research team and the iKT panels. Transferability will be accomplished by describing the study samples. Independent analysts will review the data and contest the themes to ensure dependability. Finally, confirmability will be accomplished by providing decision trails between data and interpretation [54].

Ethical Considerations

Ethics approval for phase 2 of this project will be obtained from the first author's primary institution (Holland Bloorview Kids Rehabilitation Hospital, Bloorview Research Institute). Informed consent will be obtained from participants prior to the start of the interview. Transcripts from the interviews will be deidentified to ensure privacy prior to data analysis. Participants will be compensated for their time in the form of gift cards. The amount compensated will be consistent with the Canadian Institutes of Health Research (CIHR) Patient Partner Compensation Guidelines (CAD $50 [US $34.96] per participant) [55].

Results

This work is supported by a CIHR Healthy Youth Catalyst Grant received in March 2024 (HEY- 192883; Multimedia Appendix 3). A 9-member iKT panel consisting of 6 youth and 3 family members has been established and has been actively involved in the study. We anticipate that phase 1 of the study will be completed in March 2025. Ethics approval for phase 1 was not required as it did not involve collecting or using data from participants. Ethics approval for phase 2 of the study will be applied for in winter 2025. Phase 2 of the project is anticipated to be completed in August 2025. A detailed timeline of the project can be found in Multimedia Appendix 4.

Discussion

Anticipated Findings

The findings from this study will allow us to identify what is currently known about the application of patient engagement models, theories, frameworks, and guiding principles, which are often designed for adults, in the context of youth-specific research, and to understand the importance of the components that make up these models, theories, and frameworks from the perspective of youth and their families.

Dissemination Plans

We will use a variety of passive and active end-of-grant knowledge mobilization approaches to disseminate our findings, which will be codeveloped with our iKT panels. We will ensure youth and family voices are heard to develop flexible communication plans that will suit diverse needs. Traditional knowledge translation will include dissemination through meetings locally, nationally, and internationally (eg, PxP and For Patients, By Patients) and publications in peer-reviewed journals. Members of the research team are affiliated with and situated within pediatric institutions where the UNITE framework will be disseminated and implemented. We will codevelop plain language summaries with youth and family partners with clear, simple, and individualized messages for patients and family and community service organizations to augment the accessibility of the information. Finally, members of the research team will also discuss and distribute the UNITE framework within their expansive training curriculum and a planned youth-focused engagement in research course.

Future Directions

This project lays the foundational work for developing a patient engagement framework called the UNITE framework, which will include equity, diversity, and inclusion considerations, and

the subsequent development and validation of an associated measure of engagement. Future research will involve the implementation of the UNITE framework and a subsequent measure in a learning health system context within pediatric institutions that our research teams are associated with. The UNITE framework and associated measure will contribute to meaningful and sustained engagement of youth and their families in health research by addressing gaps in current patient engagement frameworks.

Strengths and Limitations

A strength of this study is the inclusion of gray literature (eg, reports and policy literature) for phase 1 (the scoping review). This will provide a more comprehensive understanding of the concept (patient engagement in research) and context (models, theories, frameworks, and guiding principles) that we are interested in, as well as mitigate publication bias [56]. In addition, the search strategy for phase 1 has been reviewed by the iKT panel and undergone peer review using the PRESS statement checklist [34], which further strengthens the relevance, comprehensiveness, and quality of the search strategy. One limitation of this project is the potential for selection bias (specifically for phase 2), where individuals who had either very positive or very negative experiences with patient engagement in research may be more likely to participate in the study, which may limit the applicability of the study's findings. However, the adoption of the iKT approach and having the iKT panels (consisting of youth and their families) assist in the recruitment for phase 2 of the study should result in the recruitment of a variety of individuals with diverse interests.

Conclusions

The current proposal will lead to the development of a youth- and family-specific engagement in research framework, UNITE, with future research focused on the development of an associated validated measure. The UNITE framework and measure will lay the foundation for meaningful and sustained engagement in health research by youth and their families, ultimately contributing to enhanced health care service delivery, improved clinical outcomes, and increased overall well-being and quality of life for youth and their families [1-3].

Data Availability

The data collected during this study are available from the corresponding author upon reasonable request.

Authors' Contributions

SEPM, AT, and CJ conceptualized the overall study design and methods, wrote the manuscript, and approved the final manuscript as submitted. CJ, SEPM, and AT informed the design of the study engagement approach and coordinated the knowledge user engagement. SEPM, CJ, and AT contributed to the design of the study knowledge mobilization strategies. All authors provided input and guidance on the study design and approved the final manuscript as submitted.

Conflicts of Interest

SEPM is the editor-in-chief of *JMIR Rehabilitation and Assistive Technologies*.

Multimedia Appendix 1
PRISMA-P checklist.
[PDF File (Adobe PDF File), 149 KB - resprot_v14i1e65733_app1.pdf]

Multimedia Appendix 2
Medline search strategy.
[PDF File (Adobe PDF File), 95 KB - resprot_v14i1e65733_app2.pdf]

Multimedia Appendix 3
Peer-review report by the Catalyst Grant: Healthy Youth competition, Canadian Institutes of Health Research (Canada).
[PDF File (Adobe PDF File), 281 KB - resprot_v14i1e65733_app3.pdf]

Multimedia Appendix 4
Timelines and milestones for the youth- and family-specific engagement in research (UNITE) project.
[PNG File , 73 KB - resprot_v14i1e65733_app4.png]

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Abbreviations

CIHR: Canadian Institutes of Health Research
iKT: integrated knowledge translation
PCC: population, concept, and context
PEIR: patient engagement in research
PEIRS-22: Patient Engagement in Research Scale-22
PRESS: Peer Review of Electronic Search Strategies
PRISMA-P: Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols
PRISMA- ScR: Preferred Reporting Items for Systematic Reviews and Meta-Analysis Extension for Scoping Reviews
SPOR: strategy for patient-oriented research
WHO: World Health Organization

Edited by A Schwartz; submitted 25.08.24; this is a non–peer-reviewed article;accepted 27.02.25; published 28.03.25.

Please cite as:
Munce SEP, Jarrett C, Senthilnathan V, Luong D, Allemang B, Bailey K, Biddiss E, Britto MT, Buchanan F, Cassidy C, Cross A, Cunningham J, Dimitropoulos G, Hadland SE, Kastner M, Killackey T, Kokorelias K, Macarthur C, Micsinszki S, Niles C, Wright FV, Toulany A
Development of a Framework for Youth- and Family-Specific Engagement in Research: Proposal for a Scoping Review and Qualitative Descriptive Study
JMIR Res Protoc 2025;14:e65733
URL: https://www.researchprotocols.org/2025/1/e65733
doi:10.2196/65733
PMID:

Protocol

Examining Quality of Work Life in Atlantic Canadian Long-Term Care Homes: Protocol for a Cross-Sectional Survey Study

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Abstract

Background: The Canadian long-term care (LTC) workforce cares for increasingly complex residents. With greater care needs come greater demands. Despite this, LTC staffing and resources are largely unchanged and underresearched over the last decade. The Atlantic provinces are home to the oldest population in Canada, indicating a high need for LTC. The health and well-being of the LTC workforce are critical components of care quality, yet only in Western Canada are such data routinely and systematically collected. Translating Research in Elder Care is a 2-decade research program studying the LTC work environment and has found strong links between the working conditions of LTC staff and resident outcomes. We draw upon their success to generate the evidence needed to understand, support, and manage the LTC workforce in Canada's four Atlantic provinces.

Objective: This study aims (1) to assess the quality of work life among staff in LTC homes in Atlantic Canada; (2) to examine the effects of the work environment on the quality of work life; and (3) to build capacity for research in the LTC sector in Atlantic Canada among knowledge users, researchers, and trainees. The objective of this paper is to describe the approach needed to examine the quality of work life and health of care staff in LTC homes.

Methods: Stratified random sampling will be used to recruit homes in Atlantic Canada. The sampling frame was designed to recruit 25% of the LTC homes in each of the 4 provinces with proportional representation by size; ownership model; and, if applicable, region or language. Key outcome variables include measures of mental health and well-being, quality of work life, intention to leave, workplace context, and missed or rushed care. Primary data will be obtained through structured interviews with care aides and web-based surveys from registered nurses, licensed practical nurses, managers, and allied health providers. Eligible participants were from an LTC home with at least 25 residents, 90% of whom were aged 65 years or older, and had worked in the home for at least 3 months. Multivariate analyses include regression analysis for explaining predictors of quality of work-life outcomes and multilevel modeling for more complex relationships of staff outcomes by provinces and LTC home characteristics.

Results: Data collection and cleaning are complete as of October 2024 (N=2305). Care aides (n=1338), nurses (n=724), allied health providers (n=154), and managers (n=89) from 53 homes make up the sample. Data analysis is ongoing. Initially, individual reports will present descriptive data for each participating LTC home. Concurrent analysis is planned for publication in peer-reviewed journals.

Conclusions: This peer-reviewed research protocol lays the foundation for a comprehensive analysis of the effects of the work environment on the quality of work life of LTC staff in Atlantic Canada.

International Registered Report Identifier (IRRID): DERR1-10.2196/66338

(JMIR Res Protoc 2025;14:e66338) doi:10.2196/66338

KEYWORDS

residential long-term care; care staff; Atlantic Canada; quality of work life; work environment; health and well-being

Introduction

Background

This protocol is for a collaborative investigation that aims to address profound deficiencies in data to understand, support, and manage the long-term care (LTC) workforce in Canada's 4 Atlantic provinces. In Canada, LTC homes are funded by provincial governments and provide a range of health and personal care services to predominantly older adults who require 24-hour nursing, personal, and support care [1]. Residents of LTC have higher levels of acuity and have more complex care needs than in the past decade as a result of increased life expectancy and delayed entry due to an increased emphasis on home care [2]. Approximately 81% of residents in Canadian LTC homes live with mild to severe cognitive impairment, 27.1% have seven or more chronic conditions, and 51.5% have extensive limitations in activities of daily living [3]. As the care needs of residents become greater, so do the demands placed on the LTC workforce. Despite this, LTC staffing and resources have remained largely unchanged and underresearched over the last decade [4,5].

The LTC workforce cares for residents with complex needs, but their work environments are strained by heavy workloads, inadequate resources, and critical staffing shortages [4,5]. The health and well-being of the LTC workforce are critical components of care quality [5], and yet only in the Western Canadian provinces of British Columbia, Alberta, and Manitoba are such data routinely and systematically collected [6]. In Atlantic Canada, no data are available on workforce characteristics or the work experiences of LTC care providers (ie, indicators of health, well-being, or burnout). LTC in Canada is provincially regulated, meaning policies, regulations, and practices differ among provinces; fundamental differences in how LTC is organized between Western provinces and Atlantic Canada influence how staff work and care for residents, including staffing models and ratios, and education and training requirements of staff. While many other Canadian provinces have continuously relied on internationally trained care workers to supplement the domestic workforce, this is a relatively new phenomenon in the Atlantic Canadian provinces of Nova Scotia, Prince Edward Island, Newfoundland and Labrador, and New Brunswick. Chamberlain et al [7] reported in 2018 that only 35% of care aides working in Alberta LTC homes spoke English as a first language in comparison to 95% of LTC care staff in a Nova Scotian 2021 pilot study [8]. Additionally, according to the 2021 census, between 96% to 99% of the population in Nova Scotia, Prince Edward Island, Newfoundland and Labrador spoke English as a first language, and as a bilingual province, nearly 70% of the New Brunswick population spoke English as a first language while the remaining 30% spoke French [9]. While recent efforts from governments in Atlantic Canada to bring internationally educated workers into LTC have been largely deemed successful from a recruitment perspective [10-12], little is known about how the changing composition of the workforce impacts the LTC environment. More specifically, it is unknown if, and to what degree, domestic and international staff feel supported as they adjust to a more diverse workplace. Further, the combined population of all 4 Atlantic provinces is fewer than 2.5 million [13] and far fewer staff are trained internationally. These differences limit the ability to generalize workforce data from the Western provinces to Atlantic Canada.

Given the relationship between work and care conditions [14,15], data on the LTC workforce are important as they allow policy makers to identify and address workforce issues that compromise resident care and the health and well-being of care staff. Understanding the work environment will assist in future workforce planning and the strategies designed to improve work conditions and ultimately care conditions.

Translating Research in Elder Care

Translating Research in Elder Care (TREC) is a program of research spearheaded by Carole Estabrooks and a group of researchers from Alberta Canada who have been studying the LTC work environment in the Western Canadian provinces for nearly 2 decades [6]. TREC has analyzed the impact of the LTC work environment on staff quality of work life, mental health, and well-being outcomes in 7 waves of data collection [5,7,16-18]. These data enable in-depth longitudinal analysis that demonstrates the impacts of policy changes, interventions, and events such as COVID-19 [19-21]. The TREC research program also links the staff survey data within a clinical microsystem to resident outcomes using data from the Resident Assessment Instrument for LTC [22]. Evidence of strong links between the working conditions of LTC staff and resident outcomes is reported. For example, significant relationships were found between the use of best practices and care staff's social capital and organizational slack (time and staffing) [23]. In examining the demographic profile of the LTC workforce, staff who provide the majority of direct resident care had little formalized training, were racially diverse, and had high rates of English as a second language [7]. More recently, TREC has designed and delivered interventions to enhance the work environment in LTC, such as Safer Care for Older Persons in (residential) Environments [21] and Improving Nursing Home care through Feedback on Performance [24], and a coherent breathing intervention to decrease stress, insomnia, and anxiety [25].

The TREC measurement system, including the care aide structured interview and the regulated staff web-based survey, were consistent with the instruments used in this study in Atlantic Canada. The minor exceptions were because of localized staff job titles and translation of survey instruments to enable staff in designated French LTC homes in New Brunswick to participate in their French language. The goal of our team is to build upon the work of TREC and to use their comprehensive data collection tools to build an Atlantic Research Collaboration (ARC) and to generate the evidence needed to understand, support, and manage the LTC workforce in Canada's 4 Atlantic provinces. Ultimately, we will identify work environment areas that are amendable to intervention so that targeted interventions can be designed and delivered at the regional, provincial, institutional, and unit levels to enhance the quality of the LTC work environment.

Study Purpose and Objectives

This ARC on LTC (ARC LTC) involved researchers and collaborators form 4 provinces to describe and examine the relationship between the health and quality of work life of LTC staff and their work environment (organizational context). The research aims are as follows.

- To assess the quality of work life among staff in LTC homes in Nova Scotia, Prince Edward Island, Newfoundland and Labrador, and New Brunswick.
- To examine the effects of the work environment on quality of work life.
- To build capacity for research in the LTC sector in Atlantic Canada among knowledge users, early career researchers, and trainees.

Methods

Study Design

This is a cross-sectional, multilevel survey study with an integrated knowledge translation approach with knowledge users (ie, representatives from LTC homes, health authorities, provincial ministries, and key sector organizations) embedded throughout the project. We use the Checklist for Reporting Results of Internet E-Surveys (CHERRIES) reporting guidelines for web-based or internet surveys as a framework for our approach [26]. A detailed description using the CHERRIES checklist is present in Multimedia Appendix 1. Our methods are consistent with the established recruitment and data collection protocols used by TREC [23,27] and will enable comparison of data not only across the Atlantic Canadian provinces but also with the Western Canadian provinces.

Study Context

The LTC sectors in Atlantic Canada are diverse with variations in names assigned to LTC homes, regulatory oversight, ownership models, and titles given to unregulated care staff (Table 1). The study's design is sensitive to these differences with some modifications made to the sampling frame to reflect the uniqueness of individual provinces. In this protocol, we use the terms LTC home and care aide to describe the facility where care staff work or residents live, and the unregulated staff, respectively.

Table 1. Characteristics of homes by province in 2023.

Characteristics	Nova Scotia	New Brunswick	Newfoundland and Labrador	Prince Edward Island
Name of LTC[a] homes	Nursing home	Nursing home	LTC homes	Manors or nursing homes
Government responsible	Department of Seniors and LTC	Department of Social Development	Department of Health and Community Services	Department of Health
Legislative framework	Homes for Special Care Act	Nursing Home Act	Health and Community Care Services Act	Community Care Facilities and Nursing Homes Act
Ownership model	Public, private for-profit, and not-for-profit	Private corporations run by boards of directors	Public	Public, private for-profit, and not-for-profit
Title for unregulated care staff or care Aides	Continuing care assistant	Resident aide	Personal care attendant	Resident care worker
Regulated nursing staff	Registered nurses and licensed practical nurses	Registered nurses and licensed practical nurses	Registered nurses and licensed practical nurses	Registered nurses and licensed practical nurses
Allied health providers presence of these providers varies by province and LTC home	Recreation therapist, aide social worker, dietitian physiotherapist, aide occupational therapist, and aide	Recreation therapist, aide social worker, dietitian physiotherapist, aide occupational therapist, and aide	Recreation therapist, aide social worker, dietitian physiotherapist, aide occupational therapist, and aide	Recreation therapist, aide social worker, dietitian physiotherapist, aide occupational therapist, and aide

[a]LTC: long-term care.

Theoretical Framing

The critical socioecological framework [28] is used to guide this research. This framework depicts how behaviors are influenced by characteristics of, and interactions between, the individual and immediate social network (microsystem), local environment or community (mesosystem), and the larger system (macrosystem). The ecological framework supports the bidirectionality of this influence (eg, the work environment may affect individual staff feelings of well-being and vice versa). The framework highlights the complexity of staff's experiences

and agency within the LTC environment and their ability to engage in change to enhance resident care. It acknowledges how the work environment is shaped and buffered by factors in the micro, macro, and meso levels. Embedding our research in the critical socioecological framework will enable us to examine the inter-relationships among individual experiences, the work environment, and the larger provincial and regional LTC policy context.

We will examine LTC at the macro, meso, and micro levels (see Multimedia Appendix 2 [29-39] for how the survey content is organized at the meso and micro levels). At the macro level, all 4 Atlantic provinces provide public funding to LTC. Although regulations, guidelines, and staffing ratios differ by province, individual homes vary in how they operationalize them internally. At the meso level, institutional practices, policies, and work culture, along with heavy workloads associated with complex LTC residents have a major impact on staff. About 80% of resident care in Canada is provided by unregulated care aides who have little, if any, formal education [7]. Despite their pivotal role in LTC, care aides may not receive the recognition they deserve, nor do they always feel like valued members of care teams [23]. Contextual factors in work environments such as leadership, culture, and social capital, influence individual staff at the micro level and account for greater job satisfaction, empowerment, and autonomy [40,41]. The critical socioecological framework can facilitate our understanding of the multilayered influencers on LTC staff's quality of work life, and ultimately, resident care and quality of life in LTC homes in Atlantic Canada.

The dynamic nature of the LTC environment including things such as changes in the complexity of resident care needs and the increasing number of staff who speak English as a second language, could prompt changes in workplace policies and culture. Changes in both policies and culture can impact how staff work at the micro level as well as how organizations operate at the meso level. The nature of these bidirectional relationships affects how staff work, how they experience their work, and their perceived ability to support the changes needed in the work environment.

Sampling

Facility Sampling and Eligibility

A stratified random sampling technique will be used to recruit homes from each of the 4 provinces. The sampling frame was designed to recruit 25% of the LTC homes in each province (Table 2) with proportional representation by size (large: >120 beds; medium: 70-119 beds; and small: 25-69 beds); ownership model (eg, public, not-for-profit, and private for-profit); and, if applicable, region or language. These strata have been previously associated with residents' quality of care [42,43]. Oversampling will be done in Newfoundland and Labrador and Prince Edward Island to ensure a minimum of 8 homes in these provinces and a sufficient sample to enable cross-tabulation. Because Prince Edward Island only has 1 health region, and New Brunswick is a bilingual province with designated English and French homes, the region strata will not be used in Prince Edward Island, and linguistic designation will be used in New Brunswick.

To be eligible to participate, homes need to provide 24-hour, on-site housing and health care services for older adults by professional (nursing) staff, be stand-alone facilities (ie, not attached to an acute care hospital), and have a minimum of 25 LTC beds with at least 90% of the resident population aged 65 years or older. Homes will be ineligible if they are hybrid care homes integrated with an acute care facility or hospital, or share central services (eg, human resources and laundry) with an acute care facility or hospital.

Table 2. Number of LTC[a] homes included in the sample and strata by province (2023 estimates).

Characteristics	Nova Scotia	New Brunswick	Newfoundland and Labrador	Prince Edward Island	Total
Total number of LTC homes, n	92	73	43	19	227
Eligible homes, n (% of total)	81 (88%)	71 (97.3%)	27 (62.8%)	15 (78.9%)	194 (85.5%)
Sample (25% of eligible), n	20	18	8[b]	8[b]	54
Strata	Region ownership size	Language size	Region size	Ownership size	—[c]

[a]LTC: long-term care.

[b]Newfoundland and Labrador and Prince Edward Island were oversampled.

[c]Not applicable.

Staff Sample and Eligibility

Our sample will include senior administrators, managers, regulated nursing staff, unregulated care staff, and allied health providers (Table 3). All staff must have worked at the LTC home for 3 months or longer. In addition to the 3-month criteria, managers must work a minimum of 50% of the time at the LTC home, nurses must work a minimum of 6 shifts a month at the LTC home, care aides must be able to identify a unit they work on more than 50% of the time and work a minimum of 6 shifts a month on that unit, and allied health must provide at least one-third of their services that equals 6 days a month at the LTC home. Senior administrators who hold executive positions in LTC, such as chief executive and operation officers, will be required to provide the standardized facility (eg, physical design) and unit-level data (eg, staffing models).

Table 3. Estimated number of care staff in LTC[a]—both regulated and unregulated by province.

Characteristics	Nova Scotia	New Brunswick	Newfoundland and Labrador	Prince Edward Island	Total by staff group
All registered nurses or licensed practical nurses in LTC, n	1611	2625	1278	299	5813
Sample pool from LTC homes (25%), n	322	656	320	150[b]	1448
Desired sample (60% of eligible staff), n	193	394	192	90	869
All care aides, n	3866	4875	962	710	10,413
Sample pool from LTC homes (25%), n	773	1219	241	355[b]	2588
Desired sample (60% of eligible staff), n	464	731	144	213	1553
Desired care staff (registered nurses, licensed practical nurses, or care aides) sample total, n	__[c]	—	—	—	2422

[a]LTC: long-term care.

[b]Prince Edward Island was oversampled (50%).

[c]Not applicable.

Sampling Procedures

With the exception of Prince Edward Island, each province will have a team of staff responsible for recruitment and data collection. Due to the size and resources in Prince Edward Island, recruitment and data collection will be assigned to the Nova Scotia team. Each provincial research team will create a database of their LTC homes that includes information on each stratum, along with the name and contact information of facility administrators. The stratified proportional random sampling procedure will be performed centrally by a project manager who will then inform provincial teams of the randomly selected LTC homes to recruit. Homes identified in the randomization procedure will be emailed a letter of invitation from the province's lead investigator and if necessary, a follow-up phone call from a member of the research team. Meetings via Microsoft Teams will be held with homes who express interest in the study. During these meetings, the nature and purpose of the study will be explained along with details of what participation entails. Homes that agree to enroll in the study will be asked to sign a facility agreement form that outlines the expectations of participation. If approval of an operator is required for facility participation the operator is asked to sign an operational approval form prior to the home signing a facility agreement.

Once a home agrees to participate, research staff will conduct orientation meetings (one in-person visit and MS Team or telephone meetings as needed) with administrators and site liaisons to (1) verify the eligible participant pool for completing staff surveys; (2) identify the number and types of care units, staff assignment, and shifts; and (3) discuss the logistics of data collection (eg, dates for data collection, promotion and recruitment strategies, interview flow and schedule, contact information for a site liaison).

Measures

Data will be collected using TREC's suite of survey instruments. TREC data collection tools have been administered in Western Canada at several points in time [5,7,18,23] and in Nova Scotia in 2021 with 10 LTC homes [8]. A key component of the surveys is the Alberta Context Tool (ACT), which was developed to measure 10 dimensions of the organization context within health care settings (eg, leadership, culture, feedback, staffing). The ACT contains slight variations for each category of staff and was developed and refined for use in LTC [44]. In addition to the ACT, other surveys will be used to collect data on staff demographics, their perceptions of physical and mental health, well-being, burnout, job satisfaction, as well as missed and rushed care. Permission to access and use these tools has been obtained. Minor revisions to the survey instruments have been made with permission to reflect Atlantic Canada–specific context (eg, provincial term used for care aides). Details of these tools, including their psychometric properties, are outlined in Multimedia Appendix 2 [29-39].

Translation

Many of TREC's suite of tools are only available in English, which means they have to be translated to French to accommodate the New Brunswick French LTC homes. The quality of these translations is critical in maintaining the integrity of the data collected, and the comparability of data across provinces. The TREC research team has a preexisting rigorous translation protocol that was modified by Hoben et al [45] and is based on international best practices [46]. The first step in the process is to identify the proprietary rights of each survey and to establish which tools are available in French. Of the tools in the suite, 6 tools have existing French versions, and 2 of these cannot be altered. We will obtain permission to translate the remaining 6 tools from English to French (Multimedia Appendix 2).

Translation of these 6 tools and the full TREC survey will involve a rigorous systematic process of forward translation from English to French, back translation from French to English, and cognitive debriefing. Once the forward and back translation processes are completed, additional reviewers will examine the changes for accuracy and precision and, if necessary, make recommendations for the final translation.

We will recruit 4 LTC staff members to complete the translated surveys to verify the understanding, clarity, and appropriateness

of the items. This step is for language, comprehension, and cultural issues only; these pilot data will not be included in the study's sample.

Additional translations will also be required for other research materials, such as demographic questionnaires, consent forms, standardized instructions, and explanations of items within individual surveys.

Data Collection Procedures

Based on TREC's experience, data to determine care home units for the study and the number of eligible staff will be collected during the initial in-person meeting between a member of the research team and an LTC care home administrator. Data collection for staff will not begin until these data are obtained. Meetings will take approximately 1 hour and will include a tour of the LTC facility and will allow research staff to build a relationship with care home administration.

A staff member at each care home will be designated as the site liaison by the LTC administrator. The site liaison will work with research staff on promotion, participant recruitment, and scheduling of data collection. An individualized data collection schedule will be cocreated for each home that allows for maximum access to eligible staff and minimum disruptions to the home. Data collection will take place during days, evenings, nights, and weekends. Data collection will be scheduled over a 1-week period, but, if necessary, more time will be provided.

Informed consent will be obtained from all staff prior to data collection. Staff survey data will be collected through a self-administered web-based survey or during a structured interview using Microsoft Teams. Regulated staff will be provided with a link to the closed web-based survey and instructed to complete it voluntarily and independently on the web using the Nooro research platform, on which the survey was thoroughly tested by project staff prior to data collection. Codes given to staff can be used to leave and reenter the survey without losing progress; once the survey is submitted, the code can no longer be used to access the survey thus preventing duplicate entries.

Care aides (unregulated staff) will be scheduled to meet in a private and quiet space with a trained data collector via Microsoft Teams. The data collector will administer the surveys using Computer Assisted Personal Interviewing (CAPI) techniques; survey questions will be read to the participant in a structured interview format using standardized language, and the data collector will enter responses directly into the Nooro research platform. In the event of a staff member becoming upset during data collection, interviews will be paused, and a support protocol will be initiated, including the provision of a list of local mental health resources. The variation in data collection procedures between regulated staff and care aides is based on previous feasibility testing conducted by the TREC team which determined structured interviews are more effective than self-administered web-based surveys for care aides and can be conducted in less time [27].

Facility- and Unit-Level Data

One facility profile survey will be completed for each participating LTC home, and unit profile surveys will be completed for each unit in the LTC home. These surveys collect data such as the size, ownership model, unit information (ie, number and size of resident care units), types of units (eg, dementia and psychiatric), human resources (eg, physicians and nurse practitioners), care staff complement (eg, type and number of staff on each unit on a given shift), quality improvement activities, and access to programs and services. These surveys will be completed by research staff with LTC administrators or their designate (eg, a director of care or unit manager) through Microsoft Teams during or shortly after the staff data collection period.

Staff Data

Surveys or interviews can be completed during work time and will take approximately 35 minutes. Multimedia Appendix 2 details the measures that will be collected. Survey item totals varied by staff survey type: care aide surveys have 154-169 items depending on responses to adaptive questions and are answered continuously in the interview format; nurse surveys have 207-219 items across 50 pages; allied health surveys have 138-149 items across 37 pages; and manager surveys have 209-229 items across 53 pages. Items or scales were not randomly ordered. Regulated staff completing the web-based survey could review and change their answers if desired before submission. There are no automatic completion checks alerting participants if their web-based survey contains missed items. Data collectors administering the care aide survey are to check for completion, however, it is not obligatory for care aides to answer missing items.

Data Collector Training

Training will be in accordance with TREC's training program for quality assurance purposes and to ensure consistency. Data collectors will receive in-depth standardized CAPI and survey interview training, which will be done in collaboration with TREC's field coordinator and the ARC LTC staff who have experience with implementing the TREC Survey.

Data collectors will participate in 3 training sessions followed by a quality assurance test. The 3 sessions will be 2-3 hours long and delivered in-person or using Microsoft Teams meetings. These web-based sessions will be recorded for onboarding additional staff at later points in time. The sessions will include didactic teaching, group discussion, and survey practice with peers. Topics will include project background, survey overview, CAPI administration, accessing the survey platform, consent process, shift schedules and resources, and strategies for challenging interviews (eg, technology issues, managing participant distress, keeping participants on track). In addition to survey practice during the 3 sessions, data collectors will be instructed to practice on their own or with friends and family.

During the quality assurance testing, each data collector will complete a minimum of 2 surveys. Data collectors must meet all criteria (eg, obtaining proper consent, reading questions verbatim, appropriate use of scales, proper flow, correctly

inputting responses, acting professional, answering or navigating participant questions, managing technology issues, managing participant distress, keeping participants on track). If necessary, additional training will be provided to data collectors on an individual basis to ensure they are able to conduct quality interviews meeting all quality assurance criteria.

Upon completion of training, each data collector will complete at least 1 practice interview with an ARC LTC staff member. Data collectors must receive approval from the ARC LTC staff before being cleared to conduct interviews. Ongoing quality assessment will continue throughout the data collection phase to ensure proficiency in administering surveys using CAPI, consistency between data collectors, and consistency across time ensuring high-quality data.

Ethical Considerations

Ethical approval for this protocol was obtained from the research ethics boards of the academic institutions of each of the investigators. The study was first reviewed and approved by the Research Ethics Board at Mount Saint Vincent University, Nova Scotia (2023-039), and then subsequently reviewed and approved by ethics boards at Dalhousie University, Nova Scotia (2023-6887); University of New Brunswick (2023-133); Memorial University of Newfoundland (2023.212 or 2024.1112); and Health Prince Edward Island (2023-10-19 or 2024-02-12). Care staff participation will be voluntary, and the information collected will be completely confidential. Data collection with care staff will be held in a private location and no names will be stored with study data. Potential participants will be sent a copy of the consent form prior to the interview, and it will be reviewed just prior to initiating an interview. Informed consent including the purpose of the study, approximate length of completion, data storage and privacy, research team, and ability to opt-out at any time prior to survey completion will be obtained prior to starting the survey. After each care aide survey, the data collector will complete an interview checklist which will capture feedback on the interview and rate its quality. Biweekly data quality reports will be compiled and the number of interviews completed and in progress, time to complete interviews, and occurrence and nature of missing data or extreme scores will be reviewed by investigators and staff. Any unexpected issues will be reviewed with data collectors on a regular basis. Data collectors may be observed conducting interviews for ongoing quality assurance purposes. Data are anonymized upon survey entry, and as such, there is no way to identify or remove participants' responses once the survey has been submitted. Study reports at the unit level will only be available if more than 8 staff from the care unit participate; in cases where fewer than 8 staff from 1 care unit participate, reports will only be available at the facility level to protect participants from being identified. No data will be presented unless the cell size is 5 or more. The identities of the LTC homes that participate will also be held in confidence; sites will only be described by their province, size, region, and language. All the data and the results will be kept indefinitely on a secure server in the Health Research Data Repository that resides in the Faculty of Nursing, University of Alberta. The nominated principal investigator JMK is the data custodian for these data. Contingent on subsequent ethics reviews, its access will be highly restricted. The Health Research Data Repository will support storage, data analysis, and access control for all ARC LTC team members and trainees. Research team members may access the data remotely using unique usernames and strong passwords. Users are unable to download any data or access the internet while logged into the repository. Identifiable data and personal information will be stored separately from their deidentified counterparts to ensure participant confidentiality. Any print documents will be stored securely in locked file cabinets by the project lead in each of the provinces. All staff who participate in the study will receive a CAD $10 (US $7.55) coffee gift card as a token of appreciation. These cards will be supplied to the facility liaison who will hand out cards to staff who agree to participate on survey completion. In addition, LTC homes that participate will be provided with a small stipend at the completion of the study to compensate for any work associated with their participation; the stipend will be based on the size of the home (ie, small, medium, or large). All staff will be given an opportunity to obtain a copy of the study's findings.

Knowledge Translation

As part of the feedback process, tailored reports will be generated for each individual care home. These care home reports will be shared with the home administrator. Staff participants will be given the opportunity to receive a generalized report on the study's findings. If they wish to receive results, they will be asked at the end of the survey to provide an email address. Email addresses for feedback purposes will not be linked to any data provided by participants.

Data Analysis Plan

To assess the quality of work life among staff working in LTC homes in Atlantic Canada, data will be analyzed by home, by province, and in combination to identify and assess associations, interactions, and predictors of health and work-life outcomes. No correction methods will be calculated. Regression analysis and statistical modeling techniques will be used to explain how work environments within LTC homes are impacting the quality of work life and health of staff. For example, is the work environment (an independent variable) correlated with job satisfaction and burnout? In what way do demographic variables, such as age, or English as a second language mediate the effect of work environment on quality of work life and intention to leave? Multimedia Appendix 3 shows the proposed statistical approaches. Multilevel modeling will be conducted to explore the complex interplay among characteristics at the micro (eg, LTC staff), meso (eg, unit and facility), and macro (eg, province) levels and their effects on indicators of quality of work life and health. Early careers researchers, trainees, and knowledge users will be involved in all aspects of data analysis to help build capacity for research in the LTC sector in Atlantic Canada.

Results

Data collection occurred between November 2023 and June 2024 and is complete. Between July 2024 and September 2024, data were cleaned and organized for analysis. Data analysis is underway. Initially, individual reports will present descriptive data for each participating LTC home comparing their staff responses to mental health and well-being by occupational group

with those of staff from all other facilities participating in their province. A series of three reports are proposed: (1) demographics and perceptions of work life (eg, burnout, job satisfaction, and intention to leave); (2) personal health and well-being (eg, general anxiety, posttraumatic stress disorder, and insomnia); and (3) organizational context (including the 10 dimensions of the ACT [44]; eg, leadership, culture, feedback, and staffing). Concurrent with this descriptive analysis, analytical analysis is planned for publication in peer-reviewed journals.

Discussion

Overview

This study aligns with Canadian and global priorities related to creating a sustainable health workforce and improving service delivery for those residing in LTC [47]. Specifically, our study builds on the influential research of the TREC group in Western Canada who developed and refined a comprehensive methodology for understanding the context of LTC and more notably, identifying solutions for enhancing the work environment and improving the quality of resident care [15,20]. Such work has been proven effective in enriching the work life of staff and improving system efficiency [15,16]. To date, a key finding of TREC's work is the importance of organizational context to support the implementation of interventions to improve staff outcomes. Given the difference in the organization and delivery of LTC services across Canadian provinces [4], this study will generate much-needed data for enhanced and targeted planning and decision-making in the Atlantic LTC sector. Findings from this study will support a greater understanding of our LTC work environment and workforce, and to use these regional data to determine where knowledge users can introduce interventions to improve staff quality of work life.

Expected Findings

Concerns about the LTC workforce have existed for some time, but these have heightened since the COVID-19 pandemic [41]. The pandemic brought unprecedented challenges to LTC and staff were forced to navigate these stressors while maintaining the highest standards of care under difficult and often unsafe conditions. We expect to verify the extent to which these conditions continue to impact staff's health and well-being, including stress, anxiety, and quality of work life, and assess whether care aides continue to report a poorer quality of work life than other LTC staff as reported in a Nova Scotian study in 2021 [48]. This Nova Scotian study's finding is significant as it underscores the distinct struggles care aides face in LTC. These struggles may stem from providing direct care to increasingly complex residents or they may be associated with undervaluing of their work within an LTC work environment (eg, low pay, limited education), or both.

Should our research findings, across LTC settings and geographical locations, be consistent with those of the study by Keefe et al [48], it will provide further evidence to advocate for tailored supportive interventions specifically designed for care aides. For instance, our findings could inform policies related to the minimum educational requirements of care aides, which are currently lacking in some Atlantic Canadian provinces. Research findings could also support the need for job redesign, particularly efforts to provide care aides with more formal interaction within the workplace. Enhancing care aides' inclusion into decision-making processes, providing mentorship programs, or enriching team-based care in a way that acknowledges and values the perspective that care aides bring will enable greater connection to their workplace [16,49,50]. Such approaches could recognize the vital contributions of care aides, affirming their roles as essential members of care teams, and enhancing their status within the workplace.

We are confident that our study will provide data to assess recent policy initiatives within Atlantic Canada regarding the recruitment of internationally educated nurses to address the staffing shortage in LTC. These efforts include targeted recruitment campaigns, streamlined credentialing processes, and both professional and personal support programs. In the short term, these efforts appear to be successful as evidenced by the increasing number of nurses who have migrated to the region from targeted countries. However, despite these short-term successes, little is known about the long-term sustainability and effectiveness of these recruitment strategies, especially in terms of retention and overall job satisfaction. This gap is important because the long-term success of these initiatives is crucial for ensuring that Atlantic Canada can maintain a stable and skilled health care workforce in the face of ongoing human resource challenges. Our data will offer valuable insights not only into the work patterns of these migrant workers but also into their work integration experiences, including job satisfaction, relationships with colleagues, and their intentions to leave their current roles. Such information will be crucial for understanding the true impact of international recruitment efforts and for identifying areas where improvements can be made to enhance retention and overall workforce stability in our region.

It is also expected that our findings will be able to provide recommendations for how to address the deficits in the LTC system that have been exposed during the COVID-19 pandemic [51]. As the Atlantic provinces are home to the oldest population in Canada, policy makers require region-specific data to ensure sustainable and quality LTC is available for those who need it. Efforts to provide quality LTC must recognize that work conditions are care conditions, and consider the context where care takes place. The results of this study will support workforce planning and provide much-needed data on the LTC sector's current and future capacity. Study findings promise to identify elements in the work environment that are amendable to change and enable policy makers to develop strategic responses needed to support care staff, enhance worker health and well-being, and ultimately create the conditions that maximize staff's ability to provide quality care.

Limitations

The study has a number of limitations. While it is anticipated that there will be great interest among the LTC sector to participate in this research, it is possible that some homes may still be recovering from the pandemic or have human resources challenges that preclude them from participating in the study.

We are using a stratified random sample to ensure provincial representation but the strata used in the sampling frame need to be adapted to reflect the uniqueness of each province. For example, language (French and English) is a stratum used only in the sample of LTC homes in New Brunswick, and the ownership model (ie, public, private for-profit, and not-for-profit) is only being used with the LTC homes in Prince Edward Island and Nova Scotia. While the decision to modify these strata was made to ensure adequate representation of subgroups within each province, we recognize the need for our data analysis procedures to account for these differences. We will perform rigorous comparisons between provincial data to identify and account for differences in strata. If necessary, we will use statistical techniques such as multilevel modeling to account for differences across provinces. We will also acknowledge any potential threats to external validity that may arise as a result of our sampling plan during our dissemination activities.

Acknowledgments

The authors have received funding from the Canadian Institute of Health Research (FRN 186055), Research Nova Scotia (RNS 2022-2407), Newfoundland and Labrador Centre for Health Research, Nova Scotia Health, Health Prince Edward Island, and Research New Brunswick.

Data Availability

The datasets generated or analyzed during this study are not publicly available due to limited access to the University of Alberta Health Research Data Repository where they are housed. Data are available from the corresponding author on reasonable request.

Authors' Contributions

JMK is the lead researcher and nominated principal investigator who received Canadian Institute of Health Research, Research Nova Scotia, and Health Prince Edward Island funding. CAE is the principal investigator of the Translating Research in Elder Care research program whose surveys are used in the study. CAE and RM are co–principal investigators and RM received funding from Research New Brunswick. LEW, CM, AM, and MJH are coinvestigators on the research proposal. RM and JMK drafted the manuscript. MJH and CAE provided input into the statistical analysis for the study. All authors contributed to the manuscript and approved the submitted version.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Checklist for Reporting Results of Internet E-Surveys (CHERRIES).
[PDF File (Adobe PDF File), 162 KB - resprot_v14i1e66338_app1.pdf]

Multimedia Appendix 2
Overview of instruments used to measure micro- and meso-level concepts in the Atlantic Canada long-term care study: Translating Research in Elder Care survey.
[PDF File (Adobe PDF File), 336 KB - resprot_v14i1e66338_app2.pdf]

Multimedia Appendix 3
Analytic Plan.
[PDF File (Adobe PDF File), 123 KB - resprot_v14i1e66338_app3.pdf]

Multimedia Appendix 4
Peer review report.
[PDF File (Adobe PDF File), 832 KB - resprot_v14i1e66338_app4.pdf]

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Abbreviations

ACT: Alberta Context Tool
ARC LTC: Atlantic Research Collaboration on Long Term Care
CAPI: Computer Assisted Personal Interviewing
CHERRIES: Checklist for Reporting Results of Internet E-Surveys
LTC: long-term care
TREC: Translating Research in Elder Care
HRDR: Health Research Data Repository

Edited by A Schwartz; submitted 10.09.24; this is a non–peer-reviewed article;accepted 03.03.25; published 31.03.25.

Please cite as:
Keefe JM, McCloskey R, Hodgins MJ, McArthur C, MacKenzie A, Weeks LE, Estabrooks CA
Examining Quality of Work Life in Atlantic Canadian Long-Term Care Homes: Protocol for a Cross-Sectional Survey Study
JMIR Res Protoc 2025;14:e66338
URL: https://www.researchprotocols.org/2025/1/e66338
doi:10.2196/66338
PMID:

Protocol

Developing Guidelines for Conducting Stigma Research With Transgender and Nonbinary Individuals: Protocol for Creation of a Trauma-Informed Approach to Research

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Abstract

Background: Transgender and nonbinary individuals have received increasing attention within HIV research, with studies documenting the pervasive role stigma plays in creating and sustaining health inequities. However, the proliferation of HIV stigma research with this population has also raised concerns about research practices that may unintentionally stigmatize or retraumatize the very communities they are designed to benefit. Conducting stigma research is critical for generating accurate information about HIV epidemiology, risk and protective factors, and intervention strategies for transgender and nonbinary individuals. Yet, little research has directly examined the experiences of transgender and nonbinary individuals when participating in these studies or identified specific research practices (eg, recruitment materials or study framing, choice of specific survey measures, data collection protocols, and researcher behaviors) that may influence study participation, retention, and data quality. Equally important, research has not adequately examined the potential for unintended harm due to emotional distress experienced by participating in such research and what specific strategies might mitigate against potential distressful research experiences.

Objective: This study aimed to develop a set of empirically based trauma-informed guidelines for conducting HIV-related stigma research with transgender and nonbinary individuals to increase researchers' capacity to recruit and retain transgender and nonbinary individuals in HIV-related stigma research, enhance the quality of data collected, and reduce unintentional harm in stigma research methodology.

Methods: The study will engage in primary data collection using both qualitative and quantitative methodology. First, we will use in-depth qualitative interviews with 60 participants representing 3 participant groups: researchers, mental health clinicians, and transgender and nonbinary individuals who have participated in HIV-related and sexual health research. Second, the qualitative findings will be used to develop an initial set of survey items representing a preliminary set of guidelines. Third, we will engage 75 participants in a 3-round modified Delphi method, to refine the guidelines and promote their acceptability among key stakeholders.

Results: The study is funded by the National Institute of Mental Health starting in July 2022 and data collection began January 2023. The study's findings underscore the critical importance of adopting a trauma-informed approach to HIV stigma research with transgender and nonbinary individuals.

Conclusions: To make meaningful strides in stigma research, it is imperative to examine experiences of stigma that may happen within the research context and identify strategies for improving data quality and reducing unintentional harm in study recruitment, methodology, implementation, and dissemination.

International Registered Report Identifier (IRRID): DERR1-10.2196/66800

(JMIR Res Protoc 2025;14:e66800) doi:10.2196/66800

KEYWORDS

transgender; non-binary; HIV prevention and treatment; stigma research; trauma-informed

Introduction

Background

Over the past 2 decades, transgender individuals, particularly Black and Latina transgender women, have received increasing attention within HIV research [1-9]. Such research has consistently documented the pervasive role stigma plays in creating and sustaining health inequities among this population. However, this research proliferation has also raised questions about practices that may unintentionally stigmatize or retraumatize the very communities they are designed to benefit [4,10-15]. One area of particular concern is the measurement of stigma as part of HIV-related research with transgender and nonbinary individuals. First, there is concern that specific items within commonly used measures may unintentionally recreate or activate stigma. For example, many stigma and minority stress scales [16-19] include items that may be experienced as stigmatizing (eg, "Being transgender is disgusting to me") [19] or ask participants to recount and relive traumatic experiences (eg, history of physical and sexual violence, family rejection, and experiences of discrimination and harassment) to document their association with negative affect or health behavior [2]. There has been considerable debate within the larger field of trauma-related research as to whether recalling and answering questions about past trauma has negative or positive consequences for study participants [20-29]. However, there is surprisingly limited research within HIV science on the potential emotional impacts of participating in stigma research. Second, there are no evidence-based guidelines for person-centered, trauma-informed, and actively destigmatizing implementation of HIV stigma research. Conducting stigma research is critical for generating accurate information about HIV epidemiology, risk and protective factors, and intervention strategies for transgender and nonbinary individuals. Yet little research has directly examined the experiences of transgender and nonbinary individuals when participating in these studies, or identified specific research practices (eg, recruitment materials or study framing, choice of specific survey measures, data collection protocols, and researcher behaviors) that may influence study participation, retention, and data quality [30]. Equally important, research has not adequately examined the potential for unintended harm due to emotional distress experienced by participating in such research and what specific strategies might mitigate against potential distressful research experiences.

Impact of Stigma on HIV-Related Outcomes

Research documenting multiple and intersecting structural factors, including racism, sexism, transphobia, homophobia, and other systems of stigmatization, oppression, and traumatic victimization that contribute to the disproportionately high rates of HIV infection and HIV-related morbidity in this population [2-4,6,7,14,31-35]. One of the strengths of HIV research in this area has been its intersectional focus, [36] as well as the acknowledgement that stigma operates at individual, interpersonal, and structural levels. Intersectional approaches demonstrate the ways in which HIV-stigma and other sources of stigma occur simultaneously and interact to impact transgender and nonbinary individual's daily experience, health outcomes, and engagement with care. Research suggests that transgender and nonbinary individuals may experience this impact as traumatic, and support trauma-informed approaches that seek to mitigate retraumatization within the provision of care [37-43]. Transgender and nonbinary individuals health disparities have been directly linked to intersectional and multidimensional stigma processes [37,41,44,45], underscoring the extent to which this approach is essential for advancements in transgender and nonbinary individual–specific stigma frameworks, measurement, and intervention development.

Potential for Unintentional Harm

Within the fields of clinical psychology and neuroscience, there has been intense debate about the impact of research about traumatic experiences on study participants [20-29]. Some evidence suggests that such research might lead to traumatization or cause further harm to those with previous exposure to violence or abuse. One meta-analysis of studies about traumatic events found that approximately 25% (IQR 4.3%-50%) of adult participants reported distressing impacts (ie, unexpected upset, negative emotions, unwanted thoughts, or distress) as a result of research participation. Although, most people find that participating in trauma research is distressing, they also report that they find it worthwhile and meaningful [28]. Neuroscience research on memory reconsolidation suggests that the context and content of memory reactivation may determine its harmful or therapeutic impact. Data indicate that research participants anticipate or attribute negative impacts to study participation; in 1 large-scale study of traumatic experience, 94% of participants rated their participation as more than minimal risk, with participants that had greater previous exposure to trauma reporting higher levels of distress [46]. However, limited research within the field of HIV has directly examined the potential impact of stigma research itself on transgender and nonbinary participants.

Impact on Engagement in HIV Prevention and Care

Growing recognition of the importance of community partnership for HIV research with transgender and nonbinary individuals has led to a rise of studies that rely on community health centers or other service agencies for research recruitment and implementation [47-50]. It is well established that experiences of stigma within these settings may negatively impact transgender and nonbinary individual's willingness to receive needed health care, including HIV testing, treatment, or pre-exposure prophylaxis [37-39,51,52]. If stigmatizing or harmful research is conducted within these settings, there is the potential to reduce transgender and nonbinary individual's trust in the very organizations upon which they depend to access life-saving services. As such, it is essential to understand

whether and under what conditions HIV stigma research may result in unintentional harm or stigmatization of transgender and nonbinary individuals, and how harmful impacts can be reduced.

Impact on Recruitment, Engagement, and Data Quality

Evidence indicates that mistrust of research projects, study teams, or settings leads to difficulties with recruitment and retention of study participants and may be associated with false or misleading responses to study measures. Studies indicate that research mistrust is particularly strong among transgender and nonbinary participants, who may report feeling used or mistreated within HIV research contexts [53-55]. In 1 study, transgender women reported that research scripts and procedures can be experienced as microaggressions [55]. Critical HIV-related stigma research is likely to underperform and fail to provide much needed data on stigma processes if participants are discouraged from participating or alienated from the research enterprise by perceptions that stigma research is itself stigmatizing [56].

Need for Empirically Grounded Research Guidelines

Many HIV stigma studies report incorporating intentionally affirming components into their research practice, such as measures of self-esteem, community-connectedness, or other resilience factors [57,58]. However, there has been no systematic compilation of these strategies, or analysis of their potential use in reducing stigma experiences. This research gap results in a lack of consensus of what is meant by trauma-informed HIV stigma research, as well as gaps in how to best implement and evaluate stigma-reducing measures in HIV research practice. Outside of HIV research, there are models for patient-centered, trauma-informed health research [59] that could be adapted to better inform implementation strategies, but such adaptation needs to be grounded in empirical data from participants, researchers, and practitioners with direct experience in the field.

Theoretical Frameworks

This study is based on an interdisciplinary integration of minority-stress and trauma-informed theoretical frameworks to explain health inequity. Minority stress theory [60] is a strong epidemiological framework for explaining disparity but is less precise in specifying mechanisms of an individual stigmatized person's behavior, feelings, or experience. To complement this theory, we incorporate a conceptual framework developed specifically to support the mental health of TGNB individuals [61], which combines 2 trauma-informed care models to guide our research questions and analysis. The first, developed by Fallot & Harris [62,63], emphasizes five principles of interaction: safety, trustworthiness, collaboration, choice, and empowerment. The second, guiding principles of trauma-informed care created by the Substance Abuse and Mental Health Services Administration within the US Department of Health and Human Services, focuses on attention to cultural, historical, and gender issues that impact power relationships, privilege, and oppression [64]. This trauma-informed theoretical approach attends to the potential presence of trauma-related symptoms on the thoughts, feelings, needs, and reactions of TGNB research participants, and aims to actively disrupt retraumatization through the creation of interpersonal processes and settings that emphasize safety, trust, collaboration, empowerment, and choice. Rather than focusing on isolating and describing stigmatizing internal and external experiences that happen to a marginalized person, a trauma-informed approach to stigma research centers how those marginalizing experiences thwart a survivor's wellness, healing, and resilience [65]. Trauma-informed approaches are, therefore, inherently person-centered, and strengths-based in that they entail recognition of the signs and symptoms of trauma in an individual's behavior and guide clinical responses to minimize negative impact on the survivor's natural recovery process [64]. These characteristics are likely to support greater engagement, quality, and benefit of HIV research among transgender and nonbinary individuals [55].

Study Aims

The primary aim of this study is to develop empirically informed, trauma-informed guidelines for conducting HIV-related stigma research with transgender and nonbinary individuals. This work seeks to address critical gaps in the field by improving recruitment, retention, and data quality while reducing the potential for harm during research participation. Specifically, the study focuses on the following aims. First, this study aims at understanding participant experiences by conducting in-depth interviews with transgender and nonbinary participants who have engaged in HIV or sexual health-related research to explore their experiences, including factors that contribute to or mitigate distress, stigma, and harm. This aim seeks to uncover the nuanced challenges and opportunities for designing research that supports participant well-being. Second, this study aims to gather stakeholder perspectives by conducting in-depth interviews with researchers and mental health clinicians to identify current practices, challenges, and strategies for implementing trauma-informed and person-centered approaches in HIV stigma research. This aim emphasizes understanding the perspectives of professionals who interact with transgender and nonbinary populations in research and clinical settings. Third, this study aims to develop and refine trauma-informed guidelines by using findings from the first and second aims to create a preliminary set of trauma-informed research guidelines. These guidelines will be refined through a modified Delphi process involving transgender and nonbinary individuals, researchers, and mental health professionals to ensure their relevance, acceptability, and applicability across diverse research contexts.

By integrating qualitative interviews with a structured consensus-building approach, this study aims to establish actionable and evidence-based recommendations. These guidelines will enhance the ethical rigor and methodological quality of HIV stigma research, contributing to improved health equity and reducing unintentional harm in research practices.

Methods

Study Objectives

Our study is designed to address a critical gap in existing HIV stigma research with transgender and nonbinary individuals by examining experiences of stigma within the research context

and identifying strategies for improving data quality and reducing unintentional harm in study recruitment, methodology, implementation, and dissemination. This study will engage in primary data collection using both qualitative and quantitative data collection methodology. To accomplish the study aims we will first, conduct in-depth interviews with transgender and nonbinary individuals (n=30) to better understand how they understand and experience participation in HIV-related stigma research, including willingness to respond to questions about stigma and factors that may contribute to or mitigate potential distressing or stigmatizing experiences within the research context. Second we will conduct in-depth interviews with 2 groups: investigators who conduct HIV-related stigma research with transgender and nonbinary individuals, to better understand perceptions of and experiences with conducting stigma research with transgender and nonbinary individuals and compile existing strategies for mitigating harm (n=15) and mental health professionals (n=15) who provide care to transgender and nonbinary individuals to better understand ways in which experiences of stigma can be measured and studies can be conducted in a manner that is person-centered, trauma-informed, and actively destigmatizing. Third, we will develop a set of empirically informed guidelines for conducting HIV stigma research with transgender and nonbinary individuals. We will use a modified Delphi technique to engage a panel of transgender and nonbinary individuals, mental health providers, and researchers in a consensus building process to identify practical recommendations for person-centered, trauma-informed recruitment, measurement, and conduct of HIV-related stigma research with transgender and nonbinary individuals.

The sample sizes for this study were designed to ensure robust data collection and meaningful analysis across all phases. For aims 1 and 2, the sample size was chosen based on recommendations for similar qualitative inquires to ensure thematic saturation and demographic diversity [66-69]. In aim 3 the Delphi panel will consist of 75 participants (25 transgender and nonbinary individuals, 25 researchers, and 25 clinicians), aligning with best practices for achieving reliable consensus and providing robustness against attrition [68,70,71]. These sample sizes ensured methodological rigor, demographic representativeness, and the capacity to develop empirically informed, trauma-informed research guidelines.

Qualitative Interviews

Aim 1: Semistructured Qualitative Interviews With Transgender and Nonbinary Individuals

Overview

In aim 1, we will conduct a series of in-depth semistructured qualitative interviews with 30 transgender and nonbinary individuals.

Participants

Our sample will be stratified by gender identity and HIV status. We will ensure that >40% of participants will be aged 18-29 years and at least 70% people of color, due to the disproportionately high HIV infection rates among these populations and lack of access to HIV prevention and treatment services. Eligible participants will be aged >18 years; identify as transgender, nonbinary, or gender diverse; and have participated in an HIV prevention or treatment related research study.

Recruitment

Participants will be recruited through existing research panels, transgender health-related social media and listservs, and word of mouth. Interested participants will fill out an eligibility screener survey. For those who are deemed eligible, they will be provided a link to the study website [72] to schedule their interview at a day and time of their choice, with the study team member of their choice. Participants will be provided with a link to an electronic consent form on the study website, as well as the interview guide before the interview. The interviewer will review the consent form with the participant and obtain verbal consent before conducting the interview.

Interview Procedures

Interviews will be designed to last no longer than an hour and a half, and participants will be compensated US $80 for their time. All interviews will contain a core set of questions to assess how transgender and nonbinary individuals understand and experience participation in HIV-related stigma research, including decision-making processes around participation, perceptions of study purpose, risks and benefits, participants' willingness to respond to questions on stigma, factors that may contribute to or mitigate potential distressful or stigmatizing experiences within the research context, and opinions of the research after participation. Participants will also be asked to identify specific strategies to enhance researcher's capacity to design and implement stigma research that is person-centered, trauma-informed, and actively destigmatizing.

Aim 2: Semistructured Qualitative Interviews With Researchers and Mental Health Professionals

Overview

In aim 2, we will conduct a series of in-depth semistructured qualitative interviews with 2 groups, investigators who conduct HIV-related stigma research with transgender and nonbinary individuals (n=15) and mental health providers who provide care to transgender and nonbinary adults (n=15).

Participants

Investigators (n=15) will be stratified by career stage: early (n=5), middle (n=5), or late (n=5) stage investigators to represent a range of perspectives and experiences with conducting stigma research with transgender and nonbinary individuals. Our sample of mental health professionals (n=15) will include mental health clinicians with a master's degree in either social work, marriage and family therapy, or mental health counseling or a doctoral degree in clinical psychology (PhD or PsyD) who provide individual or group therapy to transgender and nonbinary adults (aged 18 years or older) and have training in providing trauma-specific or trauma-informed clinical practice.

Recruitment

Early, middle, or late-stage investigators with existing HIV-related transgender health research will be identified by Google Scholar and the National Institutes of Health (NIH) RePORTER. Investigators will be contacted by a study team

member by email and invited to participate in our study. Mental health professionals will be recruited through professional networks and word of mouth. Interested participants will fill out an eligibility screener survey. For those who are deemed eligible, they will be contacted by a study team member to schedule their interview. Participants will be provided with a copy of the study consent form. The interviewer will review the consent form with the participant and obtain verbal consent before conducting the interview.

Interview Procedures

Aim 2 will consist of 30 semistructured interviews with 2 groups, investigators who conduct HIV-related stigma research with transgender and nonbinary and mental health clinicians who provide counseling to transgender and nonbinary adults (aged 18 years or older). Interviews are designed to last no more than an hour and a half, and participants will be compensated US $50 for their time. *Interviews with investigators* will assess understanding experiences of conducting HIV-related stigma research with transgender and nonbinary individuals, including perceptions of study purpose, risks and benefits, question and measurement selection and creation, and factors that may have contributed to or mitigated against distressful or stigmatizing experiences within the research context. *Interviews with mental health professionals* will focus on identifying ways in which experiences of stigma can be measured in a manner that is person-centered, trauma-informed, and actively destigmatizing, including suggestions for using person-centered, trauma-informed language when developing questions or measures, and strategies to assist researchers around developing protocols and procedures to assess for and address potential distressful situations within the research context.

Development of Interview Guide (Aims 1 and 2)

The interview guide was developed through a collaborative, trauma-informed approach to ensure that all protocols and procedures reflected the study's goals and minimized potential harm to participants. This process involved a 3-step methodology with the transgender-identified research team. First, the team conducted an in-depth review of existing trauma-informed care models and adopted the framework developed by The Institute on Trauma and Trauma-Informed Care (ITTC) at the University of Buffalo, which emphasizes the principles of safety, choice, empowerment, collaboration, and trustworthiness. Second, components from ITTC's Trauma-Informed Organizational Change Manual [73] were adapted and integrated into the research procedures, including participant recruitment, consent, interview data collection, and analysis, to align all research activities with a trauma-informed approach. Third, the interview questions, prompts, and scripts were mapped to the ITTC framework to minimize risks of retraumatization and ensure a supportive environment for participants. Interview questions were refined to align with the study's 4 overarching research questions and tailored to the perspectives of the 3 participant groups, researchers, community stakeholders, and mental health clinicians, ensuring comparability and analytic integrity across the study phases (Multimedia Appendix 1).

Qualitative Analysis Plan (Aims 1 and 2)

Data collected in aims 1 and 2 will be analyzed using rapid qualitative analytic methods, [74-77] to identify key themes that best reflect the research decision-making process, perceptions and experiences of transgender and nonbinary individuals. We will assign four trained team members to summarize a subset of the interview transcripts independently, extracting key data into a summary template based on our framework and interview guide; triangulate key themes in the transcript through documenting observations, quotations, and reflections into the summary template; meet to compare and combine templates for each interview; and create a comprehensive matrix identifying common themes and contrasts across and within stakeholder groups.

Application of Knowledge Gained in Aims 1 and 2 to Aim 3

In preparation for aim 3, we will use the themes that were identified in the qualitative interviews to develop a preliminary list of survey items for use in the first stage of the modified Delphi process (aim 3) [78]. The use of qualitative interviews in a pre-Delphi phase [78-80] allows for all relevant stakeholder groups to guide the Delphi process by contributing to the development of the first round Delphi survey. To ensure that the Delphi survey items describe and capture the perceptions and experiences of all the stakeholder groups participating in aim 3, we will develop items using the language and narratives participants use during their interviews [78,80,81]. For example, the language used to describe and the meaning behind core concepts within stigma research may differ distinctly between stakeholder groups and could contribute to inaccurate measurement and interpretation of research findings. By integrating language from each stakeholder group into the Delphi survey we hope to better reflect the experiences of all relevant stakeholders involved in this process [79,82,83]. We will then compare the themes and associations derived from Aims 1 and 2 to better understand areas of concordance and discordance between stakeholder groups [78-81,84]. For example, it is possible that interview findings highlight similar domains across participant groups that are key to understanding and improving stigma research procedures, yet what is important to address within these domains may differ by stakeholder group. The use of qualitative interview findings will help further parse out and include survey items that address this complexity.

Aim 3: Development of Empirically Informed Guidelines for Conducting Stigma Research With Transgender and Nonbinary Individuals

Overview

To accomplish aim 3 we will use a 3-round modified Delphi method [85] to develop a set of empirically informed guidelines for conducting HIV-related stigma research with transgender and nonbinary individuals. The modified Delphi method will include 4 structured steps: panel formation, quantitative survey development, data collection and analysis, and guideline development [68,69,85,86].

Panel Formation

We will recruit 75 participants from the following 3 stakeholder groups, transgender and nonbinary individuals (n=25), researchers (n=25), and mental health professionals (n=25). Our sample size is based on previous studies which demonstrate that this sample size provides stable results robust to participant attrition or inconsistent responding [68,70,71]. Individuals who participated in aims 1 and 2 will be recruited to participate in aim 3.

Survey Development

Survey development will occur in 3 steps. First, the transcripts and codes from aims 1 and 2 will be reviewed to draft the initial survey items based on the most salient themes and domains pertinent to all aspects of the research process, including recruitment, measurement, retention, and dissemination. Each survey item will be designed to capture a single idea and be easily understood by participants. Second, we will develop a rating scale for the Delphi survey items that best capture the original content from aims 1 and 2. Third, we will finalize the items and organize the survey into the following 3 sections, Trauma-Informed Principles for Research Practice, Trauma-Informed Research Standards, and Trauma-Informed Research Competencies.

Quantitative Data Collection and Analysis

A survey will be administered online by REDCap (Research Electronic Data Capture) [87,88] at 3 time points (rounds 1-3). Participants will be compensated US $40 for their time after the completion of each survey. In each round, participants will be asked to rate each item on a 5-point scale indicating whether the item should be included in the research guidelines. Survey items will be categorized according to the decision matrix in Textbox 1, which has been widely used in previous studies [85,86]. In round 1, all items created by our study team will be included in the survey. At the end of each survey section in round 1, participants will be encouraged to provide feedback on items (ie, how to improve wording or messaging) and suggest novel items to include [68,85,86]. After round 1, we will analyze survey responses, including participant comments, and edit existing or draft new items to be included in the round 2 survey based on participant suggestions. In the second-round survey, participants will rerate items that receive a near miss in the first round and rate new items the research team crafted based on suggestions from participants in round 1. At the end of rounds 1 and 2, participants will be sent a report outlining survey results. Statements to be rerated will be displayed with the overall percentages for each rating and then by stakeholder group so participants can compare their response with others' responses. The report will allow participants to consider whether to retain or change their ratings in the next round. Finally, in round 3, only items rated for the first time in round 2 or received a near miss rating will be included in the final survey (Textbox 1).

Textbox 1. Decision matrix for developing expert consensus.

Endorsed

- If between 80%-100% of participants of each group rate a statement as either essential or important, it will be endorsed as a guideline.

Re-rated (near miss)

- If between 80%-100% of participants of each group rate a statement as either essential or important, it will be endorsed as a guideline.

Rejected

- If none of the above conditions are met, a statement will be rejected for inclusion as a guideline.

Guideline Development

At the end of round 3, the research team will create a document comprised of the endorsed items to be widely disseminated. Once the document is completed, participants will be invited to attend a 1-day virtual convening where we will present and discuss the final guidelines document as well as the goals and next steps for dissemination and implementation.

Ethical Considerations

Ethics Approval

The study received expedited approval from the City University of New York Human Research Protection Program (#2022-0280-Hunter).

Informed Consent

Participants were electronically sent a consent form and interview guide in advance to review at their own pace once their interview was scheduled. Before the start of each interview a trained study team member reviewed the consent form with participants and obtained verbal consent to participate. Before completing the Delphi survey participants affirmed that the agreed to participate.

Privacy and Confidentiality

All data were anonymized to protect participant identities.

Compensation

Participants were compensated US $40- US $80, depending on the study phase, to ensure fairness.

Results

The study was funded by the National Institute of Mental Health from July 1, 2022, to June 30, 2024. The study successfully achieved its specific aims. We successfully completed data collection and analysis for aims 1 and 2 recruiting 30

transgender and nonbinary participants (aim 1) and a total of 34 participants in aim 2 (17 researchers and 17 clinicians). As outlined above, we directly applied the knowledge gained to the development of the preliminary set of guidelines voted on in aim 3. The Delphi process for aim 3 is entering its final survey round, and we are actively preparing the finalized guidelines for dissemination (Table 1).

Table 1. Study timeline and progress by aims.

Phase	Planned timeline	Current progress
Aim 1: interviews	January 2023-June 2023	Completed (30 participants)
Aim 2: interviews	July 2023-December 2023	Completed (34 participants)
Application of knowledge gained from aims 1 and 2	January 2024-March 2024	Completed
Aim 3: Delphi survey	March 2024-June 2024	Ongoing (final survey round)

Discussion

Principal Findings

This study addresses a critical gap in HIV-related stigma research by developing trauma-informed guidelines to improve the quality of research involving transgender and nonbinary individuals. HIV stigma research has historically documented the pervasive role of stigma in shaping health inequities but has largely overlooked the unintended harms participants may experience within the research process itself. By using an interdisciplinary, trauma-informed approach grounded in qualitative data collection and a modified Delphi method, this study emphasizes principles of safety, trustworthiness, collaboration, empowerment, and cultural sensitivity. The findings aim to enhance participant engagement, reduce emotional distress, and improve data quality, thereby advancing ethical and effective research practices. Through active collaboration with community members, researchers, and clinicians, this project provides a model for addressing stigma while centering participant well-being and resilience.

The study's findings underscore the critical importance of adopting a trauma-informed approach to HIV stigma research with transgender and nonbinary individuals. Interviews with community members, researchers, and clinicians revealed the significant benefits of trauma-informed principles for enhancing participant trust, retention, and engagement while also improving the quality of collected data. Key findings include the following.

Higher Data Quality and Participant Engagement

Stakeholders across all groups emphasized that trauma-informed practices create safer and more supportive environments for participants, leading to more honest and comprehensive data. For instance, researchers noted that flexible interview formats and clear communication protocols increased participant willingness to share sensitive information.

Improved Team Dynamics and Research Outcomes

Researchers and clinicians reported that adopting trauma-informed principles, such as trustworthiness and collaboration, not only benefits participants but also enhances team cohesion and efficiency in implementing study protocols.

Ethical and Methodological Standards

The findings contributed to the development of trauma-informed research standards, including guidelines for ethical recruitment, harm minimization, and culturally sensitive data collection protocols. These standards prioritize participant autonomy and recognize the compounded effects of intersecting identities, such as race, gender, and sexual orientation.

Institutional Support Needs

Participants consistently highlighted the necessity of institutional support for implementing trauma-informed practices. Recommendations include increased funding, researcher training, and revisions to institutional review board protocols to ensure systemic integration of these practices into research frameworks.

Guidelines for Trauma-Informed Research

Preliminary guidelines developed through this study emphasize the integration of trauma-informed principles into every aspect of the research process. These include ensuring safety and dignity, using affirming language, and providing participants with opportunities for feedback and choice throughout their involvement in studies.

The findings collectively highlight the transformative potential of trauma-informed approaches for improving HIV stigma research practices. By addressing participant needs and mitigating harm, these practices ensure ethical rigor and enhance the impact of research on health equity for transgender and nonbinary populations.

Comparison to Previous Work

Previous research on HIV stigma has predominantly focused on documenting stigma and its health impacts without critically examining research practices themselves. Our study extends the NIH's Stigma and Discrimination Toolkit [89] by addressing the need for guidelines to reduce stigma within the research context. This complements existing frameworks and fills a critical gap. By focusing on the process rather than outcomes alone, this research provides a novel contribution to the field.

Strengths and Limitations

The study's strengths include a diverse, multidisciplinary research team with significant community representation, innovative use of the Delphi method, and the integration of trauma-informed principles. Limitations include the absence of a bioethicist on the team and potential challenges in generalizing findings to other populations beyond transgender and nonbinary individuals. Future research could explore the applicability of these guidelines in other contexts and populations.

Future Directions

Key next steps include developing researcher training modules and advocating for institutional review board and institutional policies that mandate trauma-informed practices. These guidelines could extend to other areas of health inequities research.

Dissemination Plan

This study prioritizes transparency and community engagement in disseminating findings. The dissemination plan aligns with trauma-informed principles by emphasizing accessibility, mutuality, and collaboration with the community and stakeholders.

Community-Focused Dissemination

A dedicated study website was created to provide participants and stakeholders with clear and accessible information about the study aims, process, and team. This platform has been instrumental in sharing updates, progress, and findings during the study period.

Two newsletters were distributed to participants and posted on the website to update stakeholders about study progress and preliminary findings. These newsletters ensured continuous engagement with the community and maintained trust.

Final study findings will be summarized in community-friendly formats, such as infographics and plain-language reports, and shared through newsletters and the website. This ensures that findings are accessible to diverse audiences, including those with varying levels of education and technical expertise.

Academic and Professional Dissemination

Findings have been shared at national and international conferences, ensuring visibility within academic and professional circles. Future presentations will focus on engaging institutional review boards, research institutions, and policy makers.

The trauma-informed research guidelines will be published in academic journals and policy briefs, targeting audiences involved in HIV research, social work, and public health.

Workshops and webinars will be conducted for researchers and community health organizations to facilitate the implementation of the guidelines. These sessions will provide practical strategies for adopting trauma-informed practices.

Collaborative Dissemination

The final guidelines will be shared during virtual or in-person gatherings with study participants and community members. These sessions will include opportunities for participants to provide feedback and discuss the next steps for implementation.

Findings will be disseminated through partnerships with community-based organizations and health centers. This approach ensures that the guidelines reach the people and institutions directly involved in HIV stigma research and care.

Sustainability and Long-Term Impact

Recommendations for integrating trauma-informed practices into institutional review board review processes, funding applications, and researcher training will be disseminated to key institutions. This will include targeted briefings and resource-sharing with institutional review boards and funders to encourage systemic change.

Training materials, including video tutorials and toolkits, will be developed to help researchers and institutions adopt the guidelines. These materials will be shared through academic and community networks. By using these dissemination strategies, this study aims to ensure that its findings are accessible, actionable, and impactful across diverse audiences, including researchers, policy makers, and the communities at the center of the research.

Conclusion

To make meaningful strides in stigma research, it is imperative to examine experiences of stigma within the research context and identify strategies to improve data quality while reducing unintentional harm in study recruitment, methodology, implementation, and dissemination. This study addresses these critical needs by developing empirically informed trauma-informed guidelines for conducting HIV-related stigma research with transgender and nonbinary individuals.

Grounded in interdisciplinary theoretical frameworks and extensive collaboration with transgender and nonbinary participants, researchers, and clinicians, this study highlights the transformative potential of trauma-informed approaches. These guidelines emphasize the principles of safety, trustworthiness, collaboration, empowerment, and cultural sensitivity, demonstrating their capacity to enhance participant engagement, foster trust, and mitigate risks of retraumatization. Findings further underscore the importance of systemic institutional support, including training programs, funding mechanisms, and policy revisions at the institutional level, to ensure the widespread adoption of these practices.

The study achieved its goals by developing and refining these guidelines through rigorous qualitative analyses and a modified Delphi process. By embedding trauma-informed principles into research methodologies, this work sets a new standard for ethical and effective research practices. These guidelines have the potential to increase researchers' capacity to recruit and retain transgender and nonbinary participants in stigma research, improve the quality of collected data, and reduce the unintended harms of research participation.

Next steps include broad dissemination of the guidelines through community-friendly formats, workshops, and academic publications. These efforts will ensure that the findings are accessible to a diverse range of stakeholders, including researchers, clinicians, policy makers, and community organizations. By reshaping HIV stigma research methodologies, this work contributes to advancing health equity and ethical research practices, with implications for other high-priority populations and fields of health disparity research.

Acknowledgments

The authors wish to thank Alexander Harris, Amiyah Guerra, Lila Starbuck, and Ash Smith for their assistance with study administration and data collection. This study is funded by the National Institute of Mental Health (R21MH131477). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Data Availability

The datasets generated during and analyzed during this study are not publicly available to protect the identity of the participants, as some of the details mentioned in the qualitative interviews include information that could help identify the individual. Data are available from the corresponding author on reasonable request.

Authors' Contributions

AK contributed to conceptualization, methodology, writing original draft, writing review and editing, supervision, and funding acquisition. SAG managed methodology, writing review and editing, supervision, and funding acquisition. DB handled methodology and writing review and editing. ERC contributed to writing review and editing, project administration.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Interview guide for Aims 1 and 2 by participant group.
[DOCX File , 480 KB - resprot_v14i1e66800_app1.docx]

Multimedia Appendix 2
Peer-reviewer report from HIV/AIDS Intra- and Inter-personal Determinants and Behavioral Interventions Study Section, Risk, Prevention and Health Behavior Integrated Review Group (HIBI) (National Institutes of Health, USA).
[PDF File (Adobe PDF File), 143 KB - resprot_v14i1e66800_app2.pdf]

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Abbreviations

ITTC: Institute on Trauma and Trauma-Informed Care
NIH: National Institutes of Health
REDCap: Research Electronic Data Capture

Edited by A Schwartz; submitted 23.09.24; this is a non–peer-reviewed article;accepted 09.12.24; published 06.01.25.

Please cite as:
Klein A, Golub SA, Berke D, Castle E
Developing Guidelines for Conducting Stigma Research With Transgender and Nonbinary Individuals: Protocol for Creation of a Trauma-Informed Approach to Research
JMIR Res Protoc 2025;14:e66800
URL: https://www.researchprotocols.org/2025/1/e66800
doi:10.2196/66800
PMID:

Protocol

Cardiometabolic Health Intervention Using Music and Exercise (CHIME) Delivered via Telehealth to Wheelchair Users: Protocol for a Randomized Controlled Trial

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Abstract

Background: Wheelchair users live predominantly sedentary lifestyles and have a substantially higher risk for cardiometabolic disease and mortality compared to people without disabilities. Exercise training has been found to be effective in improving cardiometabolic health (CMH) outcomes among people without disabilities, but research on wheelchair users is limited and of poor quality.

Objective: The primary aim of this study is to examine the immediate and sustained effects of a 24-week, telehealth, movement-to-music cardiovascular (M2M-C) exercise program on core indicators of CMH among adult wheelchair users compared to an active control group. The secondary aim is to explore the beneficial effects of M2M-C exercises on cardiovascular capacity, physical activity, and quality of life. Intervention components include tailored exercises and remote performance monitoring, delivered via live videoconference training by a telecoach and asynchronous videos.

Methods: This study's design is a parallel-arm randomized controlled trial enrolling 132 physically inactive adult wheelchair users with poor cardiometabolic profiles. The M2M-C intervention group involves 24 weeks of virtual live and monitored home exercise training (3×/wk, 15-40 min/session), followed by a 12-week maintenance period where participants have access to an online media library of exercise videos. The control group involves 36 weeks of self-guided exercise through access to a media library of exercise videos, including videos for range of motion, muscle strength, and balance. The primary outcomes are cardiometabolic indicators of health, and assessors are blinded.

Results: Recruitment procedures started in January 2024 with the first participant enrolled on March 18, 2024. All data are anticipated to be collected by November 2027, and the main results of the trial are anticipated to be published by February 2028. Secondary analyses of data will be subsequently published. A total of 16 participants have been recruited as of paper submission.

Conclusions: The knowledge obtained from this trial will provide evidence to inform exercise prescriptions aimed at improving CMH among adult wheelchair users.

Trial Registration: ClinicalTrials.gov NCT05606432; https://clinicaltrials.gov/study/NCT05606432

International Registered Report Identifier (IRRID): DERR1-10.2196/57423

(JMIR Res Protoc 2025;14:e57423) doi:10.2196/57423

KEYWORDS

exercise; physical activity; wheelchair user; telehealth; disability

Introduction

Background

People with physical disabilities have higher risks of cardiometabolic disease than the general population. For example, studies have reported that as many as one-third of people with spinal cord injury (SCI) may be diagnosed with cardiometabolic disease (ranging from n=41, 29% to n=222, 34.1%), which is nearly twice as prevalent as reported in people without SCI [1-3]. Another study found that adults living with cerebral palsy or spina bifida are 52% more likely to experience any type of cardiometabolic morbidity than adults without cerebral palsy or spina bifida (n=15,302) [4]. Meta-analyses have demonstrated that conventional aerobic exercise, such as running, walking, and cycling at a moderate-to-vigorous intensity, are effective in managing indicators of cardiometabolic health (CMH) in the general population [5-9]. However, people with physical disabilities, particularly wheelchair users, are typically unable to engage in conventional modalities of exercise long enough to obtain CMH benefits. Wheelchair users include users of any wheeled devices for their primary means of mobility, such as manual and powered wheelchairs or motorized scooters, and may include individuals in a variety of disability groups, including those with SCI, cerebral palsy, spina bifida, multiple sclerosis, or limb loss. A total of roughly 5.5 million wheelchair users in the United States would benefit from an accessible aerobic exercise program to reduce their cardiometabolic disease risk [10].

However, there is limited evidence that aerobic exercise improves CMH among wheelchair users. Most evidence is observational and nearly all randomized controlled trials (RCTs) have small sample sizes limited to a single population (eg, those with SCI). There are no large confirmatory RCTs that demonstrate that aerobic exercise improves CMH in adult wheelchair users. A recent meta-analysis of 3 RCTs, with samples of 15-21 adults with SCI, determined that 6-weeks of aerobic exercise improved CMH among adults with SCI (ie, decreased fasting glucose and insulin and increased fasting high-density lipoprotein cholesterol fraction) [11]. Another meta-analysis of 16 pre-post and controlled trials with sample sizes of 5-20 adults with SCI determined that vigorous exercise training improved cardiorespiratory fitness in adults with SCI [12] (ie, increased peak power output, muscular strength, and time to fatigue) but did not improve CMH risk factors, such as blood pressure (BP), cholesterol, and insulin sensitivity. Noted limitations of these studies included small sample sizes, inclusion of participants already within healthy ranges for CMH at baseline, lack of a control group, use of laboratory-based training, and inclusion of a single population (those with SCI). Therefore, the finding that CMH measures did not improve must be interpreted with caution.

Interventions that have sought to improve physical activity levels have also failed to improve CMH among wheelchair users. The largest physical activity trial among wheelchair users (n=128), Workout on Wheels, increased self-reported physical activity by 17 min/wk, with no significant between-group differences in cardiorespiratory fitness or CMH measures [13]. Other recent lifestyle interventions (eg, behavioral coaching) have similarly failed to elicit significant CMH benefits among people with disabilities, even while achieving large sample sizes [14]. Thus, the exercise doses or intensity studied may be suboptimal for improving CMH among people with physical disabilities. Despite failures to improve CMH, many of these physical activity trials have informed the creation of the most recent guideline related to CMH for people with SCI [15,16]. Collectively, there is an urgent need for well-designed interventions that can provide an effective exercise dose for people with disabilities, including wheelchair users, while obtaining evidence for improving CMH through physical activity.

Rationale for Telehealth Exercise Program

A telehealth exercise program was developed to overcome the barriers of participation in exercise requiring individuals to leave their homes and use expensive equipment. This study uses an exercise program that includes various movement patterns that are coupled with elements of music and imagery, referred to as movement to music (M2M) [17]. The M2M program uses a range of different muscle groups allowing for a safer form of exercise than arm ergometry. Moreover, M2M incorporates a theory-driven telehealth delivery protocol that removes the most common barriers to participation in community and clinical exercise training studies (ie, cost, transportation, and time) [18,19]. The design of the movement-to-music cardiovascular (M2M-C) intervention is based on four key elements of social cognitive theory: self-efficacy, self-regulation, outcome expectations, and social support. These components are essential for promoting positive health behavior change. To effectively integrate these principles, the M2M-C program provides a structured, individualized, and progressively challenging exercise routine. Participants receive regular feedback and personalized guidance from M2M-C instructors and telecoaches, which helps build confidence and maintain motivation. In addition, the incorporation of music enhances movement quality and motor coordination [20] while serving as a powerful motivational tool [21]. By increasing enjoyment and improving mood, music makes exercise more appealing and engaging. This approach is consistent with the broader goal of promoting sustained physical activity among wheelchair users by addressing both psychological and physical barriers to exercise adherence.

To test whether the M2M program can improve CMH outcomes among wheelchair users, this study uses a parallel-group RCT with blinded assessors. The intervention group will use the M2M program, composed primarily of cardiovascular exercises (M2M-C), which will be compared to an active control condition using prerecorded non-M2M exercise videos. The M2M-C exercises were informed by disability exercise guidelines and reviews of relevant studies [22]. This study is referred to as the Cardiometabolic Health Intervention Using Music and Exercise

(CHIME) study. The primary aim is to examine the effects of a 24-week, synchronous M2M-C program on core indicators of CMH in adult wheelchair users with ≥2 cardiometabolic risk factors. The secondary aim will explore the beneficial effects of M2M-C exercises on cardiovascular capacity, physical activity, and quality of life. We hypothesize the M2M-C intervention will yield both immediate and sustained CMH outcomes among adult wheelchair users with poor cardiometabolic profiles.

Methods

Study Design

This study's protocol follows the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) guidelines [23,24].

Aims and Design of this Study

This study's design includes three aims. The primary aim examines the immediate effect of a 24-week, synchronous M2M-C training protocol compared to a 24-week, asynchronous activity control on core indicators of CMH among 132 adult wheelchair users with ≥2 cardiometabolic risk factors. The secondary aim examines the immediate effect of M2M-C training compared to the active control condition on cardiovascular capacity, physical activity, and quality of life. The first tertiary aim evaluates the sustained effects of M2M-C training (24 to 36 wk) on physical activity participation. A second tertiary aim evaluates the potential response heterogeneity in CMH, cardiovascular capacity, and physical activity outcomes using prespecified moderator variables (eg, age, sex, body composition, diet, or ethnicity) to understand for whom the intervention is most effective.

This study's aims will be tested using a parallel-group, assessor-blinded RCT design. For primary and secondary aims, we hypothesize that a telehealth M2M-C program will lead to significantly greater improvements in CMH outcomes, peak oxygen consumption (VO_{2peak}), physical activity level, and quality of life from baseline to 24 weeks compared to controls. For the tertiary aim 1, we hypothesize that M2M-C participants will maintain physical activity levels from week 24 to week 36.

Participants

Recruitment

We are recruiting participants who receive health care from a large medical center residing in the southern United States through direct referrals from health care professionals (eg, physicians or therapists) and distribution of study materials (eg, flyers, newsletters, or advertisements) to various clinics, hospitals, and medical rehabilitation service providers.

Eligibility Criteria

Adult wheelchair users who do not participate in health-enhancing volumes of exercise [16] and have ≥2 cardiometabolic risk factors are recruited for this study. Potential participants are prescreened for the eligibility criteria via telephone screening, medication list review, and physical screening. The onsite, physical screening to confirm eligibility occurs in the baseline visit.

Textbox 1 lists the specific participant eligibility criteria. Participants undergo a 2-stage screening process. The first stage, eligibility screening, is undertaken during a scripted phone screening by the project coordinator. The presence of CMH risk factors [25] is initially screened based on the self-reported height and weight to estimate the BMI and waist circumference, as well as the physician-prescribed medications that are relevant to CMH risk factors (eg, are you taking any medications related to increased BP? Has your doctor ever expressed concerns about your cholesterol level?).

Textbox 1. Inclusion and exclusion criteria.

Inclusion criteria

- Full-time or part-time use of a wheelchair device (manual wheelchair, power wheelchair, or electric scooter) self-reported as the primary means of mobility
- Aged ≥18 years
- Able to use arms to exercise
- Obtaining <90 minutes of moderate-to-vigorous intensity exercise per week in the last month
- ≥2 cardiometabolic risk factors:
  - Elevated waist circumference: ≥102 cm in men and ≥88 cm in women
  - Elevated triglycerides: ≥150 mg/dL
  - Reduced high-density lipoprotein cholesterol fraction: <40 mg/dL in men, <50 mg/dL in women
  - Elevated blood pressure (BP): ≥130 mm Hg systolic BP or ≥85 mm Hg diastolic BP
  - Elevated fasting glucose: ≥100 mg/dL
- No contraindication to participate in moderate-to-vigorous intensity exercise as informed by physician's medical clearance for exercise
- Not currently participating in a structured exercise program
- Able to converse and read in English

Exclusion criteria

- Medically unstable to perform the prescribed home exercise as determined by their physician
- High-level tetraplegia and unable to use arms to exercise
- No internet access was determined via self-report and internet speed test
- Positive pregnancy test
- Other physical conditions that can potentially prevent them from participating in an exercise routine (eg, pressure sore and open wound)

Justification for exclusion criteria

- Exclusion of pregnant individuals: The use of dual-energy x-ray absorptiometry for body composition analysis involves minimal radiation exposure. However, to eliminate any potential risk to the fetus, pregnant individuals will be excluded.
- Exclusion of individuals with medical instability: To minimize the risk of adverse events during the intervention, participants must be medically stable and have clearance from a health care provider to engage in moderate-to-vigorous intensity exercise.
- Internet access requirement: As the intervention is delivered via a tele-exercise platform, participants must have reliable internet access to ensure they can fully engage in the program, participate in live sessions, and receive remote monitoring and feedback.

The second screening stage involves a review of participation medications (self-reported) and a physical examination by laboratory staff. The medication list is obtained before the baseline visit using a secure electronic survey, and this study's staff reviews and verbally confirms them during the baseline visit. If the potential participants currently take ≥2 medications related to CMH risk factors, then they can proceed to the baseline physical examinations. Otherwise, they proceed to physical screening in the following order: manual BP, tape-measured waist circumference, and fingerstick blood sampling for triglycerides, high-density lipoprotein cholesterol fraction, and glucose using the lipid analyzer (Cholestech LDX, Abbott). If the potential participants meet the eligibility criteria with BP and waist circumference, fingerstick blood sampling is omitted.

Ethical Considerations

Ethical approval for this study was obtained from the University of Alabama at Birmingham Institutional Review Board on December 22, 2022 (IRB-300009718). This study's protocol adheres to all relevant ethical guidelines for research involving human participants, including medical records and patient information.

Informed consent will be obtained from all participants before the baseline visit or during the baseline visit. During the consent process, participants will receive detailed instructions about this study, including its objectives, procedures, potential benefits, and any associated risks or discomforts. They are also informed of their rights, including the ability to withdraw from this study at any time, to ensure that their participation is completely voluntary. This comprehensive approach is designed to ensure that all participants fully understand this study before providing their consent.

To protect participants' privacy, all data collected will be anonymized by assigning each participant with a study number to ensure that no personally identifiable information is directly linked to the data. Demographic, personal, and exercise test

data will be securely stored in REDCap (Research Electronic Data Capture; Vanderbilt University) and Box (Box, Inc), which are secure, password-protected databases. Access to these data will be limited to authorized research personnel, and all information obtained during this study will be used for research purposes only.

Participants will receive up to US $830 for their participation in this study. Compensation will be provided in stages, with participants receiving US $150 at the baseline assessment, US $200 at the 12-week assessment, US $250 at the 24-week assessment, and US $150 at the 36-week assessment. In addition, participants will receive US $40 for each of the two interview sessions to ensure fairness and transparency in recognition of their time and effort.

Power Analysis and Sample Size

We plan to recruit 132 participants into this study (66 per treatment group), with the expectation that at least 100 (50 per group) will complete this study. We anticipate an attrition rate of 23% based on the average attrition rate between the largest home-based behavioral interventions among wheelchair users (33%) [13] and our scoping review of exercise trials for people with various disabilities (13%) [14]. Due to the nature of the proposed exercise training involving one-on-one training and supervision, we believe that the role of exercise training coaches in this study will lead to lower attrition rates as it has in our past studies [26].

Power calculations were performed using nQuery (version 8.5; Statsols). For the primary outcome of CMH, we obtained SDs of biomarkers of this outcome from our pilot study among individuals with SCI (6-wk arm crank exercise training), including SDs of 43 mg/dL for total cholesterol, 4.3% for body fat, and 22.4 mg/dL for triglycerides [27]. Assuming a final sample size of 50 participants per group, a 2-sided 2-group *t* test (2-tailed), and a significance level of .05, we will have at least 80% power to detect differences of 24.4 mg/dL for total cholesterol, 2.5% for body fat, and 12.7 mg/dL for triglycerides (and greater) between the intervention and control groups as being statistically significant. This is equivalent to detecting an effect size (Cohen *d*) of 0.566 (a moderate effect size) as statistically significant between the two groups.

Outcomes

Outcomes are assessed at baseline, midintervention (12 wk), postintervention (24 wk), and follow-up (36 wk) time points. Physiological outcomes are assessed by anonymous-to-treatment assessors. The assessors are not involved in random assignment or the intervention delivery and do not directly communicate with the M2M instructors and assistant health coaches about participants. Data collection with physiological outcomes is conducted at a local research facility affiliated with a major medical center. Self-reported outcomes are administrated via a secure electronic database, referred to as REDCap. Online platform analytics are used to assess heart rate (HR) and video minutes viewed and stored in the cloud. Figure 1 shows the schedule of assessments.

Figure 1. Example template of recommended content for the schedule of enrollment, interventions, and assessments. CMH: cardiometabolic health; M2M-C: movement-to-music cardiovascular; SET: standard exercise training.

	Study period					
	Enrollment	Allocation	Postallocation			Closeout
Time point	$-t_1$ (Week -2)	0 (Week 0)	t_1 (Week 1)	t_2 (Week 12)	t_3 (Week 24)	t_x (Week 36)
Enrollment:						
Eligibility screen	X					
Informed consent	X					
Allocation		X				
Interventions:						
M2M-C training			←	—	→	
SET control			←	—	→	
Assessments:						
CMH blood specimen or pressure	X			X	X	
Body composition	X			X	X	
Cardiovascular capacity	X			X	X	
Pulmonary function	X			X	X	
Grip strength	X			X	X	
Self-reported physical activity	X			X	X	X
Self-reported health	X			X	X	X
Exercise behavior	X			X	X	X
Self-reported diet	X			X	X	X
Exercise enjoyment or satisfaction				X	X	
Intervention analytics			X	X	X	X

Primary Outcome Measures

CMH outcomes are assessed via venipuncture blood specimen, brachial cuff BP, and body composition.

- High sensitivity C-reactive protein (hsCRP; mg/L): hsCRP is a critical marker of inflammation that contributes to proinflammatory and prothrombotic elements of cardiovascular risk. A single hsCRP measure is a strong predictor of myocardial infarction or coronary heart disease mortality and several other diseases of the circulatory system in people without a history of such conditions [28]. Changes in hsCRP may occur from as early as 8 weeks of exercise [29].
- Hemoglobin A1c (HbA1c, mmol/mol): HbA1c is a measure of red blood cell mean hemoglobin glycation over the previous 3 months. Exercise interventions without a dietary

component should yield a small to moderate effect on HbA1c after a month of training [30].

- Fasting insulin (μIU/mL): A high fasting insulin level indicates the presence of insulin resistance and whether an individual shows glucose intolerance. Exercise interventions without a dietary component should yield a small beneficial change in fasting insulin levels after a month of training [30].
- Fasting glucose (mmol/L) and homeostatic model assessment of insulin resistance: This is calculated as [fasting insulin (μU/mL) × fasting glucose (mmol/L)]/22.5 [31].
- Fasting triglycerides (mg/dL): A triglyceride level >150 mg/dL, is largely supported as an indicator of cardiovascular risk [32,33]. Exercise interventions without a dietary component should yield a small beneficial change in triglyceride levels after a month of training [30], even among people with normal triglyceride levels [34].
- Fasting cholesterol (mg/dL): Abnormalities in the lipid profile, including elevated total and LDL cholesterol as well as decreased HDL cholesterol, are predictors of future cardiovascular disease among young and middle-aged people [35,36]. Exercise interventions without a dietary component should yield a small effect after 1 month [30].
- BP (mmHg): Moderate-intensity exercise has been shown to reduce BP [37].
- Waist circumference (cm): The waist circumference is measured at the level of the superior border of the iliac crest, above the umbilical level, and at the midline level [38] using a Gulick tape.
- BMI (kg/m^2): Dual-energy x-ray absorptiometry (DXA) scan is used to measure weight-adjusted BMI, in addition to total mass, lean mass, and fat mass. It is evident that people with SCI often have elevated waist circumference (≥94 cm), but their BMI is less than 30 kg/m
  2
  [39].

Secondary Outcome Measures

Secondary outcomes include cardiovascular capacity, pulmonary function, grip strength, and self-reported physical and psychosocial health outcomes.

- VO_{2peak} (ml/kg/min): VO_{2peak} is measured during a graded exercise test as an indicator of cardiovascular capacity using an arm ergometer (Lode) and open circuit spirometry with a metabolic cart (TruOne, ParvoMedics). Arm ergometers are considered the gold standard modality for exercise testing among people with disabilities who use wheelchairs or cannot run or cycle for prolonged periods [40,41]. Before starting the test, participants rest for 3-5 minutes. They are then instructed to maintain a pace between 55 to 65 revolutions per minute throughout the testing period. The participant starts their test with 2 minutes of warm-up without any resistance, and then the resistance is increased every minute by 10 watts until the participant reaches volitional fatigue or subjective discomfort (eg, shortness of breath and chest pain) or achieves 2 or more of the following termination criteria: age-predicted maximum HR of more than 85%; rate of perceived exertion (RPE) of 8 or more on a 0-10 scale; respiratory energy exchange ratio of 1.1 or higher; or plateau in oxygen consumption [42]. HR and oxygen consumption is measured continuously.
- FEV1 (forced expiratory volume over 1 second) and FVC (forced vital capacity; liters): Pulmonary function is measured by (1) how much air the participant exhales quickly, and (2) how much air can be expelled after taking a full breath via a portable spirometer (MIR Spirobank). These will be measured 3 times, with a 1-minute resting period between each trial during the testing session.
- Grip strength (kg): Grip strength is measured using a hand-held dynamometer (Jamar Hydraulic Hand Dynamometer, Lafayette Instruments) for both hands, with 3 trials conducted for each hand and a 1-minute resting period between each trial.
- Self-reported physical activity (min/wk): The volume of physical activity is measured using the Leisure-Time Physical Activity Questionnaire for SCI [43].
- Self-reported physical and psychosocial health: Various aspects of physical and psychosocial health are measured using standardized questionnaires by the National Institutes of Health PROMIS (Patient-Reported Outcomes Measurement Information Systems) [44]. This includes Pain Intensity, Pain Interference, Fatigue, Sleep Disturbance, Global Health, Ability to Participate in Social Roles and Activities, Depression, Anxiety, and Physical Function.

Moderating Outcome Measures

The moderating outcome measures are as follows:

- Demographics and clinical characteristics of participants (eg, age, sex, ethnicity, diagnosis, or medications)
- Exercise behavior measured by Exercise Self-efficacy Scale [45,46], and Exercise Goal Setting and Planning Scale [47] based on Social Cognitive Theory constructs
- Self-reported diet using the Rapid Eating Assessment for Participants Shortened Version [48,49]
- Exercise enjoyment using the Physical Activity Enjoyment Scale [50] and satisfaction via qualitative, semistructured one-on-one interview
- Exercise session duration based on attendance rate and video minutes viewed via online platform analytics
- Exercise intensity based on minutes exercised at moderate-to-vigorous intensity using an optical HR monitor (Polar Verity Sense, Polar) and RPE scale 0-10: The RPE is periodically asked during the exercise session to adjust the intensity and at the end of the exercise session to obtain the overall exertion level. The talk test is used as a secondary measure, primarily to ensure that participants stay in the moderate-to-vigorous intensity training zone and that RPE is related to aerobic strain as opposed to anaerobic. Additionally, this is an important indicator of exercise intensity, especially for individuals with a blunted exercise HR response.

Random Assignment

After participants are determined eligible and all baseline assessments are complete, they are randomized into 1 of the 2

groups, M2M-C or control (n=66 per group), with a 1:1 allocation ratio. The randomization sequence is generated and only known by the project statistician using a computer-generated random schedule in permuted block (SAS; version 9.4; SAS Institute Inc). The block size is unknown to intervention staff.

Intervention Arm—Home-Based, Synchronous Aerobic Exercise Training Using M2M

The prescriptive exercise guideline in this proposed study was generated through a critical review of the relevant literature. To determine an appropriate exercise dose, we used data from 16 studies of moderate-intensity aerobic exercise included in a recent meta-analysis on CMH effects of exercise training in the general population [22]. Specifically, we calculated the total prescription (average prescription per week × intervention duration) for each study and the overall average. We determined that an aerobic exercise training dose of approximately 2400 minutes (40 h) over 6 months would be necessary for CMH benefits. We then spread the minutes across a 24-week intervention period for this trial with wheelchair users to ensure adequate time to safely and progressively reach the prescribed dose. The session structure and exercise minutes for each week are presented in Table 1, and the intervention components are summarized in Table 2.

Table 1. Movement-to-music cardiovascular session structure and exercise in minutes for each week.

Week	1	2	3	4	5	6	7	8	9	10	11-24
Checking in	5	5	3	3	3	3	3	3	2	2	2
Range of motion	5	5	5	5	5	5	5	5	5	5	5
Aerobic	15	15	20	20	25	25	30	30	35	35	40
Cool down	5	5	5	5	5	5	5	5	5	5	5
End discussion	5	5	5	5	5	5	5	5	3	3	3
Exercise min/session	25	25	30	30	35	35	40	40	45	45	50
Total min/session	40	40	45	45	50	50	55	55	60	60	60

Table 2. Summary of movement-to-music cardiovascular program features.

Feature	Description
Prescription	• 2400 minutes of exercise across 24 weeks • Progressive • Individualized
Frequency	• 3 times per week
Session duration	• 25 to 50 minutes
Intensity	• Moderate-to-vigorous • Maximum heart rate at or above 70% • Rate of perceived exertion between 3 and 7
Intervention length	• 24 weeks
Setting	• Home
Exercise mode	• Aerobic using M2M[a]
Supervision	
Who	• M2M instructors • Assistant telecoaches
Mode	• Remote telecoaching
Oversight	• Zoom (Zoom Communications, Qumu Corporation) and TeleRehab app (JNP Enterprises LLC) • Live, instruction sessions with M2M instructors • Monitoring sessions with assistant health coaches using recorded live session videos
Meeting with the instructor or coach	
Weeks 1-8	• 1× M2M instructors • 2× assistant telecoaches
Weeks 9-16	• 1× M2M instructors • 1× assistant telecoaches • 1× self-guided with no supervision
Weeks 17-24	• 1× assistant telecoaches • 2× self-guided with no supervision
Equipment provided	• Computer tablets • Tablet stand • Polar heart rate monitor
Intervention safety	• Zoom oversight • Adverse event or serious adverse event reporting

[a]M2M: movement to music.

During the 24-week training phase, the M2M-C group receives 1:1 synchronous training from M2M-trained exercise instructors and assistant health coaches within a remotely coached, home-based setting using telehealth monitoring platforms (ie, Zoom, TeleRehab app). The intervention is administered 3 times per week, starting at 25 minutes per session and increasing by 5 minutes every 2 weeks to a maximum of 50 minutes. The exercise program focuses on improving cardiorespiratory fitness using a series of movement patterns accompanied by music. The program is tailored to an individual's functional abilities (eg, use lower limb if able, slow vs fast tempo, level of trunk control) and preference of musical themes, including classical, country, decades (oldies), international, jazz or blues, and pop.

For the first 8 weeks of the training phase, participants attend 1 instructional session with an M2M instructor per week, and the live session is video-recorded via Zoom. Participants attend 2 monitoring sessions in the same week to repeat the exercise using the prerecorded video of the week with assistant telecoaches. For the second 8 weeks (wk 9-16), participants continue to attend 1 instructional session with an M2M instructor per week, and the live sessions are video recorded. Participants attend 1 monitoring session with assistant telecoaches and 1

self-guided session without any supervision. For the third 8 weeks (wk 17-24), participants no longer meet with M2M instructors. Using the recorded videos between weeks 11 and 16 (ie, 40 minutes per video; archived with no instructions), participants attend 1 monitoring session per week with assistant telecoaches and 2 self-guided sessions in the same week.

Telehealth Monitoring Platform

The exercise intensity is prescribed at a moderate-to-vigorous intensity level, which is monitored through a web-based platform with physiologic devices to support remote telehealth supervision of the intervention. The platform, referred to as TeleRehab, includes an Android (Google LLC) app that is installed on a computer tablet with Bluetooth capability (Samsung FE S7, Samsung USA), which sends data and allows 2-way communications to a secure web server. HR data are recorded and transmitted for real-time viewing by both the user and research staff using an optic HR sensor (Polar Verity Sense, Polar). The device instructions from the manufacturer state that the sensor can be worn on the head, forearm, or upper arm. For the M2M-C exercise intervention, the HR sensor is placed on a thin, elastic sports headband and worn on the temple of the head. Based on internal testing among research staff (nonpublished findings), the head placement resulted in more accurate readings during intervention exercise than when the device was worn on the forearm or upper arm. The head placement avoided signal disruption caused by the rapid and consistent arm movements required for the exercise intervention. At the end of each session, the platform provides the summary of exercise minutes (ie, light or moderate-to-vigorous) based on the predetermined HR zone. For participants with blunted HR, RPE is used. The TeleRehab app was an upgraded version of one used previously in a tele-monitored feasibility exercise study among people with SCI [51].

Control Arm—Home-Based, Asynchronous Standard Exercise Training

For ethical and engagement purposes, the control group receives access to a YouTube playlist of standard exercise training (SET) videos adapted for people with physical disabilities. They are advised a similar prescription as the intervention group of 3 exercise sessions per week. The SET program is based on the National Center on Health, Physical Activity, and Disability 14-Weeks to a Healthier You program launched in 2008. It involves various exercises that are performed in both standing and seated positions, including the upper and lower extremity range of motion (2 videos, 5 min each), muscle strength (3 videos, 5 min each), aerobic fitness (1 video, 5 min; 2 videos, 10 min each), balance (1 video, 2 min; 2 videos, 5 min each), and a cool down (1 video, 5 min) [52].

Procedure

This study's procedure is administered by a project coordinator with oversight by the principal investigator (PI) and coinvestigators and monitored through a fidelity monitoring plan. Our intervention fidelity plan is based on the best practices and recommendations from the Behavior Change Consortium [26]. These recommendations are intended to link theory and application across 5 primary study phases, including study design, provider training, monitoring and improving the delivery of the intervention, and monitoring and improving the enactment of intervention skills.

The project coordinator, who is specific to participant engagement, contacts interested participants via telephone, describes this study and its requirements, and conducts the screening based on this study's inclusion and exclusion criteria. For eligible individuals, the project coordinator then obtains physician approval. Upon approval by the physician, the project coordinator then distributes the informed consent document electronically as a final step in enrollment. After completing the informed consent, a baseline self-report questionnaire packet and a current medication list form are sent electronically. The project coordinator follows up with a telephone call to schedule a baseline data collection visit and provide verbal and written instructions regarding the baseline testing procedure, completion of the questionnaire packet and medication list, and directions with parking information. The project coordinator contacts the participant by telephone 24 hours before the appointment as a reminder. Upon arrival at the adaptive human performance laboratory, the project coordinator reviews this study's procedures with the participant and then initiates the baseline data collection. The baseline data collection is undertaken by treatment-anonymous research staff who will administer the second level of eligibility screening based on CMH indicators. The eligible participant then undertakes a series of physiological tests, and the composition of those measures takes approximately 2 hours.

Once the baseline assessment is completed, participants are randomly assigned to either the intervention or control conditions using a random numbers sequence with concealed allocation. The project coordinator unfolds the allocation information via this study's database, communicates the condition of assignment with the participant and, if allocated to the M2M-C intervention, prepares the necessary equipment for program participation. The participant will also meet with instructors and assistant telecoaches. If allocated to the control condition (SET), the project coordinator prepares the tablet with access to the SET videos. Lastly, the project coordinator will schedule a goal-setting session to be completed within 2 weeks between the participant and PI. This is carried out for both groups.

Participants in both intervention and control groups receive a 15-minute, individual goal-setting session at each time point from the PI, who is trained in physical activity counseling. They discuss participant's outcome expectations from the program and review the goal of the program based on the given exercise prescription. The participants are prompted to share any foreseen barriers to complying with the program and guided to develop a relapse prevention plan (eg, identifying activities and social support to reactivate participation; outlining consequences for continuing and discontinuing the program). Additionally, the participants are prompted to share additional health goals and receive guidance on making them specific, measurable, attainable, relevant, and time-bound.

The intervention and control participants complete the same measurement procedures at the 12-week (midintervention) and

the 24-week (postintervention) time points. There is no physiological data collection at the 36-week follow-up, as the aim to be addressed is sustaining physical activity behavior.

Participants receive up to US $830 for completing the measures per assessment period, including baseline as well as 12-, 24-, and 36-week assessments, and 12- and 24-week interviews. Semistructured exit interviews are conducted at the 24-week assessment for the first 30 participants to identify opportunities for intervention improvement and refinement.

Data Analyses

All data will be exported into and analyzed using SAS software (version 9.4 or later). Statistical tests will be 2-sided and will be performed using a significance level of 5%. Data analyses will follow intent-to-treat principles. Data will be initially examined for variations, outliers, errors, and patterns of missing values. Missing data will be inputted using multiple imputation techniques where necessary based on the assumption that the missingness mechanism is at random. Descriptive statistics, such as means, SDs, frequencies, and proportions, will be obtained for this study's variables.

Primary and Secondary Aims

We will analyze between-group differences (differences between the intervention and control groups) and within-group changes from preintervention to the 12-week midintervention (immediate effects of the intervention) time point. "Clinically significant improvement" was defined for each risk factor based on the minimum change deemed clinically important; for our purposes, "clinically significant improvement" equates to the following: approximately 10% decrease in total cholesterol, 30% reduction in triglycerides, and 5% reduction in body fat from the beginning of care to the most recent measure.

Tertiary Aims

Our analyses will focus on only the within-group changes from the preintervention to the 12-week midintervention to the 24-week postintervention (sustained effects of the intervention) time point. For all 3 aims, comparisons of cardiometabolic indicators, measures of fitness, and scores of self-reported questionnaires between and within the 2 groups will be performed using generalized linear mixed model techniques, including mixed models repeated measures analyses. The specific covariance matrix, such as the unstructured covariance matrix, will be selected based on the final data. The Tukey-Kramer multiple comparisons test will be used as the post hoc test for pairwise comparisons of means. These models will allow us to assess the between-group effect, the within-group effect, and the group-by-time interaction. Covariates of scientific interest such as wheelchair use status (full-time vs part-time), medication use (use vs nonuse), and participant characteristics (eg, age, sex, race, and severity of disease) may be included in some of these models. Pearson (or Spearman, if needed) correlation analyses will be performed between pairs of study variables. Analyses of categorical variables will be performed using the Pearson chi-square test (or Fisher exact test, if needed). Baseline characteristics will be evaluated using the 2-group *t* test for continuous variables or the chi-square test for categorical variables. For all aims, missing data that is not rectified through ongoing review of source documents may be managed with multiple imputation, and the influence of the missing data assessed with sensitivity analysis. Continuous variables will be examined for normality of distribution using graphical techniques and tests of normality. Transformations will be performed for continuous variables that are not normally distributed, or nonparametric methods will be used for these variables.

Adherence and compliance data are logged onto the online training platform. Adherence and compliance rates will be assessed as proportions and their corresponding exact 95% CIs will be obtained. These rates will be obtained overall and separately by age, sex, body composition, and ethnicity. These rates will be compared separately for age group, sex, body composition, and ethnicity using the chi-square test or Fisher exact test if the assumptions for the chi-square test are not met.

We will consider the suggested outcomes as potential moderators and test effect modification by including appropriate interaction terms in our repeated measure of mixed models, including the severity of motor impairment (ie, PROMIS Physical Function 12a), clinical diagnosis (eg, SCI vs multiple sclerosis vs stroke), psychosocial metrics specific to readiness to change (eg, self-efficacy and goal setting skills), and other factors, such as wheelchair use status (full-time vs part-time), medication (use vs nonuse), and diet quality (healthy diet vs less healthy diet).

Results

Recruitment procedures started in January 2024 with the first participant enrolled on March 18, 2024. All data are anticipated to be collected by November 2027, and the main results of the trial are anticipated to be published by February 2028. Secondary analyses of data will be subsequently published. A total of 16 participants have been recruited as of August 20, 2024.

Discussion

Principal Findings

The CHIME study proposes a parallel-group RCT for examining the 24-week effects of an evidence-based M2M program compared with a control condition for yielding immediate and sustained CMH outcomes among adult wheelchair users with poor cardiometabolic profiles. This study anticipates that after 24 weeks, participants in the M2M-C intervention group will show significant improvements in key cardiometabolic risk factors, such as reduced HbA_{1c} levels; lower fasting glucose and triglycerides; and decreased BP, waist circumference, and body fat percentage, compared to the control group. Furthermore, the M2M-C intervention is expected to improve health-related physical fitness, including measurements such as VO_{2peak}, FEV1, FVC, and grip strength, in line with self-reported psychosocial health outcomes. In addition to the improvements in CMH and physical fitness, we anticipate that these benefits will be sustained during the maintenance phase (up to 36 wk). This suggests that wheelchair users may be able to adhere to telehealth-based exercise programs over the long

term. If successful, this study will be the largest and sufficiently powered confirmatory RCT trial targeting CMH outcomes in this population. The prescribed exercise dose was informed by the review of the relevant literature [22]. If successful, this study will establish an evidence-based recommendation of adequate exercise dosing for adult wheelchair users with poor CMH profiles.

Strength and Limitations

This study uses an evidence-based M2M program with modifications to focus on aerobic training and telehealth delivery [53,54]. The M2M program has been specifically designed and tested for safety and effectiveness for balance, walking endurance, and volume of physical activity among people with various disabilities (eg, multiple sclerosis, stroke, and SCI) [17,55,56]. Studies involving fitness training and traditional modes of exercise, such as riding a stationary bike and lifting weights, often result in low adherence rates for many people due to a lack of enjoyment or social interaction [57,58]. Several studies have reported that adding music improves exercise adherence [59] and enjoyment [60,61]. The enjoyment was a highlighted component of the M2M program in addition to its safety and effectiveness, and it has the potential to improve aerobic fitness and CMH when the exercise intensity is regulated by trained instructors.

This study has been designed to deliver quality exercise interventions in the convenience of the participant's home with minimal exercise equipment. However, many exercise interventions often fail to be made available after research trials due to a lack of resources and support. To support the sustained exercise behaviors and gains, postintervention resources will be provided to study participants for their maintenance period (wk 25-36) and can be used after that time. The M2M-C intervention participants will have access to an online library of exercise videos, including their 24-week M2M-C videos, and the control participants will have access to the SET exercise videos. In addition, all participants will be introduced to the National Center on Health, Physical Activity and Disability (to receive continuous support through various health-related programs that are specifically designed for people with disabilities. Participants will be given the center's website and email addresses, in addition to their toll-free hotline.

Limitations

One of the major limitations of this study is that it relies on self-reported data for certain outcomes, such as physical activity, exercise behavior, and diet. Self-reported data can sometimes overestimate or underestimate actual behavior and can be affected by recall bias, where participants may not accurately recall their physical activity or exercise habits [62]. In addition, the time frame for these questionnaires is limited to a 1-week period, which may not fully capture participants' typical physical activity and exercise patterns over time. To address these limitations, future studies could incorporate objective measures, such as wearable devices and activity trackers, to supplement self-reported data. These tools would provide a more comprehensive and accurate understanding of physical activity patterns and engagement, helping to mitigate the biases associated with self-reported data. An additional limitation of the trial is that participants are not blinded to treatment due to the nature of the intervention being an online exercise program.

We may experience problems with the participants adhering to this study's protocol due to the requirement of onsite physiological data collection. Transportation is a well-documented barrier for people with disabilities, especially our target population who may require assistance with transferring in and out of a vehicle or obtaining accessible public transportation. To overcome this barrier, we have arranged a ride service that contains accessible vehicles. In addition, there may be some attrition during the maintenance period (wk 25-36) wherein there is no planned coaching and contact. Potential attrition is expected from this study but we have developed a plan to minimize it using the taper-down approach of coaching and contact during the 24-week training period.

Lastly, the current design of the trial involves intensive supervision of training by the M2M instructors and assistant health coaches, which is approximately 43 hours per participant over the 24-week training period (ie, 19, 16, and 8 hours for each 8-wk phase). The high volume of staff time to implement this study may hinder the scalability of the program in its current form.

Clinical and Practical Implications

The M2M-C intervention has potential clinical and practical implications if proven successful. First, the M2M-C program would demonstrate the feasibility of delivering a structured, individualized tele-exercise platform. This approach effectively addresses common barriers faced by wheelchair users, such as transportation challenges, limited access to fitness facilities, and a lack of tailored exercise programs. The M2M-C program offers a convenient and accessible solution for engaging in physical activity from the comfort of one's own home. Its adaptability makes it suitable for various settings, including rural or underserved areas where traditional exercise programs may not be available. The use of telecoaching also allows for regular interaction and personalized support, which are essential for maintaining motivation and long-term adherence. Moreover, if the M2M-C intervention proves successful, there is the potential for it to be expanded to serve a broader range of clinical populations. The program's emphasis on individualization—adjusting exercises to align with each participant's physical capabilities and fitness level—makes it adaptable. With appropriate modifications, the M2M-C program could be extended to other groups, including individuals with different types of mobility impairments and older adults with physical disabilities. This flexibility highlights the M2M-C intervention as a versatile tool for promoting physical activity on a larger scale, potentially reaching diverse populations in need of accessible exercise solutions.

Acknowledgments

This study is supported by the Eunice Kennedy Shriver National Institute of Child and Human Development (grant R01 HD111059). The contents of this article do not necessarily represent the policy of these groups, and you should not assume endorsement by the US Federal Government.

Data Availability

The data generated as part of this study will be made available through a data repository. Additionally, deidentified datasets will be made available as supplementary material with each relevant publication.

Authors' Contributions

All authors contributed to the final draft of this paper and project design. JW and Yumi K created the initial manuscript draft. All authors contributed to either this study's design or procedures.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer review report from the National Institute of Child Health and Human Development Special Emphasis Panel Home and Community-Based Physical Activity Interventions to Improve the Health of Wheelchair Users (National Institutes of Health, USA).
[PDF File (Adobe PDF File), 241 KB - resprot_v14i1e57423_app1.pdf]

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Abbreviations

BP: blood pressure
CHIME: Cardiometabolic Health Intervention Using Music and Exercise
CMH: cardiometabolic health
FEV1: forced expiratory volume over 1 second
FVC: forced vital capacity
HbA1c: hemoglobin A1c
HR: heart rate
hsCRP: high sensitivity C-reactive protein
M2M: movement to music
M2M-C: movement-to-music cardiovascular
PI: principal investigator
PROMIS: Patient-Reported Outcomes Measurement Information Systems
RCT: randomized controlled trial
REDCap: Research Electronic Data Capture
RPE: rate of perceived exertion
SCI: spinal cord injury
SET: standard exercise training
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials
VO2peak: peak oxygen consumption

Edited by A Schwartz; submitted 26.08.24; this is a non–peer-reviewed article;accepted 17.12.24; published 15.01.25.

Please cite as:
Kim Y, Rimmer JH, Lai B, Oster R, Cowan R, Young HJ, Fisher G, Kim Y, Giannone J, Wilroy JD
Cardiometabolic Health Intervention Using Music and Exercise (CHIME) Delivered via Telehealth to Wheelchair Users: Protocol for a Randomized Controlled Trial
JMIR Res Protoc 2025;14:e57423
URL: https://www.researchprotocols.org/2025/1/e57423
doi:10.2196/57423
PMID:

Protocol

Harnessing Human-Centered Design for Evidence-Based Psychosocial Interventions and Implementation Strategies in Community Settings: Protocol for Redesign to Improve Usability, Engagement, and Appropriateness

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Abstract

Background: Although substantial progress has been made in establishing evidence-based psychosocial clinical interventions and implementation strategies for mental health, translating research into practice—particularly in more accessible, community settings—has been slow.

Objective: This protocol outlines the renewal of the National Institute of Mental Health–funded University of Washington Advanced Laboratories for Accelerating the Reach and Impact of Treatments for Youth and Adults with Mental Illness Center, which draws from human-centered design (HCD) and implementation science to improve clinical interventions and implementation strategies. The Center's second round of funding (2023-2028) focuses on using the Discover, Design and Build, and Test (DDBT) framework to address 3 priority clinical intervention and implementation strategy mechanisms (ie, usability, engagement, and

appropriateness), which we identified as challenges to implementation and scalability during the first iteration of the center. Local redesign teams work collaboratively and share decision-making to carry out DDBT.

Methods: All 4 core studies received institutional review board approval by June 2024, and each pilot project will pursue institutional review board approval when awarded. We will provide research infrastructure to 1 large effectiveness study and 3 exploratory pilot studies as part of the center grant. At least 4 additional small pilot studies will be solicited and funded by the center. All studies will explore the use of DDBT for clinical interventions and implementation strategies to identify modification targets to improve usability, engagement, and appropriateness in accessible nonspecialty settings (Discover phase); develop redesign solutions with local teams to address modification targets (Design and Build phase); and determine if redesign improves usability, engagement, and appropriateness (Test phase), as well as implementation outcomes. Center staff will collaborate with local redesign teams to develop and test clinical interventions and implementation strategies for community settings. We will collaborate with teams to use methods and centerwide measures that facilitate cross-project analysis of the effects of DDBT-driven redesign on outcomes of interest.

Results: As of January 2025, three of the 4 core studies are underway. We will generate additional evidence on the robustness of DDBT and whether combining HCD and implementation science is an asset for improving clinical interventions and implementation strategies.

Conclusions: During the first round of the center, we established that DDBT is a useful approach to systematically identify and address chronic challenges of implementing clinical interventions and implementation strategies. In this subsequent grant, we expect to increase evidence of DDBT's impact on clinical interventions and implementation strategies by expanding a list of common challenges that could benefit from modification, a list of exemplary solutions to address these challenges, and guidance on using the DDBT framework. These resources will contribute to broader discourse on how to enhance implementation of clinical interventions and implementation strategies that integrate HCD and implementation science.

International Registered Report Identifier (IRRID): PRR1-10.2196/65446

(JMIR Res Protoc 2025;14:e65446) doi:10.2196/65446

KEYWORDS

implementation science; human-centered design; evidence-based psychosocial interventions; mental health

Introduction

Background

Psychosocial clinical interventions such as psychotherapy, counseling, and case management are a preferred mode of treatment by most people seeking care for mental health problems [1-5]. Access to evidence-based clinical interventions remains variable among diverse groups, leading to mental health disparities across racial and ethnic, geographic, and socioeconomic status [6-16]. Furthermore, implementing clinical interventions in nontraditional and integrated settings (eg, primary care, telehealth platforms, and schools) has shown mixed success. These settings can serve as a *safety net* for accessing mental health treatment when traditional options are inaccessible [17-20]. Addressing barriers to implementing clinical interventions in these settings is vital to promote more equitable access to mental health services for all.

Poor availability of clinical interventions is often due to intervention complexity and suboptimal fit with many settings where clinical interventions are deployed [21]. Implementation strategies—"systematic intervention process(es) to promote the uptake of evidence-based health innovations into usual care"—have often taken the form of complex tools and processes (eg, train the trainer, booster training, incentive models, and decision supports) [22,23]. However, these often fall short because they can be excessively costly and cumbersome [22,24]. Different needs of recipients and settings can lead to high rates of reactive adaptations of clinical interventions and implementation strategies by their intended users in many settings where they are deployed. Reactive adaptations are unplanned or improvised changes during an implementation process in response to unanticipated challenges [25]. While reactive adaptations can compromise clinical potency, those that are proactively tailored to different care settings can improve sustainability and impact [26-29]. A systematic review of cultural adaptations to health and mental health services highlighted how adaptations motivated by cultural sensitivity are not guaranteed to demonstrate increased efficacy [30]. Instead, patient-centered approaches that account for individualized needs and barriers to service are recommended to guide adaptations [30,31].

Human-Centered Design and Implementation Science

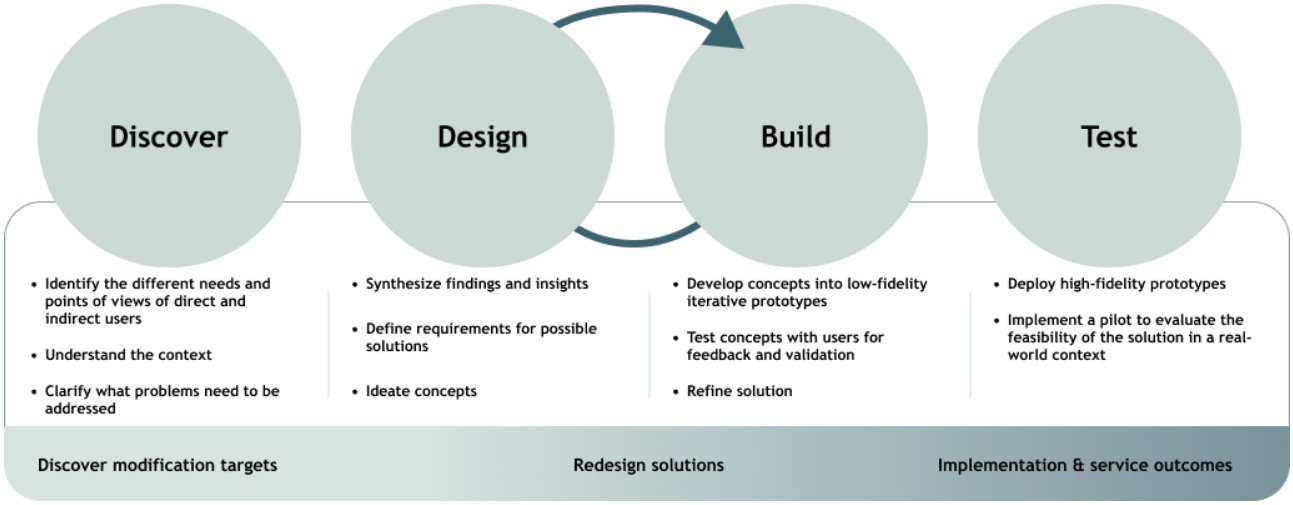
Human-centered design (HCD) and the closely related discipline user-centered design offer a suite of methods to develop useful, compelling, intuitive, and enjoyable products, services, and tools based on people's needs [32,33]. HCD relates to the evolution of human-computer interaction (HCI), a multidisciplinary field that incorporates computer science, cognitive science, and human factors engineering as a response to personal computing, collaborative work, and interconnected technologies in everyday life [34]. While HCD's origins are rooted in technology, it has been used beyond the context of digital technologies to address therapeutic elements and implementation supports [35]. HCD has been applied to improve usability, reduce burden, and increase the contextual appropriateness of clinical interventions and implementation strategies [36-40].

The fields of HCD and implementation science share common objectives and offer complementary methods that can support clinical interventions and implementation strategies innovation and redesign [41-44]. HCD techniques are particularly well positioned to help with redesign, which we define as adaptations to clinical interventions and implementation strategies while preserving effective components (ie, fidelity-consistent adaptation) [45]. HCD's traditions of situating problem discovery and solutions in user needs, usability, engagement, innovation, and rapid exploration are core strengths that align with implementation science's goal of improved adoption, fidelity, reach, and adaptation of clinical interventions and implementation strategies [41]. Combining HCD and implementation science traditions for clinical intervention and implementation strategy redesign grounds novelty in empirical evidence.

Integrating HCD and Implementation Science Through the Discover, Design and Build, and Test Framework

The University of Washington Advanced Laboratories for Accelerating the Reach and Impact of Treatments for Youth and Adults with Mental Illness Center (UWAC), which is funded by a grant from the National Institute of Mental Health (NIMH), is a multidisciplinary team of experts from the fields of mental health, implementation science, and HCD focused on improving usability, engagement, and appropriateness of clinical interventions and implementation strategies in diverse and nonspecialty settings (eg, rural, urban, low-income, primary care, and schools). Drawing on strengths from different disciplines, UWAC developed the Discover, Design and Build, and Test (DDBT) framework (Figure 1) at the start of the center (ie, "UWAC 1.0"). The current DDBT framework guides teams in redesigning clinical interventions and implementation strategies to improve usability, engagement, appropriateness, and implementation outcomes while preserving clinical interventions' core components [46]. Key principles underlying this model include the following: (1) not all clinical interventions and implementation strategies are designed for all settings; (2) "there is no implementation without adaptation" [47]; (3) unchecked, reactive adaptations have the potential to exclude essential active ingredients [48,49]; and (4) reactively adapted clinical interventions and implementation strategies can negatively impact implementation and clinical outcomes.

Figure 1. Discover, Design and Build, and Test (DDBT) redesign framework.

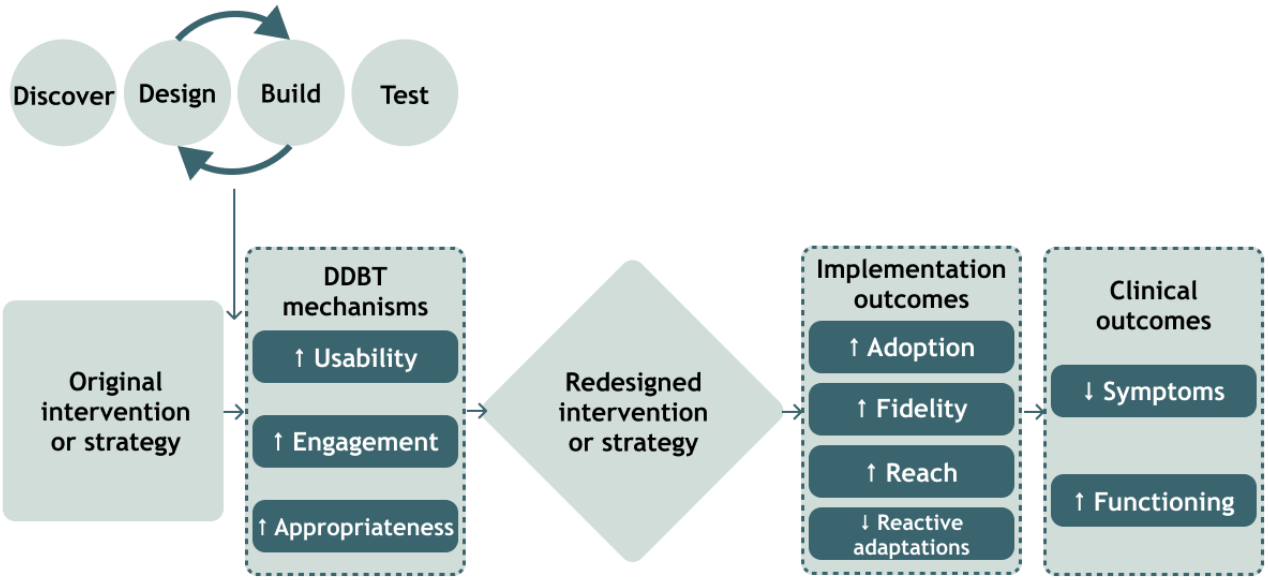


The DDBT framework is modeled after existing HCD frameworks [50] and is an iterative stepped approach to systematically (1) understand usability constraints of existing clinical interventions and implementation strategies, (2) iteratively design solutions for usability challenges with redesign teams of direct and indirect users, and (3) test and refine prototypes. We define direct users (also known as "primary users") as people who directly interact with the clinical intervention and implementation strategy and indirect users (also known as "secondary users") as people affected by the clinical intervention and implementation strategy. HCD places a strong emphasis on explicitly identifying relevant community collaborators and users to ensure that new products effectively meet their needs [51,52]. DDBT starts by identifying multilevel factors that drive clinical intervention and implementation strategy usability problems, engagement challenges, and problems with contextual appropriateness (Discover phase). Once problems and challenges are identified, modifications are iteratively created between the design team and practitioners and clients, until a new version of the clinical interventions and implementation strategies is developed to address crucial issues and enhance usability, engagement, and appropriateness (Figure 2; Design and Build phase). Early prototypes of clinical interventions and implementation strategies are assessed with small samples (eg, 5-25 participants) to answer design questions using paper or other "low-fidelity" (ie, sufficient to communicate a concept but potentially lacking functionality, some content, and look and feel of final materials) versions of modifications, which reduces waste of unnecessary investment in programming and development until as late in the process as possible. Findings from the Design and Build phase are incorporated to develop high-fidelity prototypes, which are tested against the unadapted version to ascertain if the modified clinical interventions and implementation strategies result in improved implementation (eg, increased adoption, fidelity, reach, and reduced reactive adaptations) and equivalent or better mental and behavioral health outcomes because of the changes to usability, engagement, and appropriateness (Test phase). Additional details

on the DDBT framework are outlined in our UWAC 1.0 protocol paper [46].

All UWAC research uses the DDBT framework, which is applied flexibly based on project needs and allows us to evaluate the extent to which incorporating HCD and implementation science methods impacts clinical interventions and implementation strategies. Since 2018, DDBT has been used in >18 UWAC studies and 16 National Institutes of Health (NIH)–funded awards external to UWAC. During UWAC 1.0, we originally assessed impact of DDBT on 3 mechanisms: learnability (ie, extent to which users can understand or facilitate use) [46], usability (ie, extent to which users can achieve specified goals of effectiveness, efficiency, and satisfaction) [50], and sustained quality of care (ie, extent of treatment fidelity and impact on target outcomes) [46]. Analysis of UWAC 1.0 projects resulted in (1) identification of common usability issues in clinical interventions and implementation strategies that could benefit from modification (ie, "typology of modification targets") and corresponding heuristics to guide their design [53], (2) reflections on potential exemplary solutions to these challenges (ie, library of clinical interventions and implementation strategies redesign solutions), and (3) guidelines for using the DDBT framework [46].

Figure 2. University of Washington Advanced Laboratories for Accelerating the Reach and Impact of Treatments for Youth and Adults with Mental Illness Center (UWAC) theory of change for clinical intervention and implementation strategy redesign. DDBT: Discover, Design and Build, and Test.



UWAC Theory of Change for Clinical Intervention and Implementation Strategy Redesign

Our UWAC 1.0 findings and the implementation literature [21] outline how limited availability and the use of clinical interventions and implementation strategies are persistently attributable to organizational and system characteristics (eg, readiness to adopt, resources and culture, and leadership), clinician and adopter characteristics (eg, appropriateness and perceived efficacy of clinical interventions and implementation strategies for patients) [28,54,55], and incentives to engage in clinical interventions and implementation strategies [29,56].

As a result, we updated DDBT's underlying theory of change to highlight how adoption of clinical interventions and implementation strategies are largely due to usability (eg, extent to which clinical interventions and implementation strategies can be used to achieve specified goals with effectiveness, efficiency, and satisfaction) [53]; engagement (eg, degree of user participation and enthusiasm for the aspects of clinical interventions and implementation strategies that require user involvement) [57]; and appropriateness (eg, perceived fit, relevance, or compatibility of clinical interventions and implementation strategies for a given practice setting, practitioner, or consumer) [58] (Figure 2). These mechanisms are direct targets of DDBT-driven redesign and the focus of the new iteration of funding between 2023 and 2028 (ie, "UWAC 2.0"). We ultimately expect DDBT to result in changes to proximal implementation outcomes (adoption, fidelity, reach, and reactive adaptation) and clinical outcomes.

DDBT Mechanisms

Usability

Usability is an underlying outcome at all stages of the HCD process. Understanding the extent to which designs are unusable and opportunities to increase an existing solution's usability can inspire innovation and adoption [53]. Deployment of clinical interventions and implementation strategies will continue to be subpar unless usability can be addressed, the historically unidirectional relationship between developers and users can be overcome, and insufficient incorporation of user perspectives can be remedied [59]. Usability is assessed through usability evaluations and usability testing, where prototypes are evaluated using established heuristics [60] and observing users complete critical tasks [61]. Usability assessment methods stem from evaluating technologies; however, these techniques have been used to improve usability, decrease burden, and increase contextual appropriateness of nontechnological mental health clinical interventions and implementation strategies [5,36,39,53].

Approaches to assessing usability frequently couple interview-type questions with surveys and observation [62]. As a form of usability evaluation, metrics such as the System Usability Scale (SUS) [63] are questionnaires that assess perceived usability. The SUS is a widely used instrument to measure usability of technologies by industry. Task-based usability testing involves asking participants to complete tasks while using a prototype or product. This method can be used to gather baseline usability data for an existing clinical intervention and implementation strategy and assess usability of clinical intervention and implementation strategy prototypes [53]. The think-aloud protocol (TAP) involves participants verbalizing thought processes as they use clinical interventions and implementation strategies [39] to complete assigned tasks, including actions they consider taking and reactions to materials as they encounter them. Similarly, the Cognitive Walkthrough for Implementation Strategies (CWIS) is a 6-step method for evaluating clinical interventions and implementation strategies usability, which can include interviews as part of task-based usability testing [39].

UWAC 1.0 projects assessed usability through usability questionnaires, CWIS [39], and TAP [64,65]. We developed the Intervention Usability Scale (IUS) [37] and Implementation Strategy Usability Scale (ISUS) [39] to better measure clinical intervention and implementation strategy usability; these scales are closely aligned with SUS. SUS scores of ≥70 out of 100 are considered adequate usability, and we anticipate a similar threshold for IUS and ISUS. Cross-project usability data informed the typology of modification targets: 12 unique categories of clinical intervention and implementation strategy usability issues of varying severity. These categories help researchers understand common barriers to clinical intervention and implementation strategy use that can be prevented and addressed during clinical intervention and implementation strategy redesign [53].

Engagement

Engagement, and adaptations to improve engagement, relates to clinical interventions fidelity and clinical outcomes [66-69] and is a defining feature of quality of care [70-72]. Engagement describes user connection to clinical interventions and implementation strategies and their capacity to sustain a connection [57]. Engagement is distinct from common health concepts of compliance, adherence, and coverage because it incorporates a dimension of quality and welcomes the possibility that different people may engage differently with different parts of clinical interventions and implementation strategies based on varying needs. Typical users include the practitioners who deliver them (eg, clinicians, implementation practitioners, and intermediaries) and the individuals who receive them (eg, clients, practitioners, and service system administrators). Our work has found that engagement can be negatively impacted by insufficient buy-in, components that are inaccessible to different users, little support for communication or rapport building, and requirements or constraints that inadvertently shift one user's responsibilities to another (eg, practitioners completing client tasks) [53].

Engagement is a common focus in HCI literature [57,73-75], where there is an active conversation around how to best assess the quality of interactions rather than quantity of interactions. Multidisciplinary UWAC project teams present an opportunity to incorporate different approaches to improving engagement in translational research [76-78]. We conceptualize engagement as a multifaceted construct focused on interaction quality (ie, participation and enthusiasm) that is enhanced by clinical interventions and implementation strategies that are well designed and result in improved adoption, fidelity, reach, and adaptations. There are subjectivity-oriented and objectivity-oriented approaches to measuring engagement [57]. Subjectivity-oriented measures are self-reported and include questionnaires, observation, perceived task outcomes, and interviews. Objectivity-oriented measures minimize researcher involvement and can include behavior logging, psychophysiological measurements, or telemetry. Within HCI, objectivity-oriented measures such as user data—logs, time, number of interactions, and frequency of log-ins—are commonly used.

Appropriateness

Appropriateness captures perceived fit between clinical interventions and implementation strategies and the settings to which they are deployed [58]. Client needs and therapeutic style drive how mental health practitioners modify clinical interventions and implementation strategies in practice [26]. During UWAC 1.0, we observed how practitioners and recipients felt that exciting innovations can be inappropriate for specific contexts (eg, schools) or for users facing challenges with identifying and selecting goals or implementation plans. Challenges included clinical interventions and implementation strategies' excessive time demands in their delivery, incompatibility with existing workflows or roles, unavailable system infrastructure requirements, overreliance on digital technology, and, importantly, practitioner perceptions of the fit of the clinical interventions and implementation strategies to specific client problem types. These issues are well documented as multifaceted factors that influence clinical intervention and implementation strategy adaptations [29,45]. During UWAC 1.0, we used the Intervention Appropriateness Measure (IAM) [79] across projects to assess appropriateness.

Study Purpose

Center Aims and Structure

Our goal is to overcome obstacles that prevent quality mental health interventions from reaching historically marginalized groups through addressing critical clinical intervention and implementation strategy problems with the DDBT framework. Building on learnings during the first iteration of the center, UWAC 2.0 focuses on addressing longstanding problems with *usability*, *engagement*, and *appropriateness* of clinical interventions and implementation strategies that result in high rates of reactive adaptations in settings where they are deployed. Within UWAC, the Methods Core team provides methodological and technical support to all projects and maintains cross-cutting project data on UWAC outcomes to determine the impact of DDBT on clinical interventions and implementation strategies. These data will be used to refine and expand UWAC's typology

of modification targets and library of redesign solutions. This iteration of the center emphasizes increased leadership and application of DDBT methods by local project redesign teams (eg, administrators or champions) that receive methodological training and supports from the Methods Core team to work alongside investigators, increasing their decision-making at all stages of the design process. This is a shift from the previous centralized model, where projects engaged users, but project principal investigators (PIs) and UWAC Methods Core team members often led the design process. The Methods Core team will address the subsequent aims during UWAC 2.0.

Aim 1: Identify Clinical Intervention and Implementation Strategy Modification Targets to Improve Usability, Engagement, and Appropriateness in Accessible Nonspecialty Settings (Discover Phase)

Known determinants of successful clinical intervention and implementation strategy use exist at several levels, including clinical interventions (eg, complexity); practitioner and client (eg, training, attitudes, and intention to use); and organizational (eg, climate, leadership, resources, and supervision). Historically, adaptations of clinical interventions and implementation strategies have been driven by academics rather than the lived experiences of recipients. Using the Consolidated Framework for Implementation Research (CFIR) [80] as our guide in the Discover phase of each UWAC project, we support project redesign teams to use HCD methods to identify targets within our typology of modification targets [53]. Qualitative analyses will allow us to compare targets identified via local DDBT, characterized by user involvement in redesign teams and shared decision-making about target prioritization and solutions, with those derived from our original, centralized application of DDBT [46]. Aim 1 outcomes will inform typology revisions and allow for comparisons between the original, centralized DDBT and the local DDBT. An updated typology will be broadly disseminated to inform future research.

Aim 2: Develop Redesign Solutions With Local Teams to Address Clinical Intervention and Implementation Strategy Modification Targets (Design and Build Phase)

Using rapid, iterative design principles, we are supporting research project teams in redesigning clinical interventions and implementation strategies to enhance usability, engagement, and appropriateness. We will systematically catalog these design solutions using the Framework for Modifications and Adaptations of Evidence-Based Interventions (FRAME) or FRAME for Implementation Strategies (FRAME-IS) [26,29,45]. We will examine solutions and the populations, organization types or structures, practitioner types, and clinical interventions and implementation strategies in which they work, identifying solutions that transfer across different contexts or are uniquely suited to specific contexts. Aim 2 outcomes will be compared with centralized DDBT outputs, resulting in an updated library of redesign solutions organized by target and redesign method (ie, localized vs centralized), and shared with the interested community.

Aim 3: Determine If Redesign Affects Changes in Usability, Engagement, and Appropriateness (Test Phase)

Each project conducting a Test phase will include a hybrid effectiveness-implementation trial [81,82] with a primary comparison between the original clinical intervention and implementation strategy and the DDBT-adapted version on theorized mechanisms (usability, engagement, and appropriateness), implementation outcomes (adoption, fidelity, reach, and adaptations), and client outcomes. Projects will apply FRAME or FRAME-IS [29,45] to examine the extent to which DDBT decreases reactive adaptations to the clinical intervention and implementation strategy (ie, unplanned or due to unanticipated obstacles) during implementation. We hypothesize that DDBT-informed, prospective, and planned adaptations will reduce the number and extent of reactive adaptations. The Methods Core team will systematically integrate new data from the UWAC projects with existing data in an integrated cross-project analysis of how redesign affects theorized mechanisms, implementation outcomes, and patient outcomes. Aim 3 outcomes will be disseminated to the field and inform new projects designed to test which redesign strategies best improve DDBT mechanisms and outcomes.

Methods

Overview

Composed of an interdisciplinary team and advisory board with experience in HCD, implementation science, psychosocial clinical interventions, and research methods and data, the Methods Core team supports one large hybrid effectiveness-implementation study (NIH R01), 3 exploratory pilot studies (NIH R34s; Multimedia Appendix 1), and at least 4 pilot projects (NIH R03s) during UWAC 2.0. These projects aim to improve clinical intervention and implementation strategy access and scale in diverse settings. The R01 Problem Solving Treatment-Aid (PST-Aid; NCT06494384; PIs: IB, PR, and SAM) will test a DDBT-designed decision support tool for Problem Solving Treatment (PST) in a large network of primary care clinics. R34 Research Units on Behavioral Intervention in Educational Settings (RUBIES; NCT06508515; PIs: KB and JL) will create a novel implementation strategy to support the delivery of evidence-based classroom supports for students with autism. R34 Trauma-Focused Cognitive Behavioral Therapy (TF-CBT; PIs: ARL and DW) will redesign and test an evidence-based clinical intervention for youth trauma for use in education settings. R34 Brief Intervention for School Clinicians (BRISC; PIs: EB, JVD, and Elizabeth McCauley) will adapt an existing set of effective implementation strategies to enhance delivery of a school-based engagement, assessment, brief mental health intervention, and triage strategy. Funding for all core projects began in 2023. Multimedia Appendix 2 outlines key details (eg, study design and sample) of each study. PST-Aid and RUBIES were part of UWAC 1.0 as R34 and R03 projects, respectively, highlighting how UWAC 2.0 activities build on previous accomplishments. UWAC funds pilot projects through a competitive solicitation process, with a particular focus on supporting and mentoring investigators from

historically marginalized groups. All projects use the DDBT framework to address clinical intervention and implementation strategy usability, engagement, and appropriateness in partnership with local community collaborators. UWAC provides projects direct support for integrating methods and measurement approaches and professional development that centers diversity, equity, and inclusion (DEI) values.

DDBT Constructs

Projects collect common data on DDBT mechanisms and constructs to determine the impact of modifying clinical intervention and implementation strategy targets. The Methods Core team maintains a list of recommended and required measures for projects to gather at each DDBT phase ("Center Measures and Guidance"; Multimedia Appendix 2). We developed Center Measures and Guidance to facilitate DDBT hypothesis testing and data management across UWAC, help teams select methods based on project design objectives, and satisfy NIMH reporting requirements. Center Measures and Guidance include 15 constructs with 26 quantitative and qualitative measures across DDBT phases. The Methods Core team provides project teams support with integrating and adapting these measures for projects through a consultation model. This is a shift from our approach in UWAC 1.0, where the Methods Core team provided more personalized measurement support to project teams. Multimedia Appendix 3 [83] outlines each construct with a description of related measures and activities, and relevance to each DDBT phase. The Methods Core team provides data management for all projects, maintains survey instruments in REDCap (Research Electronic Data Capture; Vanderbilt University), and conducts cross-project analyses. Each project is responsible for conducting its own analyses. The Methods Core team provides guidance on ensuring recruitment, data analysis, and dissemination practices incorporate diverse perspectives and accurately represent the lived experiences of participants to inform clinical intervention and implementation strategy redesign.

DDBT Theory of Change Mechanisms

Usability

All projects are expected to report usability issues on existing or redesigned clinical interventions and implementation strategies and standardized usability metrics to the Methods Core team. Because interviews alone can be limiting for identifying usability issues because of issues with recall or challenges with describing behavior, UWAC projects are encouraged to combine interviews with other methods such as CWIS and TAP. This helps projects learn what a participant is considering doing next and why, better understand their in-the-moment goals, and identify misconceptions. For example, R34 BRISC will use TAP and a cognitive walk-through methodology with users to identify opportunities for redesign and improve implementation based on user needs [39]. The Methods Core team supports projects with adapting surveys (eg, SUS, IUS, and SUS) and implementing cognitive walkthroughs and usability testing for projects.

Engagement

We expect all projects to assess engagement quantitatively using the User Responsiveness Scale and qualitatively (ie, thematic findings from observation or other chosen methods) during the Discover and Test phases of existing and redesigned clinical intervention and implementation strategy. The Methods Core team developed the User Responsiveness Scale based on the Patient Responsiveness Scale [66]. The User Responsiveness Scale has 10 statements that cover participation and enthusiasm for a clinical intervention and implementation strategy that participants rate on a Likert scale. The original Patient Responsiveness Scale has demonstrated strong internal consistency (Cronbach α=0.86) and construct validity.

Appropriateness

R01 and R34s are expected to administer the IAM [79] or revised goodness-of-fit interview [84] during the Discover and Test phases of existing and redesigned clinical interventions and implementation strategies to probe areas of alignment and misalignment on goals and expectations, roles, etc. IAM is a 4-item survey and the leading instrument for measuring clinical intervention and implementation strategy contextual fit with good internal consistency (Cronbach α=0.87) and adequate test-retest reliability (r=0.73). The goodness-of-fit interview is particularly well-suited to probe on clinical intervention and implementation strategy appropriateness issues identified through IAM. We will use content analysis to analyze goodness-of-fit interview data. For example, R34 RUBIES will conduct goodness-of-fit interviews to explore the appropriateness of the RUBIES implementation strategy ("RUBIES-Team") for the school environment using the CFIR domains to drive questioning.

Proximal Implementation Outcomes

Adoption and Reach

Adoption and reach are implementation outcomes specified in the CFIR [58] and Reach, Effectiveness, Adoption, Implementation, and Maintenance [85] frameworks. We expect projects to report on adoption and reach as part of the Design (if feasible) and Test phases. All projects will report adoption and reach of the intervention. For redesigned implementation strategies, the approach to measuring adoption and reach depends on the project. For example, R34 RUBIES defines adoption as educators' first use of the RUBIES-Team at any point during the study and will measure reach for both RUBIES-Individual (ie, an original implementation strategy) or RUBIES-Team in three ways: (1) the number of other educators with whom trained educators share RUBIES strategies; (2) the number of other students with whom trained educators share RUBIES strategies; and (3) the number of other contexts and settings in which they applied RUBIES strategies.

Intervention and Implementation Strategy Fidelity

Fidelity is a core implementation outcome [58]. We expect projects to report on fidelity as part of the Design (for existing clinical interventions and implementation strategies) and Test phases. Teams choose an approach to measuring fidelity based on redesign goals. For example, R34 RUBIES rates paraeducator fidelity to treatment (eg, weekly ratings of the paraeducator's

homework completion and behavior support plan implementation). R34 TF-CBT will code session recordings using the Therapy Process Observational Coding Scale [86] and the Therapy Process Observational Coding Scale–Self-Reported Therapist Intervention Fidelity for Youth [87] at baseline, 3 months, and 6 months. Finally, R01 PST-Aid will measure initial and sustained fidelity using a PST Fidelity Scale. Initial fidelity will be measured as the number of sessions it takes providers to get certified; providers must have 2 sessions rated as "satisfactory" on the PST Fidelity Scale to receive certification. Sustained fidelity will be measured as the number of "satisfactory" sessions during the 6 months after certification, as measured by the PST Fidelity Scale.

Planned Adaptations

Characterizing adaptations, or redesign solutions, is key to all 3 Methods Core team aims to better understand and address challenges to clinical interventions and implementation strategies. We expect projects to characterize adaptations with FRAME or FRAME-IS [29] as part of the Design and Build phase, where planned and proactive changes will be made as a part of the redesign process. For example, R34 BRISC will analyze recorded intervention sessions using FRAME or FRAME-IS. The R01 PST-Aid will code randomly selected session audio recordings per client for fidelity and adaptations using FRAME or FRAME-IS. Projects will share adaptations made with the Methods Core team and describe whether these adaptions were made proactively (eg, as part of the redesign process in the design and build phases) or reactively (eg, unplanned or due to unanticipated obstacles in the test phase). Across projects, the Methods Core team will systematically categorize adaptations to examine solutions and the populations, organization types or structures, practitioner types, and clinical interventions and implementation strategies in which they work. Our objective is to identify transferable and unique solutions to different contexts and clinical interventions and implementation strategies. This information will ultimately inform an updated version of the library of redesign solutions.

Unplanned or Reactive Modifications

Reactive or unplanned modifications during the Test phase will be measured using a 17-item Center-developed measure based on the FRAME or FRAME-IS to assess the nature of modifications. Providers will self-report any changes they made while they administer the intervention.

Distal Service Recipient Outcomes

During the Test phase, projects are expected to collect clinical and functional outcomes. Teams will administer standardized assessments (eg, Patient Health Questionnaire [88], Quality of Life in Neurological Disorders [Neuro-QOL] [89], Satisfaction with Social Roles for adults [90], and the Neuro-QOL Social Relations Scale for youth [91]). The Neuro-QOL measures are widely used to assess functioning in usual social roles, activities, and responsibilities. The scales have been evaluated with thousands of participants from the general population of the United States and in clinical inpatient and outpatient settings who have a wide variety of presenting problems [89-91]. All projects will also use idiographic (ie, individualized) client outcome monitoring based on the Top Problems Assessment [92], an approach informed by goal attainment scaling [93,94] that has been found to be highly sensitive for monitoring clinical intervention outcomes and thus is preferred over standardized or nomothetic assessments by both practitioners and clients [95].

Demographic and Process Measures

Demographics

All projects are expected to collect participant demographic data mandated by the NIMH at all phases. Teams collect additional demographic data on the basis of the project needs. For example, the R34 RUBIES collects required educator and student demographics (eg, age, gender, and race) and additional data on school characteristics (eg, school size, percentage eligible for free or reduced lunch, racial and ethnic composition, percentage of English language learners, percentage in special education, annual funding for external resources, and per capita number of community-based organizations). Data will be tabulated to satisfy federal demographic and data reporting requirements as well as cross-project meta-analyses and comparisons.

User Needs and Experience

All projects are expected to clearly identify direct and indirect users and incorporate methods that address user needs. Explicit user identification produces more usable products and ensures that the design team does not underestimate user diversity [96] or create designs based on the team's own needs [36,97,98]. clinical intervention and implementation strategy users should include the deliverers (eg, providers of clinical interventions) and recipients (eg, clients and implementation strategy targets such as administrators or clinicians). Identification of users for a clinical intervention and implementation strategy includes (1) generating a preliminary user list, (2) articulating the most relevant characteristics that reflect anticipated users, (3) describing and prioritizing main user groups, and (4) selecting typical and representative users [96]. For example, in R34 TF-CBT, direct users are school counselors and social workers who provide mental health services, as well as public school students with histories of traumatic stress. Potential indirect users in this project include caregivers of students. We included users who are diverse with respect to characteristics such as age (eg, students), race and ethnicity (eg, students and practitioners), culture (eg, students and practitioners), and clinical domain experience (eg, practitioners), which are features known to impact experiences of usability, engagement, or appropriateness [53,99-101].

Projects will use interviews to identify key challenges that users might face when applying clinical interventions and implementation strategies. Interviews consist of questions derived from HCD principles such as organizational and community culture, values, and challenges in applying clinical interventions and implementation strategies. For example, in R34 RUBIES, the team will interview educators about their existing opportunities to learn behavioral management strategies for students with autism who exhibit challenging behavior. Interviews will identify promising professional development approaches and areas to improve the existing RUBIES

multifaceted implementation strategy. Additional interviews with school administrators or lead special educators are likely to surface critical organizational factors that can serve as design constraints for any subsequent redesign solution [102,103].

As described earlier, interviews can be supplemented through observation methods to better understand interactions in real-world settings. Projects can use an adapted form of TAP, where participants (eg, clinicians or clients) and researchers watch recordings of sessions while the participant explains what they were thinking in the moment. This approach can offer additional suggestions for improvement on the design of a clinical intervention or offer ideas for tools that could support the clinician during implementation. Interviews can also supplement comparative testing (eg, A/B testing) to explore and evaluate a broader landscape of design options and reach more robust solutions. A/B testing is an evaluation method in which ≥2 versions of a prototype are compared sequentially or in parallel to determine which version is easier to use and better meets user needs [104]. For example, R34 BRISC will build prototypes of digital asynchronous learning modules for novel users as well as posttraining support tools; initial prototypes will undergo comparative testing to finalize solutions to be evaluated in the Test phase. The pragmatic applicability and match of potential designs to the targeted service environments and resource constraints will be systematically addressed.

Participant Research Burden, Incentive Appropriateness, and Research Satisfaction

At the end of the Test phase, projects are expected to measure the burden of participation in the study. This instrument includes 6 questions to understand participants' perceived burden of participating in the study, appropriateness of the level of compensation offered, and overall satisfaction with the study experience. This information will be used to help improve future protocols. Response frequencies will be tabulated for the 4 close-ended responses and themes will be summarized from open-ended responses.

Adherence to DDBT Process (DDBT Fidelity and Cost Measure)

All projects are expected to complete a Fidelity and Cost survey in REDCap about their application of HCD techniques at the end of each DDBT phase. We are developing the survey to systematically collect data on how the DDBT framework guides clinical intervention and implementation strategy redesign and link design activities with project goals. To facilitate teams in drawing on a range of methods, the Fidelity and Cost survey focuses on understanding which goals of each DDBT process teams completed (Figure 1) and the methods they used to support each goal. We will conduct descriptive statistical analyses and content analysis of data to understand the frequency of goals completed and HCD strategies used, links between strategies and goals, and modifications made to strategies during their use.

We will measure the costs of applying DDBT to help understand the resource requirements involved in its use, which can be a major challenge of HCD and coproduction methods [105]. Projects are expected to report total costs of redesign, reported through a Fidelity and Cost Survey in REDCap at the end of each phase (this is optional for R03 projects). We will aggregate activity-based costs (eg, time to create, complete, and analyze each activity; participant payments or time) across individuals, use budgets or other institutional records to assign hourly costs by role, and then add in any fixed costs (eg, materials and activity-specific software). We will calculate total DDBT costs, as well as phase-specific and activity-specific DDBT costs. Analyses will follow best practices by placing all US dollar values onto the same metric, including an index year to account for inflation; local or national average cost-of-living values to account for geographic variation in prices; and discounting of costs from different years due to preferences for delayed over immediate costs. We will conduct sensitivity analyses to examine the robustness of our cost estimates [106,107] by identifying areas of uncertainty in measuring units and prices for our ingredients, and then calculating costs across a range of plausible values (eg, we can substitute limits of 95% CIs for uncertain prices).

Team Collaboration, Trust, and Respect

At the end of each DDBT phase, R01 and R34s team members are expected to complete a survey that assesses satisfaction with the collaboration, impact of collaboration, trust, and respect. This survey is modeled after the Transdisciplinary Tobacco Use Research Center's measure of Team Collaboration and Transdisciplinary Integration, which assesses satisfaction with the collaboration, impact of collaboration, trust, and respect [108]. Continuous review of outcomes will allow for critical assessment and course correction as needed and recommended by these bodies. Participation is confidential, and teams will receive an aggregate report of the number of team member participants and average scores for each item. Any free-response comments are additionally summarized. We will encourage teams to discuss results to improve their projects.

Community Participation in Research

The collaboration survey questions described earlier will be administered with additional questions to characterize the extent to which redesign teams engage users in a localized DDBT process. This instrument is based on an existing measure of community participation in research [109,110], which has been modified to target the design of clinical interventions and implementation strategies across 6 dimensions: identification of design issues, design activities, use of resources, design methods, indicators of success, and sustainability. Redesign teams will complete the measure at or near the end of each DDBT phase and then discuss ratings in an interview.

Investigator Satisfaction With the Support They Receive From the Center

At the conclusion of projects, we will ask investigators to share their level of satisfaction with support from UWAC through a 5-item Likert survey adapted from a survey used by the University of Washington IMPACT Center [111]. We intend to use these data to improve how the Methods Core team provides projects technical support.

Data Analysis

The Methods Core team provides data management and guidance on all DDBT constructs. For Aim 3, fundamental

comparisons are the differences in DDBT mechanisms (usability, engagement, and appropriateness) and implementation outcomes (adoption, reach, adaptation, and fidelity [and sustainment for the R01 PST]) for the original (unadapted) clinical intervention and implementation strategy versus the DDBT-informed (localized) clinical intervention and implementation strategy. We will conduct a (1) qualitative multiple case study analysis and (2) quantitative meta-analysis across projects. Case studies will examine each project's context, implementation, mechanisms, and outcomes.

For each project, we will also develop analytical summaries to facilitate between-project comparisons. Using the constant comparative method [112], we will compare projects to group common and divergent themes. The meta-analytic synthesis will increase our inferential ability by combining results from the underpowered R34s. For the meta-analysis, each project's mechanism and outcome will be summarized as a Cohen *d* effect size comparing localized DDBT with original clinical intervention and implementation strategy and corresponding 95% CI, using random effects weighting by the inverse of the within- and between-studies variance. Standard data screening and adjustments will be made to the data (eg, to limit the effect of outliers, they will be winsorized). Each project will be additionally advised on how to address possible confounders in analysis and reporting. For instance, projects will be encouraged to use naive participants in the Design and Build and Test phases, recognizing that adaptations of smaller elements of complex clinical interventions may require the participation of experienced participants during the Design and Build phase. In addition, randomization will occur at appropriate levels to avoid contamination by intralevel communication. Nonmonotonic missing data will be addressed via inverse probability weighting or multiple imputation, as appropriate [113]. The Methods Core will aggregate these data across projects into a series of working meta-analyses of the effectiveness of DDBT on each mechanism and outcome.

Finally, determining whether a DDBT-modified clinical intervention and implementation strategy leads to better implementation and clinical outcomes is ultimately a question of mediation. Although the initial R34 and R03 studies are not likely to yield large sufficient sample sizes to meaningfully test such an implementation mechanism question, the R01 PST will provide a direct test of the DDBT theory of change (Figure 2). Aggregating project data over time will allow us to eventually test a range of mediation-focused hypotheses via multivariate network meta-analyses.

Incorporating DEI

During UWAC 2.0, we are improving the integration of DEI initiatives throughout Center activities. Projects selected for UWAC 2.0 and pilots must demonstrate potential substantial impact on clinical or public health outcomes, especially for historically marginalized communities. The Methods Core team provides mentorship on incorporating and adapting methods so that teams are positioned to conduct research that respects diverse populations and maximizes community benefits. Project teams will be provided training and consultation on the Adapting strategies to promote implementation reach and equity method, a 3-step process for adapting implementation science to promote equity, and expertise in methods for explicitly incorporating equity into the measurement of implementation outcomes [114]. We will also collaborate with projects to ensure diverse representation and decision-making during the DDBT phases, crucial stages where diverse viewpoints and demographically representative samples are essential. To facilitate diverse engagement, we will offer resources on building equitable research-practice partnerships, contextualizing implementation science to specific communities, and enhancing community collaborator capacities for community-engaged research. Consultation on quantitative critical research [115] will be provided to examine the treatment of race within quantitative methods and support equity testing through disaggregation, moderator exploration, and mixed methods triangulation.

UWAC additionally supports faculty and staff as part of its DEI work. The center team engages with historically marginalized investigators in planning and conducting center activities so that DEI efforts are integrated throughout center mentoring, pilot funding, methods support, and support for investigators planning future proposals. These measures include enhancing communication strategies based on team science [77] and avoiding a "minority tax," which refers to assigning additional responsibilities to marginalized or underrepresented team members to promote diversity [116,117]. The Methods Core team also advises investigators on using patient-centered and nonstigmatizing language when reporting findings.

Ethical Considerations

The University of Washington Institutional Review Board (IRB) approved materials and procedures for all 4 core projects and deemed projects minimal risk by June 2024 (PST-Aid: STUDY00017272; RUBIES: STUDY00017261; TF-CBT: STUDY00017262 and STUDY00019451; and BRISC: STUDY00017263 and STUDY00019682). All studies follow best practices across studies: review and collect informed consent and Health Insurance Portability and Accountability Act authorizations (when not waived) from participants; collect parental assent for individuals <18 years of age; compensate participants financially for their time and, when appropriate, with continuing education credits; and ensure participants are aware that they may opt out or leave the study at any time. When personal health information (eg, name, date of birth, and contact information) is collected, we preserve participant privacy and confidentiality by storing those identifiers separately from the study data and only linking them to study data via a code. The Methods Core team will provide support to pilot project teams on institutional review board applications after studies are funded.

Results

Overview

UWAC 2.0, including the 4 core projects detailed in Multimedia Appendix 3, received funding in June 2023. We provide a brief synopsis of each study's progress as of January 2025 in the subsequent sections. Across studies, as well as the to-be-funded R03 pilots, we anticipate DDBT will result in changes to the clinical intervention and implementation strategy mechanisms,

proximal implementation outcomes (ie, adoption, fidelity, reach, and adaptation), and clinical outcomes.

R01 PST-Aid

This study began in the Design and Build phase, as the Discover phase was completed during an R34 in UWAC 1.0. For the Discover phase, the study team has completed a codesign workshop and user testing with patients and providers from a nonprofit, health informatics network with independent community-based health centers. The study is beginning the Test phase, and the team is recruiting the first cohort of providers. Providers will be randomized to receive training in either PST implementation as usual (ie, training and sessions supported by paper worksheets for practitioners and clients to use as they complete PST) or PST-Aid (ie, a web-based app that promotes practitioner-client collaboration in the use of PST for goal setting and action planning).

R34 TF-CBT

At the time of submission, the study team has completed a task analysis of unadapted TF-CBT to prioritize components to develop scenarios for testing with students and school-based mental health practitioners. The study has finalized TF-CBT user-testing scenarios and are actively recruiting students and practitioners to begin the first of 3 waves of testing for the study. These data will then inform the redesign of TF-CBT, which aims to be more usable in school settings.

R34 RUBIES

Discover and Design and Build phase study activities, including focus groups, cognitive walkthroughs, and user testing with paraeducators and other school personnel (eg, principals and teachers), are complete. These data are being used to inform the Test phase where the study team is recruiting paraeducators and students and their caregivers to begin RUBIES training. Once recruited, this Test phase will include a 2-year randomized controlled trial enrolling paraeducators and students who will then be randomized to 1 of 2 implementation strategies: RUBIES-Individual or RUBIES-Team.

R34 BRISC

This study is scheduled to begin in April 2025, and the study team has received institutional review board approval.

Discussion

Charting New Research Directions

Our vision is to address persistent issues with usability, engagement, and appropriateness that are barriers to clinical intervention and implementation strategy use by drawing from the fields of HCD and implementation science. The first iteration of the center advanced our understanding of how DDBT can guide clinical intervention and implementation strategy adaptations for uptake in historically marginalized communities. During UWAC 2.0, we aim to continue serving as a multidisciplinary incubator to find viable solutions for improving implementation of clinical interventions and implementation strategies using DDBT through the R01, R34s, and pilot projects. Table 1 summarizes potential outputs and future directions by aim. Focusing on usability, engagement, and appropriateness and providing and testing ways to measure engagement in a clinical intervention and implementation strategy context is particularly novel. UWAC 2.0 will further test the robustness of the DDBT theory of change, expand the potential evidence base for its utility in combining HCD and implementation science for clinical intervention and implementation strategy redesign, and add to the field's understanding of how to apply DDBT to a variety of clinical intervention and implementation strategies and contexts.

Our experiences underscore a benefit of developing additional resources for DDBT, HCD, and implementation science. UWAC 1.0 outputs contributed to foundational conversations on the intersection of HCD and implementation science and produced potential pathways to address conceptual overlap and distinctions [43] and terminology [42]. We additionally developed resources such as CWIS [39], IUS [37], the ISUS [39], and a typology of modification targets and usability issues [53]. We have accumulated substantial experience adapting common HCD methods for different contexts and communities, and we hope these adaptations can support future teams in their use these methods. We plan to build on these methodological advancements, which have been used beyond the UWAC team by a broader research community interested in HCD and implementation science methods and measurement. As we learn with UWAC 2.0 project teams, we will continue to identify and develop additional resources for UWAC project teams and the broader research community on specific methods, team science, equity-oriented design practices, and grant writing. Developing additional resources aligns with the Methods Core team shifting to a consultation model on using the DDBT framework during UWAC 2.0. UWAC projects receive technical support from the Methods Core team with greater emphasis on building local capacity to apply DDBT rather than having the Methods Core team members conduct some of the DDBT activities.

Table 1. Expected center-level outputs and future directions by aim.

Aim	Expected outputs	Potential future work
Aim 1: identify clinical intervention and implementation strategy modification targets to improve usability, engagement, and appropriateness in accessible nonspecialty settings (Discover phase)	• Updated Typology of Modification Targets that expands the previously identified usability issue categories [53] • New insights on engagement and appropriateness issues in clinical intervention and implementation strategy redesign	• Incorporate additional findings from non–UWAC[a]-funded projects that have used the typology of modification targets
Aim 2: develop redesign solutions with local teams to address clinical intervention and implementation strategy modification targets (Design and Build phase)	• Updated Library of Redesign Solutions	• Recommendations on how to approach measuring engagement and appropriateness with a focus on clinical intervention and implementation strategy redesign
Aim 3: determine if redesign affects changes in usability, engagement, and appropriateness (Test phase)	• Integrated cross-project analyses to demonstrate the impact of DDBT[b]-informed redesign	• Further expansion of DDBT and associated methods to new domains in health and social services

[a]UWAC: University of Washington Advanced Laboratories for Accelerating the Reach and Impact of Treatments for Youth and Adults with Mental Illness Center.

[b]DDBT: Discover, Design and Build, and Test.

Limitations

UWAC 2.0 and the DDBT framework represent a robust effort to integrate HCD with implementation science, although several methodological limitations merit consideration. The standardized measures we are using to assess usability, appropriateness, and engagement have evidence of psychometric soundness, but these measures have not yet been evaluated in all the contexts in which they will be applied. Redesign solutions developed by local teams may rely primarily on context-specific adaptations, which may not generalize to other settings and may not address systemic barriers that impact usability or accessibility. Therefore, reactive modifications (ie, primary outcome) needed to address additional barriers may not be reduced. In this work, there is a tension between our desire to standardize DDBT phases and measures, to facilitate center-wide learning, with promoting the adaptability and flexibility to adapt to specific goals, contexts, and populations that is necessary for good design projects. This, combined with the variability of research project contexts, the small sample sizes of redesign teams and subjective nature of the proposed mechanisms may impede our ability to make inferences across projects.

Conclusions and Impact

There is a pressing need to ensure that clinical interventions and implementation strategies are easily implementable and meet the needs of the communities they aim to help. Integrating HCD and implementation science offers promising approaches to tackle this challenge. UWAC 2.0 expands and strengthens our efforts to ensure that accessible community service settings and marginalized communities see the benefit of decades of research on effective clinical interventions and implementation strategies.

Acknowledgments

This project is funded by the National Institute of Mental Health (2 P50MH115837; principal investigators: ARL and SAM). The funding body had no role in the study design, writing of the manuscript, or decision to submit the paper for publication.

Data Availability

Clinical outcome data for the R01s and R34s will be made publicly available through the National Institute of Mental Health National Data Archive. The quantitative datasets generated and analyzed during this study are available from the corresponding author on reasonable request.

Authors' Contributions

All authors contributed to conceptualizing the study. ARL, SAM, and MDP led funding acquisition and created the protocol with support from the team on methodology. MDP led plans for data curation and formal analysis. ARL, SAM, BM, and TA wrote the original draft with review and editing support from all authors. BM and KPO oversaw project administration.

Conflicts of Interest

KB reports royalties from Oxford University Press.

Multimedia Appendix 1
Peer-review report by the National Institute of Mental Health Special Emphasis Panel - National Institute of Mental Health - Advanced Laboratories for Accelerating the Reach and Impact of Treatments for Youth and Adults with Mental Illness (National Institutes of Health, USA).
[PDF File (Adobe PDF File), 211 KB - resprot_v14i1e65446_app1.pdf]

Multimedia Appendix 2
Summary of projects.
[DOCX File , 32 KB - resprot_v14i1e65446_app2.docx]

Multimedia Appendix 3
Center measures and guidance.
[DOCX File , 29 KB - resprot_v14i1e65446_app3.docx]

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Abbreviations

BRISC: Brief Intervention for School Clinicians
CFIR: Consolidated Framework for Implementation Research
CWIS: Cognitive Walkthrough for Implementation Strategies
DDBT: Discover, Design and Build, and Test
DEI: Diversity, Equity, and Inclusion
FRAME: Framework for Modifications and Adaptations of Evidence-Based Interventions
FRAME-IS: Framework for Modifications and Adaptations of Evidence-Based Interventions for Implementation Strategies
HCD: human-centered design
HCI: human-computer interaction
IAM: Intervention Appropriateness Measure
ISUS: Implementation Strategy Usability Scale
IUS: Intervention Usability Scale
Neuro-QOL: Quality of Life in Neurological Disorders
NIH: National Institutes of Health
NIMH: National Institute of Mental Health
PI: principal investigator
PST: Problem Solving Treatment
PST-Aid: Problem Solving Treatment-Aid
REDCap: Research Electronic Data Capture
RUBIES: Research Units on Behavioral Intervention in Educational Settings
SUS: System Usability Scale
TAP: think-aloud protocol
TF-CBT: Trauma-Focused Cognitive Behavioral Therapy
UWAC: University of Washington Advanced Laboratories for Accelerating the Reach and Impact of Treatments for Youth and Adults with Mental Illness Center

Edited by A Schwartz; submitted 19.08.24; this is a non–peer-reviewed article;accepted 02.12.24; published 29.01.25.

Please cite as:
Lyon AR, Munson SA, Pullmann MD, Mosser B, Aung T, Fortney J, Dopp A, Osterhage KP, Haile HG, Bruzios KE, Blanchard BE, Allred R, Fuller MR, Raue PJ, Bennett I, Locke J, Bearss K, Walker D, Connors E, Bruns E, Van Draanen J, Darnell D, Areán PA
Harnessing Human-Centered Design for Evidence-Based Psychosocial Interventions and Implementation Strategies in Community Settings: Protocol for Redesign to Improve Usability, Engagement, and Appropriateness
JMIR Res Protoc 2025;14:e65446
URL: https://www.researchprotocols.org/2025/1/e65446
doi:10.2196/65446
PMID:

Protocol

Investigation of Information Overload in Electronic Health Records: Protocol for Usability Study

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Abstract

Background: Electronic health records (EHRs) have been associated with information overload, causing providers to miss critical information, make errors, and delay care. Information overload can be especially prevalent in medical intensive care units (ICUs) where patients are often critically ill and their charts contain large amounts of data points such as vitals, test and laboratory results, medications, and notes.

Objective: We propose to study the relationship between information overload and EHR use among medical ICU providers in 4 major United States medical centers. In this study, we examined 2 prominent EHR systems in the United States to generate reproducible and generalizable findings.

Methods: Our study collected physiological and objective data through the use of a screen-mounted eye-tracker. We aim to characterize information overload in the EHR by examining ICU providers' decision-making and EHR usability. We also surveyed providers on their institution's EHR to better understand how they rate the system's task load and usability using the NASA (National Aeronautics and Space Administration) Task Load Index and Computer System Usability Questionnaire. Primary outcomes include the number of eye fixations during each case, the number of correct decisions, the time to complete each case, and number of screens visited. Secondary outcomes include case complexity performance, frequency of mouse clicks, and EHR task load and usability using provided surveys.

Results: This EHR usability study was funded in 2021. The study was initiated in 2022 with a completion date of 2025. Data collection for this study was completed in December 2023 and data analysis is ongoing with a total of 81 provider sessions recorded.

Conclusions: Our study aims to characterize information overload in the EHR among medical ICU providers. By conducting a multisite, cross-sectional usability assessment of information overload in 2 leading EHRs, we hope to reveal mechanisms that explain information overload. The insights gained from this study may lead to potential improvements in EHR usability and interface design, which could improve health care delivery and patient safety.

International Registered Report Identifier (IRRID): DERR1-10.2196/66127

(JMIR Res Protoc 2025;14:e66127) doi:10.2196/66127

KEYWORDS

electronic health records; information overload; eye-tracking; EHR usability; EHR interface

Introduction

Electronic health records (EHRs) can be a source of information overload for providers; however, the mechanisms that explain overload and their link to patient safety are not understood. Information overload in the EHR is associated with missing critical information that affects the decision-making process [1-3]. Studies have relied on secondary data analysis or subjective measures to assess the effect of information overload on decision-making processes; however, the use of physiological and objective data to study information overload has shown great potential in other domains [4]. We propose using eye-tracking approaches coupled with objective patient safety measures to investigate current EHR design flaws [5-9]. These methods reveal mechanisms that explain overload, such as fatigue and degradation in performance. Furthermore, poor EHR interface design contributes to inefficiencies [10], frustration [11], and medication errors [12].

Although advantageous over paper-based documentation, EHR use is associated with new physician-related challenges that may increase medical errors [13]. EHR interface design can lead 50% of providers to make an error when ordering medication tapering [12]. In addition, too much information contributes to patient safety risks, such as 30% of providers missing test results in the EHR, leading to care delays [2,14]. Information overload increases cognitive load and error rates among physicians during clinical simulations. Common issues contributing to information overload included an overabundance of clinically irrelevant information, poor data presentation, and excessive alert notifications [15]. However, we have limited knowledge of the relationship between information overload and EHR usability.

Our study uses objective eye-tracking data along with self-reported task load and usability surveys to better understand the challenges Intensive care unit (ICU) providers face in using EHRs to provide patient care. By measuring providers' performance, information seeking load, and information processing load, we aim to characterize information overload in the EHR by examining decision-making and usability outcomes.

Methods

We conducted a multisite, cross-sectional usability assessment of information overload in 2 leading EHRs among medical ICU providers in 4 US medical centers. Between the 4 sites, 2 leading EHR systems are used. The ICUs at the medical centers vary in terms of the catchment area; however, all 4 medical centers in the study are considered level I trauma centers, each with level 3 ICU support. The number of ICU beds between the 4 medical centers ranges from approximately 74 to 200 ICU beds each.

Providers will be recruited by the individual study site teams at each medical system using emails, flyers, and word of mouth. Interested providers will be asked to complete an initial screening survey before scheduling a session to ensure that they are an ICU provider or, if they are a resident, that they have completed at least one ICU rotation.

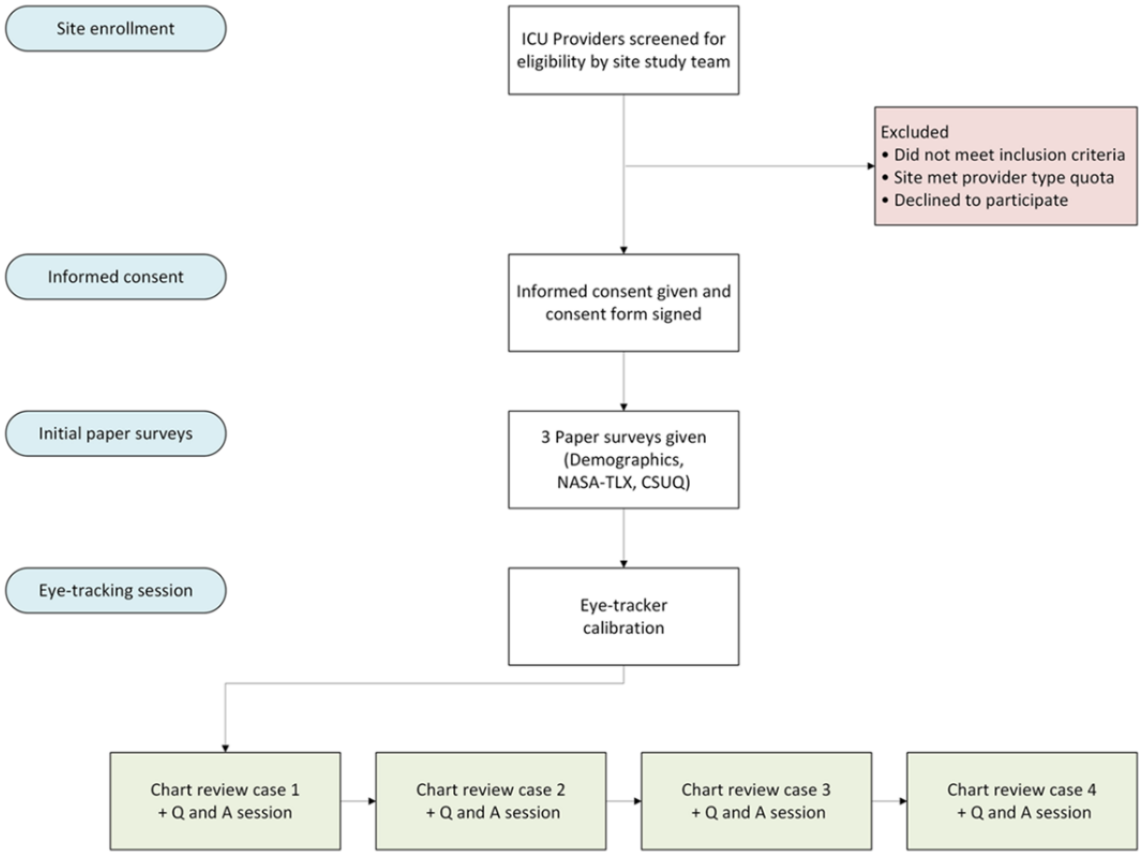
The sessions will occur in a simulation laboratory or private space that mimics the ergonomics of natural inpatient settings. Our team used the standard computer screen in each practice setting, with ICU-like ergonomic placement, ambient lighting, and seating. To ensure standardization among the cases, the lead investigators at each site met via Zoom (Zoom Video Communications) to determine a rubric for patient records to be included in the study. The study team created 4 ICU patient cases for inclusion, based on reviews of our 2 domain experts. Next, the domain experts created a set of universal experimental questions and tasks for providers to complete for each patient.

Before each session, the usability specialist explained the study and consent forms to providers, assuring them that the goal is to assess EHR usability rather than clinical knowledge. Participants are informed that their participation is voluntary and that they can decline to participate at any time. After the informed consent has been obtained, each provider will be asked to complete 3 pages of paper surveys.

We then ask providers to complete a basic calibration exercise while looking at the monitor which allows the eye-tracking software to be calibrated to each provider's eye shape and eye size. We record pupil diameter and fixation points on the screen continuously during the study session. All sessions used the same screen-based eye tracker.

Each provider was then logged in to their institution's EHR environment, where 4 simulated ICU patient records are presented in random order to eliminate selection bias. Providers reviewed 1 patient case at a time and were encouraged to review the patient chart as if they were prerounding on this patient, using their typical workflow. The provider then indicated to the research assistant (RA) when they completed their chart review and were ready to begin a series of question-and-answer activities about that specific patient. The RA asked the provider a series of questions in which the provider responded verbally, and the RA recorded the answers using both audio and written recordings. Providers were allowed to navigate through the EHR to answer these questions. After completion of question-and-answer activities, the provider then reviewed the next patient record. A process map detailing the study procedure from enrollment to usability session can be seen in Figure 1.

Figure 1. Process map illustrating the various study steps from recruitment to completion of the usability session. CSUQ: Computer System Usability Questionnaire; ICU: intensive care unit; NASA-TLX: National Aeronautics and Space Administration–Task Load Index; Q and A: question and answer.



Patient Cases

A team of critical care physicians created 4 patient cases. Each patient was representative of a patient that could be hospitalized in an ICU setting. Of the 4 patients, 2 were considered basic or "standard" ICU patients while 2 were considered to be complex patients. The 2 basic patients were less critically ill, not currently ventilated, on fewer medications, and had fewer abnormal laboratory values. The 2 complex patients were critically ill with many abnormal laboratory values, on the ventilator with poor oxygenation, and on complicated medication regimens.

The nurse informatician on the study team worked with the primary investigator and each site's study team to build the patient cases in their institution's EHR test environment. The same 4 cases were used at all study sites, and the nurse informatician monitored case builds to ensure consistency and accuracy across study sites.

Case Questions

Providers were asked 5 questions for each patient following their preliminary chart review. These questions were created by a critical care physician (TB) and reviewed by a critical care physician team before data collection. Questions were written to ensure the answer is present within the EHR and that providers at different levels of experience can realistically locate the answer. While some questions were considered more basic and only needed 1 EHR screen or data point to answer, other questions were more complex and required synthesizing multiple data points or locating information not frequently accessed. This approach allows us to analyze the time it takes to answer these questions and how many EHR screens and mouse clicks each provider uses before answering a question. Questions were scored as either correct, partially correct, or incorrect by the team nurse informatician. Alternate answers will be reviewed by a critical care physician (SC) for scoring.

Sample

Our initial goal was to recruit 80 ICU providers, 20 at each site, with the following distribution: 15 physicians and 5 advance practice providers (APPs). The physician group will be divided into 3 subgroups: 5 attending physicians, 5 fellow physicians, 5 resident physicians, and 5 APPs including nurse practitioners and physician assistants. Our actual recruitment was 81 ICU providers, comprised of 53 physicians and 28 APPs. Each study team's local RAs circulated departmental emails and flyers at each site. They provided interested individuals with a link to an online calendar showing available time slots to facilitate appointment scheduling. Once an appointment was scheduled, the RA emailed each participant their appointment time and location with a map, as well as a contact number for same-day inquiries or cancellations. Inclusion criteria: ICU physicians and APPs on active full-time ICU service OR Residents who have completed at least 1 ICU rotation, use an institutional EHR, and speak English.

Statistical Power

The design effect arising from the clustering within-person inherent to the study's design is estimated using the following formula: $D_{eff}=1+(m-1)$, where m=average cluster size (4 cases)

and *P*=intraclass correlation coefficient (ICC). Assuming an ICC of .6 (a common ICC for similar intensive repeated measures designs), the application of this equation results in D_{eff} of 1.09, for an effective sample size of 294 (320/2.8). In a multivariable linear regression context assuming N=114, 5 person-level effects, 3 case level effects, a 2-tailed critical *P*=.05, and 80% power, the minimum detectable effect size is represented by a Cohen f^2 of 0.10, which is considered a small effect. In a multiple logistic regression with 2 tailed critical *P*=.05 and 80% power, the minimum detectable odds ratio is 3.23, which is considered a medium-sized effect.

Materials and Software

To measure the extent and effect of EHR information overload, we used several tools during the 1-hour sessions.

Providers were asked to complete 3 paper surveys before the eye-tracking session. The first survey asked basic demographic questions, including age, gender, years since graduation (medical school or APP schooling), years of experience with their institution's EHR, and the estimated number of hours they use their institution's EHR each week. We also asked the providers if they are on service that day (pre- or post-usability session) and to rate their level of sleepiness and stress on a Likert scale. The second paper survey used was the NASA (National Aeronautics and Space Administration) Task Load Index (NASA-TLX) which asked providers to rate the task load of their institution's EHR, including how mentally and physically demanding it is to use and their level of satisfaction and confidence with using the EHR [16]. The third and final paper survey was the Computer System Usability Questionnaire (CSUQ) which asked providers to rate their satisfaction with their institution's EHR system including questions about usability, ease of use, the system interface, and overall functionality [17].

Our study used a noninvasive screen-based eye tracker to provide further insights into a provider's cognitive processing during the sessions. The Tobii Pro Fusion is an advanced eye-tracking system with 2 eye-tracking cameras taking up to 250 images per second to ensure accuracy. The Pro Fusion mounts onto the bottom of any monitor, allowing us to record eye-tracking data seamlessly. The Tobii eye-tracker was used with Tobii Pro Lab software to create a seamless recording that includes eye-tracking data and screen recording. Used by renowned researchers in medicine and psychology [18,19], the Tobii eye-tracker and software will provide us with fixation points, gaze areas, and eye movement type. These measures will provide us with insight regarding providers' information processing behaviors, in particular, the relationship between fixation points (a measure of concentration) and the outcome variable (decision-making accuracy). We have expertise in analyzing large and complex data sets from Tobii, considered the most accurate eye-tracking device manufacturer in the world.

Outcomes

Primary outcomes are cognitive overload (ie, fixation points), usability (clicks and completion time), and performance score. Secondary outcomes are the provider reported EHR workload and usability using the NASA-TLX and computer system usability questionnaire surveys.

To characterize information overload, we will explore under what conditions providers experience EHR information overload. We will accomplish this by determining which patient cases create the highest level of information overload, indicated by the least number of eye fixations, meaning a loss of concentration. We also want to understand the consequences of a lack of concentration as it relates to decision accuracy and time. Understanding the underlying factors and the consequences of information overload will fill a significant gap in the literature.

Analytical Plan

Each participant will receive a single score for each question determined by the domain expert (0: incorrect, 0.5: partial, and 1: correct). Correct decisions are the aggregate of the correct answers, and errors are the aggregate of the incorrect answers. For each participant, we will compute a score for each patient case and a total score for all the patient cases. Case scores will depend on the number of questions asked, such that if a case has 5 questions to be answered, the total score of this case will be equivalent to the highest possible points (5).

Our past work will inform ways to compute case scores [10,12]. Responses and scores will be assigned by 2 domain experts (the site-Principal Investigator and a senior ICU provider).

Eye-tracking data gives the frequency and duration of fixations for each participant. We will calculate participants' fixation points based on (1) total fixations for the study, (2) total fixations per patient case, and (3) total fixations per EHR screen visited.

We will compute descriptive statistics for patient and case characteristics, employing chi-square tests, *t* tests, and ANOVAs to examine between-group differences, where appropriate. We will examine differences between provider types (physicians and APPs), as well as between sites. Given the nested nature of the data (ie, repeated case assessments nested within providers), we will use multilevel modeling as the primary analytic approach. Each patient case will be coded based on the days of ICU stay and the presence or absence of key characteristics such as vent settings and intake and output, to determine the level of complexity. Case variables will be entered into the model as case-level (Level 1) predictors. Models will also account for person-level (Level 2) factors such as participant gender, age, clinical role, site, and years of EHR experience. We will use SAS (version 9.4; IBM Corp) using PROC MIXED for continuous outcomes and SAS PROC GLIMMIX for binary and count outcomes.

Ethical Considerations

Recruitment and site testing occurred sequentially, such that the study was implemented at one site at a time, allowing the study team to be present on site to add organization to the data collection process. Each participant was required to read and sign a consent form specific to their medical center, witnessed by a representative of that medical center. Participants were allowed to opt out of the study at any time. We used one

screen-based eye-tracker device for data collection at each site. We recruited through flyers and departmental email communications at each site. Participants were compensated with a US $100 gift card for their participation. All data collected were deidentified and study participants and their data were assigned a unique identification number. Study data entry and management systems are secured and password protected to ensure participant privacy and confidentiality. The University of North Carolina at Chapel Hill's institutional review board (IRB) approved this study (IRB #20-3384).

Results

This EHR usability study was funded in 2021. The study was initiated in 2022 with a completion date of 2025. Data collection was completed in December 2023 with a total of 81 provider sessions recorded. The primary analysis is ongoing and expected to be published in early 2025.

Discussion

Study Significance and Strengths

This study aims to characterize information overload in the EHR and uncover possible improvements to EHR interfaces and user skills. We will deploy a mixed methods approach to better study providers' reactions to information overload in the EHR. We will use usability evaluation metrics, eye-tracking, and surveys to assess the aforementioned relationship. The use of physiologic data, namely eye-tracking, will produce new knowledge about providers' cognitive performance during EHR interaction. Eye-tracking will allow us to quantify fixation points, a measurement of cognitive overload, as providers interact with basic and complex ICU patient cases. In this study, we examine the 2 most prominent EHR systems in the US, which will generate reproducible and generalizable findings that can be applied to clinical settings using an EHR system. Another strength of this study is the inclusion of different professional roles, including residents, APPs, fellows, and attending. This diverse sample will enable subgroup analysis to test if information overload has similar effects on different professional roles.

Examining information overload within EHRs will demonstrate the critical impact of EHR usability on clinical decision-making, especially in high-pressure environments like ICUs. By measuring and assessing information overload, we can identify design opportunities in EHRs that may improve providers' ability to access and process vital information. This knowledge enables health systems to enhance patient safety and the quality of care by tailoring training and support systems that address specific challenges faced by providers. Future research needs to involve longitudinal studies to evaluate the long-term effects of information overload on clinical performance and patient outcomes. Incorporating qualitative methods, such as interviews with providers, will complement our quantitative findings to create a comprehensive understanding of EHR interactions. Potential interventions may include the implementation of information visualization within EHRs to facilitate information processing, implementing tailored training programs for providers, and developing integrated decision support tools. These research goals aim to enhance EHR usability, reduce the cognitive burden on health care professionals, and promote a safer and more efficient health care delivery system.

Limitations

Although we proposed adequate recruitment numbers, we understood that recruiting the exact number of participants in each professional role may be challenging. Alternatively, we expanded recruitment to include medical ICUs in other affiliated hospitals within the same health care system. All study sites include multiple hospitals to enable expanding recruitment within the same system and under the same IRB. Potential bias may occur from recruiting participants who are technology enthusiasts. We attempted to mitigate this bias by predefining a quota for every professional role to ensure we have representation from junior and senior providers. This mix of roles was done to include persons with varying degrees of technological astuteness.

Variations in EHR design and performance may affect the study findings. We account for this limitation by including the 2 most prominent EHR systems and 4 different medical centers, leading to more generalizable findings. The study protocol was not published earlier to keep the study design and the components of the patient cases undisclosed to avoid introducing bias to potential participants.

Future Directions

We will use our findings from this study to guide future research on information overload in the EHR. Observations of the current opinions and functionality of each of the 2 institutional EHRs will be used to prepare for a randomized controlled trial using the same 4 US medical centers. This randomized controlled trial will compare the current institutional EHR's interface with a visualization dashboard, examining the differences in provider efficiency and fatigue.

Conclusions

Our study aims to characterize information overload in the EHR by examining decision-making and usability outcomes among medical ICU providers. By conducting a multisite, cross-sectional usability assessment of information overload in leading EHRs, we hope to reveal mechanisms that explain overload, such as fatigue and degradation in performance. Through the use of eye-tracking approaches coupled with objective patient safety measures, we aim to investigate current EHR design flaws and their impact on decision-making processes. The insights gained from this study will contribute to a better understanding of the relationship between information overload, EHR usability, and patient safety, ultimately leading to potential improvements in EHR interface design and health care delivery.

Acknowledgments

We sincerely thank the study site teams at Mayo Clinic, Medstar, and UPMC for their collaboration on this important work.

Research reported in this publication was supported by the National Library of Medicine of the National Institutes of Health (award R01LM013606). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Data Availability

The data that support the findings of this study are not openly available due to reasons of sensitivity and are available from the corresponding author upon reasonable request. Data are located in controlled access data storage at the University of North Carolina at Chapel Hill.

Authors' Contributions

All authors contributed to the conceptualization, methodology, and design of the study and established the hypothesis. SK and JM wrote the first draft of the manuscript. All authors contributed to the writing review & editing. All authors were invited to revise the manuscript and approved the final version of the manuscript.

Conflicts of Interest

None declared.

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Abbreviations

APP: advance practice provider
CSUQ: Computer System Usability Questionnaire
EHR: electronic health record
ICC: intraclass correlation coefficient
ICU: intensive care unit
IRB: institutional review board
NASA-TLX: National Aeronautics and Space Administration–Task Load Index
RA: research assistant

Edited by A Schwartz; submitted 06.09.24; this is a non–peer-reviewed article;accepted 18.12.24; published 11.02.25.

Please cite as:
Khairat S, Morelli J, Boynton MH, Bice T, Gold JA, Carson SS
Investigation of Information Overload in Electronic Health Records: Protocol for Usability Study
JMIR Res Protoc 2025;14:e66127
URL: https://www.researchprotocols.org/2025/1/e66127
doi:10.2196/66127
PMID:39932774

Protocol

Digital Mental Health Screening, Feedback, and Referral System for Teens With Socially Complex Needs: Protocol for a Randomized Controlled Trial Integrating the Teen Assess, Check, and Heal System into Pediatric Primary Care

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Abstract

Background: Teens with socially complex needs—those who face multiple and potentially overlapping adversities—are disproportionately affected by several barriers to mental health screening and treatment. Pediatric primary care (PPC) is a typically low-stigmatized setting for teens that is visited at least annually. As such, implementing digital mental health tools (DMH), as low-intensity treatments in PPCs may increase the reach of such tools for teens with socially complex needs.

Objective: This study aimed to evaluate the Teen Assess, Check, and Heal (TeACH) System in comparison to a control condition while integrated into PPCs at 2 Medical Centers serving teen patients in Chicago, Illinois. Through collaboration with key players throughout the design and implementation planning phases, the TeACH System is hypothesized to increase teen patient self-reported engagement with DMH and address specific individual-level barriers to mental health care, compared with a digital psychoeducation control condition.

Methods: Eligible participants will be recruited through PPC clinics housed within the University of Illinois Chicago (UIC) and Rush University Medical Center (RUSH). Recruitment involves invitations from research staff members and primary care clinicians and staff members, as well as posting flyers with QR codes at the specified clinics. All participants complete a brief demographic survey, baseline survey, and Kiddie-Computerized Adaptive Tests Anxiety Module. Participants are randomized to receive either the control condition (digital evidence-based workbook) or the intervention (TeACH System Feedback and Resources). All randomized participants will then be invited to complete an immediate and 1-week follow-up survey. The primary outcomes assess changes in engagement with DMH (ie, likelihood to use DMH for anxiety and actual DMH use) and individual-level barriers to mental health care (ie, symptom understanding and confidence to act). Descriptive analyses will be conducted to characterize the sample and usability ratings of the TeACH System. Linear or generalized linear mixed effects regression models will examine differences in primary outcomes over time.

Results: Recruitment began in July 2024 and data collection is expected to be completed by August 2025. To date, 122 teens have assented to complete study activities, 80 have been randomized (an additional 24 teens have had subthreshold anxiety symptoms and were therefore not randomized), and 42 teens have completed the 1-week follow-up assessment.

Conclusions: This study will provide preliminary feasibility data that may inform how the TeACH System and other DMH low-intensity treatments might better engage and support teens with socially complex needs.

Trial Registration: ClinicalTrials.gov NCT05466929; https://clinicaltrials.gov/study/NCT05466929

International Registered Report Identifier (IRRID): DERR1-10.2196/65245

(JMIR Res Protoc 2025;14:e65245) doi:10.2196/65245

KEYWORDS

teens; primary care; digital mental health; low intensity treatments; disparities

Introduction

Background

Even before the multiple endemics occurring since 2020, pediatric mental health disorders and symptoms were the leading causes of disability and negative sequelae for youth [1]. For some time, mental health disorders have been the most common disease of childhood in the United States, surpassing the *combined* rates of multiple pediatric conditions (eg, cancer and diabetes) [2-4]. Despite the tremendous impact of mental health disorders on teens, millions do not receive mental health care [2]. Anxiety is particularly untreated, as up to 80% of youth with a diagnosable anxiety disorder do not receive mental health care [2,3,5]. Most exposed to this failure of mental health care are teens with socially complex needs, those who face multiple and potentially overlapping adversities, such as (1) enduring adverse childhood experiences, (2) residing in a systemically excluded community that experiences disproportionate disparities in health outcomes and health care access, or (3) being minoritized due to socioeconomic status as well as racial, ethnic, gender, or sexual identity or identities [1,6-8]. Teens with socially complex needs have multiple barriers placed between them and mental health care, which the current system is failing to address [9-15]. As such, traditional methods for reaching such teens are not working, resulting in life-long health disparities and a significant public health impact [2,6,7,16,17].

Digital Tools Implemented in Primary Care to Extend Care Capacity

Pediatric primary care (PPC) is one setting with strong potential as an environment to engage and screen teens with socially complex needs. Indeed, nearly all youth visit a PPC office annually for well-child visits as well as illnesses or injuries that necessitate care (eg, ear infection) [18]. As such, PPC is a centralized and typically low-stigmatized setting for teens of all backgrounds. Mental health care is increasingly warranted in PPC, with the American Academy of Pediatrics recommending universal anxiety screening for all children and adolescents, aged 8-18 years, during PPC visits [19]. However, PPC providers report variable administration of standardized assessment measures [20] and multiple barriers to mental health screening, broadly [20-22]. Further, when mental health needs, such as anxiety, are screened or arise in PPC, pediatricians report multiple barriers to assessing mental health needs and connecting patients to therapy [23,24], adding to the obstacles to care noted above. Even in the case of using a collaborative care model for depression in primary care [25], a pragmatic approach for anxiety that embraces the logistical realities that providers face in delivering mental health screening and ensuing recommendations is lacking [26,27]. A potential solution to these barriers is to incorporate digital mental health tools (DMH) as a low-intensity treatment (LIT) into PPCs. LITs are patient-facing tools that may provide screening, psychoeducation, resources, or combinations of these items. Given the long-standing efficacy of LITs in digital and other delivery mechanisms for mild to moderate symptom presentations (eg, self-help books) [28], DMH LITs have been proposed as a scalable and strategic first-line model of care in PPC and similar care environments [29].

Integrating DMH LITs into spaces that teens already visit, such as PPC, has the potential to increase mental health care reach. However, uptake and subsequent clinical outcomes will not be impacted if teens do not engage with DMH in their daily lives [30]. One problem is a lack of implementation planning early on in the design processes for DMH [31,32]. Also implicated in poor engagement is a failure to address the range of multilevel implementation barriers, spanning from individual-level barriers (eg, problem recognition, stigma, and confidence to act), intervention barriers (eg, usability and relevance), and systemic barriers (eg, accessibility and cost) [24-27,33]. Interventions such as incorporating motivational interviewing [34] and usage incentivizes [35-37] have improved DMH engagement, but diminish scalability [38]. As such, means to target barriers must be identified and harnessed to address poor engagement, the perennial failure of DMH deployment to date.

Objectives

In this study, human-centered design methodologies and an implementation science framework [39-41] were used to guide the development and implementation of the Teen Assess, Check, and Heal (TeACH System). Through the use of these methodologies and frameworks, the TeACH System was designed to target individual-level barriers to care (eg, feedback to directly respond to problem recognition, stigma, and confidence to act on symptoms), DMH intervention barriers (eg, human-centered design methodologies to optimize usability and relevance), and systemic barriers to care (eg, increase accessibility by integrating in a space already visited by teens, remove cost barrier by providing a freely accessible service and resources) [24-27,33]. Our primary aim was to increase DMH

engagement for teens with socially complex needs through: (1) engaging teens and caregivers from the systemically-excluded and underserved communities of Chicago, Illinois, to refine the TeACH System to be engaging, appropriate, and in line with cultural and user needs; and (2) integrating the TeACH System into PPCs serving teens on the West Side of Chicago. The West Side of Chicago was selected for initial implementation planning and integration evaluations as part of a larger body of research focusing on adapting DMH LITs for and with teens living in communities disproportionately inflicted with health disparities, violence exposure, and higher economic hardship (eg, [42]). Through collaboration with key players throughout the design and implementation planning phases, the TeACH System was hypothesized to increase teen patient self-reported engagement with DMH and address specific individual-level barriers to mental health care, compared with a digital psychoeducation control condition. This hypothesis is being evaluated through a pilot feasibility randomized controlled trial in Chicago PPCs, comparing engagement outcomes for teens with anxiety randomized to use the full TeACH System to those who are provided access to a publicly available, digital evidence-based workbook for teens (psychoeducation control) [43,44].

Methods

Positionality

Positionality influences all aspects of a research study and is connected to the researchers' personal and philosophical views [45]. In recognition of this influence, the positionality of the lead author of this study has been reported elsewhere [23] and is similarly described: (1) author CSS is a lifelong Chicagoan, (2) trained social worker, and (3) a pediatric psychologist who believes that engaging youth with DMH and in health environments they already frequent maybe 1 path to get more resources directly to youth to use as they need and want, but that DMH will not become a panacea to disparities. As a monolingual, White woman trained in health care settings, she has biases and experiences that may impact her interpretation of findings (eg, she is comfortable in health settings; DMH has primarily been tested with individuals who have overlapping identities with her [eg, college-educated and White women] [46]). To minimize bias, author CSS partnered with key players, by establishing interdisciplinary mentor and peer collaborator teams, to learn with teens, caregivers, and providers about their wants and needs for DMH in health care settings.

Procedures

Study Design

The study design is a pilot feasibility randomized controlled trial. The participant focus is teen patients in PPCs with anxiety. While universal anxiety screening is recommended [19], pediatric anxiety has a long-standing history of being underrecognized and often untreated [47-49]. Participants first answer initial screening eligibility questions (ie, age, clinic location, and ability to complete and read surveys in English), followed by completing a digital assent. While a waiver of guardian consent was obtained from the institutional review board, participants are able to "opt in" to have a guardian provide consent in English or Spanish, should they elect to do so. Following assent and optional guardian permission, participants complete a brief demographic survey, indicate their preference for future contact (ie, text message or email), and complete a brief assessment of the primary outcomes (Measures section). All participants then complete the Kiddie-Computerized Adaptive Tests (K-CAT) Anxiety Module [50] to ensure eligibility (ie, a score >29 and indicating mild or greater anxiety symptoms). Participants who do not meet these criteria are excluded and offered access to a publicly available, digital evidence-based workbook for teens [43,44]. Participants who do meet the criteria for mild or greater symptoms of anxiety are randomized into either the control arm (digital evidence-based workbook [43,44]) or the Intervention Arm (TeACH System Feedback and Resources). Randomization is automated through the Research Electronic Data Capture (REDCap, Vanderbilt University) platform, and study staff members are blind to allocation. Following a review of these resources, all participants are invited to complete an immediate follow-up survey. One week following this interaction, participants are invited to complete the same follow-up survey. Figures 1 and 2 display the study design flow.

Figure 1. Participant flow through TeACH system trial in pediatric primary care K-CAT: Kiddie-Computerized Adaptive Tests.

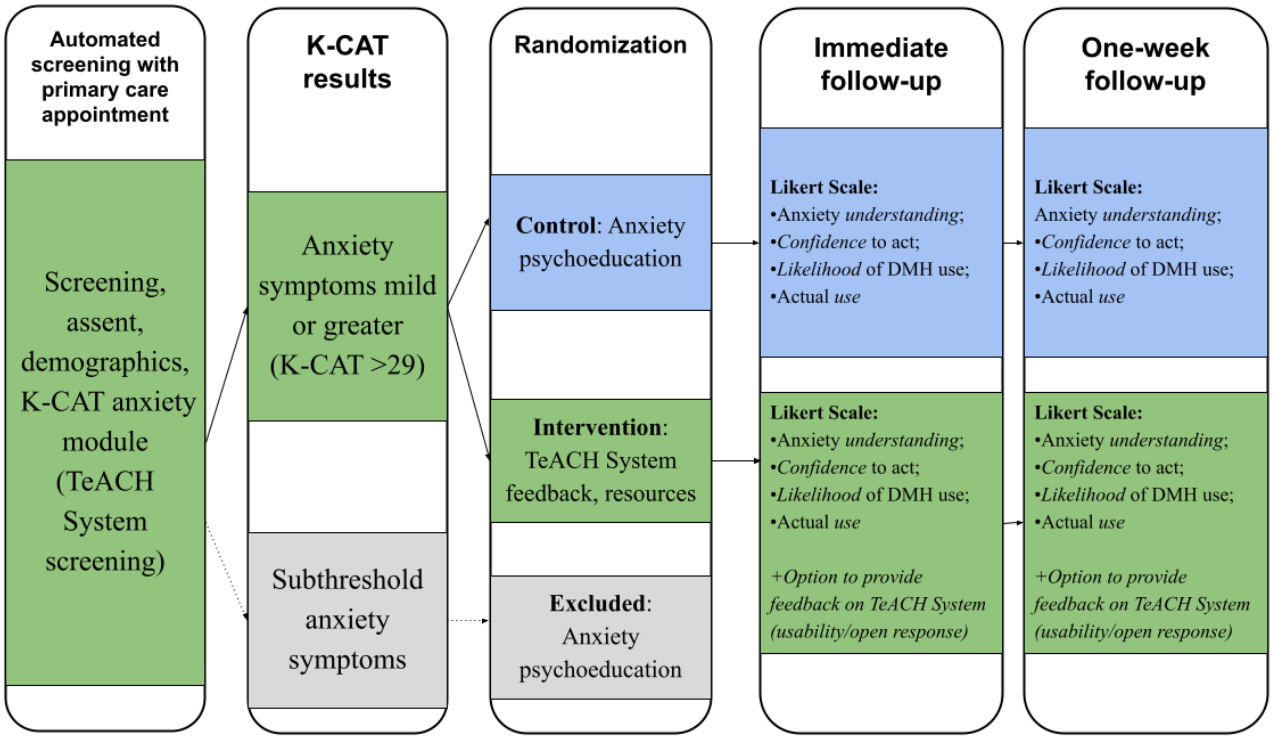
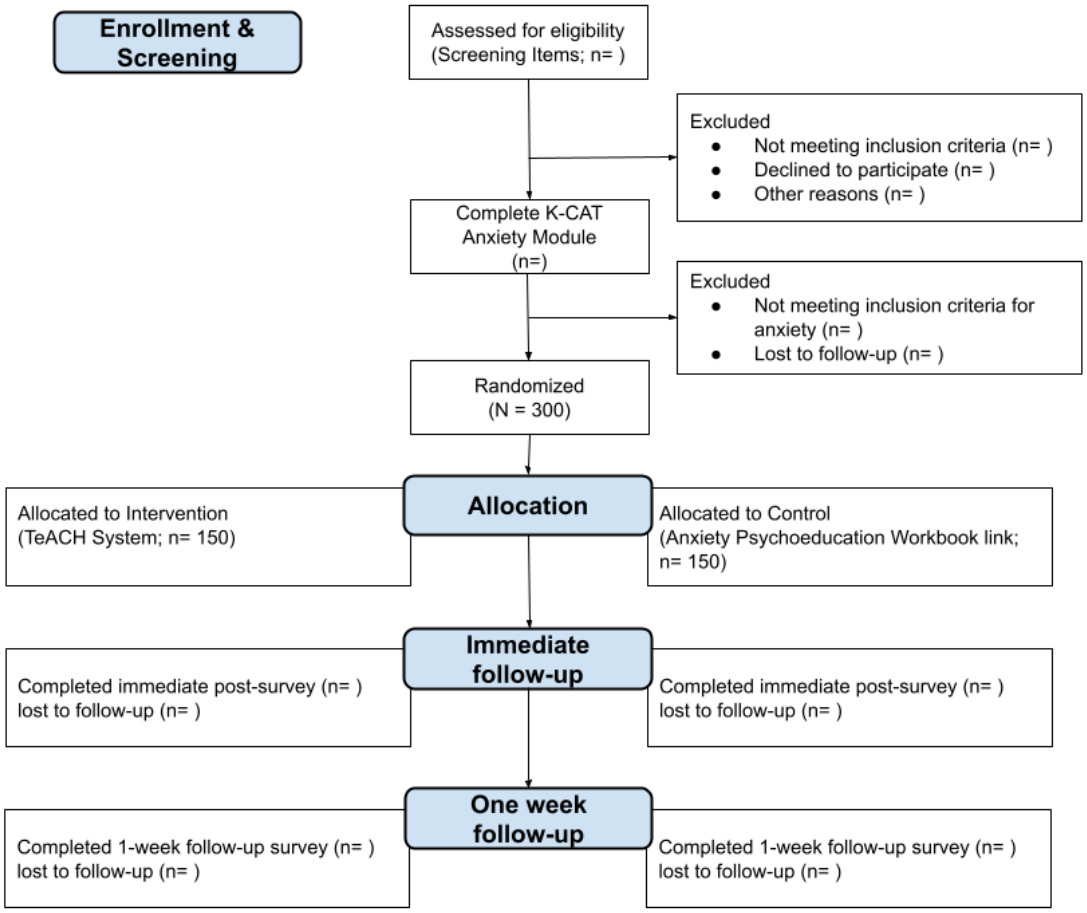


Figure 2. Study flow diagram.



Setting and Recruitment

Eligible participants are being recruited through PPC clinics housed within the University of Illinois Chicago (UIC) and Rush University Medical Center (RUSH). Both hospital systems' primary campuses are situated on the West Side of Chicago and serve diverse patient populations [51,52]. Eligible participants are being recruited in clinics through (1) QR codes on displayed and circulated flyers, including sharing of the flyer by PPC pediatricians, trainees, and staff; and (2) invitation from research staff (ie, offered tablet in the clinic waiting room or while waiting in an exam room) or PPC clinicians and staff members.

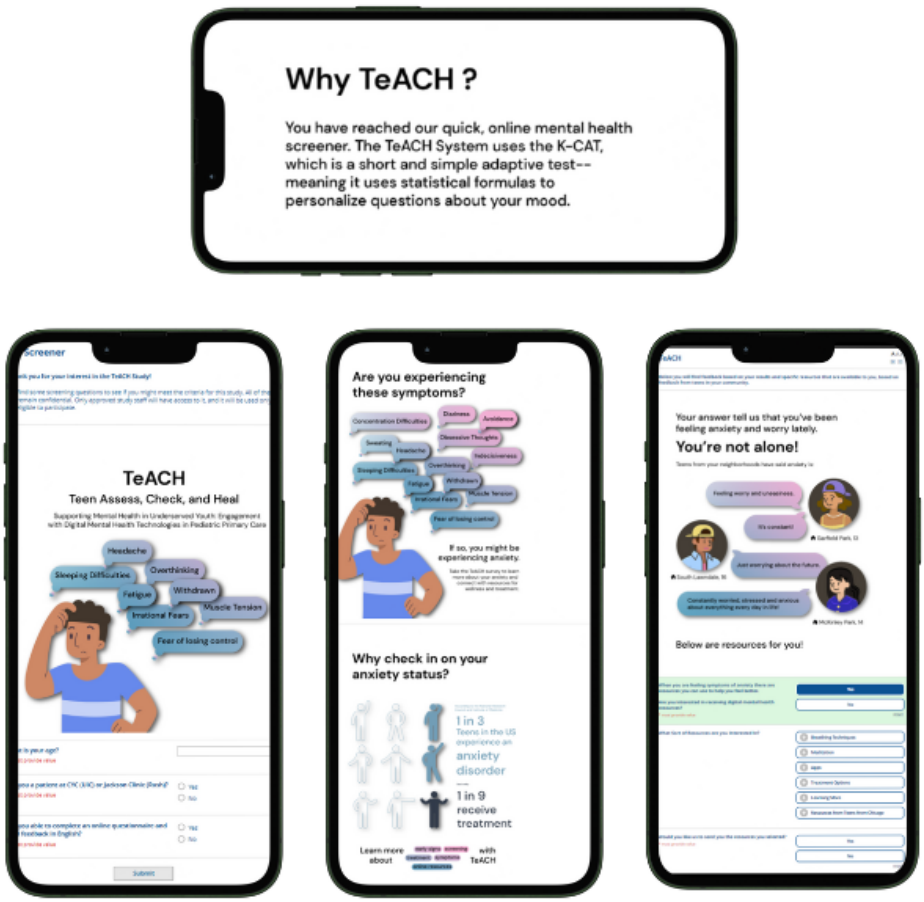
Inclusion and Exclusion Criteria

For study inclusion, participants must be (1) receiving care at the specified clinics at UIC or RUSH; (2) between 13 and 17 years of age; and (3) able to speak and read in English. These inclusion criteria are determined by teen self-report (ie, answering 3 screening questions based on these criteria). Following assent and completion of a demographics and engagement survey (Measures section), final inclusion criteria are assessed based on responses to the K-CAT Anxiety Module. Namely, to be randomized, participants must also meet criteria for mild or greater symptoms of anxiety (ie, K-CAT Anxiety Module score >29) [50]. There are no assessments for comorbidities, nor any exclusion criteria beyond not meeting the inclusion criteria noted above.

TeACH System

The TeACH System is a DMH LIT that includes teen patient-facing brief assessment, feedback, and resources for symptoms of anxiety (sample screenshots displayed in Figure 3. Increasing DMH engagement for teens with socially complex needs is the primary aim of the current iteration of the TeACH System. The mechanism to achieve this outcome includes the use of key player involvement throughout the design and implementation planning processes. Consistent with a broad spectrum of community-engaged research practices [53], involvement of teens and caregivers from the West and South Side Communities of Chicago have ranged from 1-time interviews and focus groups to co-design activities, with plans to form a community advisory board for the broader line of research led by this team [42,54,55]. Most relevant to the design of the current iteration of the TeACH System (eg, direct quotes described below), formative usability testing sessions were completed remotely with 10 teens (mean age 15.9, SD 0.99 years; female: n=8, 80.0%; Hispanic or Latino: n=6, 60.0%; Middle Eastern of North African: n=1, 14.3%; White: n=6, 60.0%) and 7 parents of teens (mean age 41.86, SD 8.7 years; female: n=5, 71.4%; Hispanic or Latiné: n=1, 14.3%; Middle Eastern or North African: n=1, 14.3%; Black or African American: n=4, 57.1%) from the West and South Side Communities of Chicago.

Figure 3. Sample screenshots of the TeACH system.



TeACH System Assessment

The TeACH System uses the Kiddie-Computerized Adaptive Tests (K-CAT) Anxiety Module to assess teen patient anxiety symptoms [50]. The K-CAT Anxiety Module (youth report; ages 7 to 17 years) uses an item bank of more than 200 items, typically offering 10 questions to a teen user to predict the likelihood of a diagnosis of generalized anxiety disorder (area under the receiver operating characteristic curve=0.83). However, the module is not limited to generalized anxiety disorder and may also be used for general anxiety screening in youth [50]. Future iterations of the TeACH System may use the full K-CAT (ie, assessing anxiety, depression, substance misuse, oppositional defiant disorder, attention-deficit/hyperactivity disorder, mania, conduct disorder, and suicidality), but the current version of the TeACH System is solely assessing anxiety. This decision was driven by input from PPC clinicians and staff members who expressed concern about follow-up mental health care, safety, and workflow disruptions around more expansive digital mental health assessments [23]. Participants in the current study are eligible for randomization with a score greater than 29 on the K-CAT Anxiety Module, indicating mild, or higher anxiety symptoms [50].

TeACH System Feedback

Following the completion of the K-CAT, the TeACH System informs users that they will be provided feedback and specific resources that were informed by feedback from "teens in your community." The feedback provides an infographic that starts by stating: "Your answer tells us that you've been feeling anxiety and worry lately," followed by the validation that "You're not alone!" Following this, 4 quotes from Chicago teens describe anxiety as: "feeling worry and uneasiness"; "It's constant!"; "Just worrying about the future"; and "Constantly worried, stressed, and anxious about every day in life!" before proceeding to viewing resources, users are prompted that "When you are feeling symptoms of anxiety, there are resources you can use to help you feel better." In sum, the feedback section aims to briefly address multiple individual barriers to care, including problem recognition (ie, "Your answers tell us that you've been feeling anxiety and worry lately."), stigma (ie, "You're not alone!" and quotes from "Teens from your neighborhoods"), and confidence to act (ie, "When you are feeling symptoms of anxiety, there are resources you can use to help you feel better") [24-26].

TeACH System Resources

Following the feedback, users are asked if they would like to receive DMH resources. The resources are all freely accessible online and are presented to participants through both sample screenshots and links to their direct sources (eg, App Store, YouTube, and TikTok). All resources are grounded in evidence-based skills (eg, progressive muscle relaxation and diaphragmatic breathing) and psychoeducation (including brief videos from teens and young adults with lived experience with anxiety). If participants indicate that they do not wish to receive DMH resources, they are asked to provide a reason as to why. If they would like to receive DMH resources, they are asked what types of resources they would prefer (eg, "Breathing Techniques," "Apps," and "Learning More"). This checkbox selection allows teens to view the content they wish, as opposed to getting all options at once, which can be overwhelming. Users may also opt to have the resources sent to them at their preferred method of contact (ie, email or text message).

TeACH System Platform

The TeACH System is intended to be adaptable and scalable. As such, using a simple but secure platform that may be easily edited at minimal cost was ideal. UIC's instance of REDCap was therefore selected as the platform to build and manage the TeACH System [56]. REDCap is housed and managed by the University, as is common across multiple university and health care systems. To enhance the aesthetic appeal and engagement of the TeACH System for teen users, the UIC Innovation Center collaborated on its development within REDCap. An interdisciplinary team of researchers applied human-centered design techniques and analysis frameworks to effectively present the survey and maintain participant interaction throughout. They used user journey maps and extensive user testing to ensure a smooth and intuitive survey flow. The team also crafted a distinct visual language for the TeACH System, incorporating contemporary graphic elements inspired by popular social media platforms, calming color choices, and clear, simple language to appeal to the teen audience and put users at ease.

Control Condition

Following screening, assent, demographic characteristic assessment, and completion of the K-CAT Anxiety Module, participants randomized to the control condition receive different feedback and resources than those allocated to interact with the full TeACH System. The control condition includes immediate feedback about anxiety symptoms (ie, "Your answers tell us that you've been feeling anxiety and worry lately."). Following this, participants are queried whether they would like access to a digital resource. If they respond negatively, they are prompted to provide their reasoning. If they respond positively, they are provided with a direct link to a free download of an evidence-based workbook for teens with anxiety [43,44].

Measures

Demographics

Following assent, teens are asked to report the following demographic information: name, age, ethnicity (Hispanic or Latiné and Middle Eastern or North African), race, pronouns, gender, preferred language, the reason for visiting primary care, and preferred method for contact (ie, email or text message).

Primary Outcomes

The primary outcomes are administered within REDCap and are assessed at 3 time points for all participants: (1) baseline: following assent and before administration of the K-CAT; (2) post interaction: immediately after receiving the allocated feedback and resources; and (3) maintenance: 1 week following the interaction. The primary outcomes are discrete variables focusing on individual-level barriers to mental health care (ie, symptom understanding, confidence to act [24-26]) and engagement with DMH (ie, likelihood to use DMH for anxiety, actual DMH use). Namely, through a questionnaire created for this study, participants rate on a Likert scale (1=not at all to

5=completely): (1) anxiety *understanding* (ie, "I understand what anxiety is."); (2) *confidence to act* (ie, "I feel confident I can do something if I feel anxiety."); and (3) *likelihood* to use digital tools for anxiety (ie, "If I feel anxiety, I would use a digital tool to help (app, website, and reel or video)."). Following this, participants indicate whether they have used a digital tool for their anxiety before (ie, yes, no, and unsure).

Usability

Usability of the TeACH System and its control arm are assessed post interaction (ie, immediately after receiving the allocated feedback and resources) and 1 week after the interaction through the After Scenario Questionnaire, a 3-item measure of usability [57].

Data Analyses

Overview

Descriptive analyses will be conducted to characterize the sample, primary outcomes, and usability ratings of the TeACH System. To assess changes in the engagement outcomes over time and account for missing data, linear or generalized linear mixed effects regression models will examine differences in responses to the baseline, postinteraction, and maintenance questionnaires. Demographic variables and existing DMH use, as well as their interactions with time, will be examined as covariates to assess differential engagement outcomes based on these variables.

Sample Size and Power

Power and sample size computations were based on previously published work [58,59]. Conservative estimates of sample sizes were estimated (ie, anticipating a 15% attrition rate on the follow-up survey), which indicated that 300 patients were deemed appropriate to examine the initial TeACH System use (ie, K-CAT Anxiety module, feedback, and resources) after being invited during their PPC appointment. With an expected 15% attrition rate for the follow-up questionnaire 1 week later, we would be adequately powered for within-subjects (pre vs post using the main effect of time) and between groups comparisons (TeACH System vs Control condition using treatment by time interaction). For within-subjects comparison, our proposed sample size is overpowered such that we should exceed 90% power to detect differences generally considered to be moderate in size (d=0.5) with a sample size exceeding approximately 70 participants. To detect within-subjects differences from baseline to endpoint equivalent to d=0.34 for the engagement outcomes, we would require a sample size of approximately 136 for 95% power. As such, our proposed sample is more than adequate for the planned within-subjects comparisons. For between-group comparisons with the anticipated 15% attrition rate, we should have 95% power to detect differences generally considered moderate in size (d=0.5) with 240 participants. With our proposed sample size of 300 participants, we will have 80% power to detect smaller differences equivalent to d=0.34.

Ethical Considerations

All procedures were approved by the institutional review boards of the University of Illinois Chicago (2024-0252) and Rush University Medical Center (20051313). Further, ongoing study monitoring is being overseen by an independent Data Safety and Monitoring Board. All participants complete a digital assent and are compensated for completing a follow-up assessment with a US $15 Amazon e-gift code (see the section Study Design below).

Results

This study received funding from the National Institute of Mental Health on September 13, 2021 (K08 MH125069), and began recruiting at UIC in July 2024 and at Rush in August 2024. Earlier funded activities informed the design and implementation planning for the current trial [23,32,42,54]. To date, 122 teens have assented to complete study activities, 80 have been randomized (an additional 24 teens have had subthreshold anxiety symptoms and were therefore not randomized), and 42 teens have completed the one-week follow-up assessment. We expect data collection to be completed by August 2025.

Discussion

Overview

The current feasibility study aims to evaluate the TeACH System in terms of (1) increasing engagement with DMH and (2) addressing individual-level barriers to mental health care. These outcomes are being examined in the context of integration in urban PPC clinics and in comparison to a control condition (ie, access to a digital workbook). The design and implementation plan for the TeACH System involved collaborative input from key players (ie, teens, caregivers, and PPC staff and clinicians) to increase the likelihood of teen engagement and acceptability in a dynamic health care setting [23,42,54].

The TeACH System stands as one of a growing number of DMH LITs being evaluated and implemented in care settings (eg, [60,61]). DMH LITs have demonstrated promise in increasing engagement for minoritized teens, compared with more intensive digital and traditional care models [37]. Amid this landscape, some unique aspects of the TeACH System situate it to adapt and scale well based on user and setting needs. First, the TeACH System is housed on a secure, stable, and editable platform (ie, REDCap [56]) and may therefore be adapted across iterations and for differing populations and settings. For example, screening may be expanded from self-reported anxiety only (current version) to up to 8 diagnostic categories assessed through the K-CAT (ie, anxiety, attention-deficit/hyperactivity disorder, conduct disorder, depression, mania, oppositional defiant disorder, substance use disorder, and suicidality [50]). Second, infographics and other design features may be changed to reflect the language and design preferences of different target groups. Similarly, resources may be edited or changed based on availability (eg, open access removal of a video), population preferences, and platform safety and availability (eg, if a "TikTok ban" results in higher teen use of a different platform). Finally, the TeACH System–and any future iterations are grounded in human-centered design with input from key players to target DMH engagement. Such targeting is hypothesized to serve as a mechanism of DMH to ultimately impact clinical

outcomes [62]. In sum, the TeACH System has been designed for teens with both anxiety and socially complex needs while visiting primary care. However, future iterations may be easily adapted at any level for integration in settings youth visit regularly and trust.

Future Directions

The scope of this study is associated with specific limitations and caveats, all of which inform future research directions. First, the current iteration of the TeACH System focuses solely on anxiety. While originally aimed to include the full K-CAT assessment, the scope was limited to anxiety to meet the implementation needs of PPC clinicians and staff members [23]. Anxiety was also selected to establish proof of concept for this first iteration, as anxiety is highly prevalent and socially minimized by clinicians and the public, making it less likely to be effectively screened and treated. Once the TeACH System establishes initial feasibility, it can be broadened to address multiple disorders through a larger study. Second, the K-CAT demonstrates the strongest accuracy when the parent proxy report and child self-report are integrated [50]. While the current iteration of the TeACH System is solely teen-facing, there is the potential for the TeACH System to have both caregiver and teen-facing elements in the future. Alternatively, summative feedback from this study may indicate that teens or families prefer for this to be a teen-facing tool, but with the option to inform trusted adults in their life about the indication of anxiety from the K-CAT. Further, the K-CAT is available and validated in both English and Spanish. As such, future iterations may also include cultural and linguistic adaptations to serve teens and caregivers who speak Spanish. Finally, while PPC is typically visited annually by most teens, integration in this care setting does not ensure that all teens will be reached. PPC was selected to establish feasibility for reasons detailed above, but future iterations may be adapted and integrated in other community spaces in which teens and families spend their time (eg, schools, parks, libraries, and churches).

Conclusions

LITs have a long-standing history of benefiting individuals with mild to moderate mental health symptoms [28], implicating DMH LITs as a promising first-line approach in care settings [29]. The TeACH System represents 1 possible DMH LIT that may provide brief assessment, feedback, and resources for teen patients without unduly burdening a busy health care environment nor requiring the approval of a guardian to use. This study will provide preliminary feasibility data that may inform how the TeACH System and other DMH LITs might better engage and support teens with socially complex needs.

Acknowledgments

The team wishes to thank the clinicians, staff members, and patients at the Child and Youth Center at the University of Illinois Chicago and the Pediatric Primary Care clinics of Rush University Medical Center.

Research reported in this publication was supported by the United States National Institute of Mental Health grant (K08 MH125069). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Authors' Contributions

CST led all aspects of this work, including conceptualization, funding acquisition, methodology, and writing the original draft of the manuscript. GB, KR, and ML conducted project administration and supervision. DLS led formal analysis. CF, CA, GD, RMC, NM, GM, AT, and KMW completed visualization and design activities. ELG, WAJ, and NSK provided additional supervision.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer-review report from the Mental Health Services Study Section, National Institute of Mental Health Initial Review Group (NIH).
[PDF File (Adobe PDF File), 92 KB - resprot_v14i1e65245_app1.pdf]

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Abbreviations

DMH: digital mental health tools
K-CAT: Kiddie Computerized Adaptive Test
LIT: low-intensity treatment
PPC: pediatric primary care
REDCap: Research Electronic Data Capture
RUSH: Rush University Medical Center
TeACH System: Teen Assess, Check, and Heal System
UIC: University of Illinois Chicago

Edited by A Schwartz; submitted 19.08.24; this is a non–peer-reviewed article;accepted 16.12.24; published 18.02.25.

Please cite as:
Stiles-Shields C, Bobadilla G, Reyes K, Gustafson EL, Lowther M, Smith DL, Frisbie C, Antognini C, Dyer G, MacCarthy R, Martinengo N, Morris G, Touranachun A, Wilkens KM, Julion WA, Karnik NS
Digital Mental Health Screening, Feedback, and Referral System for Teens With Socially Complex Needs: Protocol for a Randomized Controlled Trial Integrating the Teen Assess, Check, and Heal System into Pediatric Primary Care
JMIR Res Protoc 2025;14:e65245
URL: https://www.researchprotocols.org/2025/1/e65245
doi:10.2196/65245
PMID:

Protocol

Integration of a Patient-Centered mHealth Intervention (Support-Moms) Into Routine Antenatal Care to Improve Maternal Health Among Pregnant Women in Southwestern Uganda: Protocol for a Randomized Controlled Trial

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Abstract

Background: Mobile health (mHealth) interventions that leverage social support (SS) can improve partner involvement and pregnancy experiences and promote antenatal care (ANC) attendance and skilled births. In our previous studies, we used behavioral frameworks to develop a user-centered mHealth-based, audio SMS text messaging app to support pregnant individuals to use maternity care services in rural Uganda (Support-Moms app). In our pilot study, we observed high intervention uptake, acceptability, and feasibility, as well as increased ANC attendance and skilled births.

Objective: With the promising pilot data, we propose a type 1 hybrid implementation-effectiveness trial to test if this novel patient-centered automated and customized mHealth-based SS intervention is effective and cost-effective enough to warrant future large-scale implementation into Uganda's routine maternity care.

Methods: We will physically recruit 824 pregnant women at <20 weeks of gestation living in Mbarara and Mitooma districts, southwestern Uganda, and randomize them (1:1) to receive standard of care or the Support-Moms app, with at least 2 of their identified social supporters. Our primary outcome will be the proportion of skilled births. Secondary outcomes will include number of ANC visits, institution-based delivery, mode of infant delivery, preterm birth, birth weight, SS, obstetric complications, and deaths (maternal, fetal, and newborn). We will assess other implementation, service, and client outcomes through study records, the mHealth platform, and questionnaires with all women in the intervention, their social supporters, health care providers (HCPs), and managers from participating facilities. We will conduct face-to-face in-depth exit interviews with 30 purposively selected intervention participants and 15 facility HCPs and managers to explore implementation strategies for scale-up. Annual maternity resource allocations, costs, number of ANC visits, and deliveries will be assessed from facility records up to 36 months after implementation. We will estimate incremental cost-effectiveness ratios concerning cost per additional HCP-led delivery, per death averted, and per quality-adjusted life year gained as cost-effectiveness measures.

Results: This study was funded in September 2023. Ethics approval was obtained in February 2024, and actual data collection started in March 2024. As of January 2025, 75% (618/824) of all projected study participants provided consent and were recruited into the study. Participants are expected to be followed up until delivery, and 15% (124/824) have so far exited. Data analysis for the trial is expected to start as soon as the last participant exits from the study. The qualitative interviews will start in April 2025, and data will be analyzed and published as soon as data collection is done, which is expected in March 2027.

Conclusions: We are testing the feasibility, acceptability, and cost-effectiveness of implementing Support-Moms into routine maternity care from individual and facility perspectives. We hypothesize that Support-Moms will be an effective and cost-effective strategy to improve maternity service use for women in rural Uganda and similar settings.

Trial Registration: ClinicalTrials.gov NCT05940831; https://clinicaltrials.gov/study/NCT05940831
International Registered Report Identifier (IRRID): DERR1-10.2196/67049

(JMIR Res Protoc 2025;14:e67049) doi:10.2196/67049

KEYWORDS

social support; intervention development; maternal health; antenatal care attendance; skilled births; Uganda

Introduction

Background

While maternal mortality has fallen over the last 20 years, an estimated 300,000 women die each year from preventable causes related to pregnancy and childbirth, and 99% of the deaths occur in low- and middle-income countries (LMICs) [1]. Over 99% of infant deaths also occur in LMICs [2,3]. Persistently high maternal mortality ratios (MMRs) in LMICs are partly attributed to challenges accessing care, with undiagnosed or poorly managed pregnancy-related complications from direct or indirect causes [1]. Recurrence risks of fatal episodes increase exponentially among women who survive previous fatal episodes unless preventive measures for early detection and monitoring throughout the perinatal period are adopted [2,4-6]. Antenatal care (ANC) prevents perinatal and maternal morbidity and mortality by early detection and treatment of prenatal complications and identifying women at high risk to ensure delivery in skilled settings [7-11]. ANC supports women, their families, and communities to navigate challenges at a critical time during pregnancy; debunks misconceptions; increases information transfer; and can motivate women to seek facility delivery and care [9]. The World Health Organization (WHO) and other authorities have called for urgent evaluation of adaptable and context-specific health solutions to promote ANC uptake and maternity services to reduce maternal and early childhood mortality and morbidity [9,11-14]. Identifying and scaling up interventions that improve access to and the use of available health care in pregnancy and childbirth has the potential to prevent 823,000 stillbirths, 1,145,000 neonatal deaths, and 166,000 maternal deaths annually in the 75 highest-burden countries [2,4-6].

Despite expanded capacity to increase the number of skilled birth attendants at community facilities, Ugandan women still have low rates of ANC use and skilled births, resulting in one of the highest MMR (189/100,000) and perinatal mortality rates (34 deaths/1000 births) in the world [15]. Women's lack of information, social support (SS), financial independence for emotional and economic provisions, decision-making autonomy regarding childbirth, birth preparedness, and perceived need for maternity care services are important challenges to using available maternity services in these settings [1,16-19]. One analysis showed that women at risk of unskilled home births needed relevant and context-specific strategies to encourage ANC attendance and skilled delivery [20]. The high cost of MMR highlights the need for adaptable interventions that boost ANC and maternity services use to reduce MMR and early childhood deaths [12].

SS is an important pillar of health promotion that has been directly linked to health care–seeking behavior, infant care practices among mothers, and HIV care in sub-Saharan Africa (SSA) [21-25]. SS can mitigate structural and physical barriers to health care access at individual and societal levels, including facilitating self-efficacy to complete positive health behaviors [26-28]. Spouses, relatives, and friends have been the sources of SS among individuals living with HIV in SSA [23-25]. Community health workers (CHWs) can provide or promote additional SS during pregnancy, leading to better health outcomes [29,30]. Village health teams (VHTs), which comprise community members identified by their community who are trained on major health programs, improve timely care seeking for facility delivery [31-35]. VHTs have historically focused on the treatment of infectious diseases, such as malaria, pneumonia, and tuberculosis [35]. Their role as an additional resource for peripartum women has not been harnessed. Therefore, social network involvement not only addresses individual but also family- and societal- or community-level barriers to care in a setting with modest availability of health centers (HCs) providing needed services [17,25,36-38].

Mobile health (mHealth) interventions can be practical, effective, and scalable tools to improve maternal health care delivery and outcomes. Many SMS text messaging and other mHealth interventions can help individuals internalize risks and potential impact of various medical conditions as well as the needs and benefits of health services [11,13]. mHealth approaches can empower individuals to seek help, address specific health concerns, strengthen informed decision-making, and improve outcomes in the perinatal period [14,39]. Scheduled SMS reminders and telephone voice messaging approaches can enable people to increase control over their health by improving knowledge transfer, learning, and comprehension. These gains may improve the perceived need to use available services, especially when interventions are well directed and executed to provide accurate and relevant information on the promoted behavior [11,13,14,25,39-42]. Several studies have found that mobile phone–based messages can be motivational as a source of individual or family SS [43], cues to action [44], or to challenge societal negative beliefs [45]. Mobile phone interventions have also been shown to increase ANC attendance [46,47], institutional delivery [48,49] and vaccination rates (such as tetanus toxoid) [11,49].

mHealth interventions that specifically bolster SS can improve pregnancy experiences by decreasing anxiety and depression [50-53] and increasing perinatal bonding [52] and communication within social networks [53]. These benefits are mediated by promoting existing family structure and social networks, which in turn foster financial and emotional coping mechanisms to enable women to overcome socioeconomic and

physical barriers to care, such as food insecurity, transportation, and provision of delegated service to overcome competing priorities [25,53-55]. Community and social network engagements toward mobilization of resources to enable health care access are practical, scalable, and sustainable approaches toward participatory health care financing and use [56]**.** Although SMS alone is a convenient and lower cost approach to support health care interventions with higher delivery success, the provision of multiple messaging options, such as voice messages and social networks involvement, has been crucial to extend reach beyond the individual literate personal phone owners in SSA [57,58].

Health awareness and motivating health care use are key elements of developing effective behavior change interventions [59]. However, mHealth interventions are not always effective in improving health care and use. Whereas the failure of impact has been attributed to a mismatch between the function, adaptability, and need for mHealth interventions in some settings [11,14], end-user designs that use iterative approaches in app development can improve health care service use [60]. In a formative study, we observed that knowledge gaps influenced women's past and future decisions to not attend ANC and pursue unskilled home births [17,20]. Women were also largely dependent on their significant others for economic provisions, which, together with the existing gender and traditional norms, limited women's ability and freedom to make family or health decisions to seek skilled care. Therefore, we developed an mHealth-based SS intervention (the Support-Moms intervention) using the health care use model by Andersen [61] that incorporates predisposing-, enabling-, and need-based factors to improve intervention uptake and service use. We then considered the framework by Bendixen et al [62] to personalize the information and tailor the system for our targeted end users. Our novel mHealth app was developed as part of a career development award (NIH-K43TW011004). This app or intervention was compatible with local regular mobile phone types, providing varying text and audio delivery mediums for individuals who were literate and who were not. In a randomized 3-arm pilot study (N=120) pregnant women who had not presented for ANC by their second trimester were equally randomized to receive (1) standard of care, which is the routine ANC information given at the maternity centers (control); (2) scheduled SMS audio messages from the final messaging prototype (scheduled messaging [SM]); and (3) SM, plus social supporter engagement through SMS (SS) [63].

We observed high intervention acceptability and feasibility, with >80% of women receiving ≥85% of intended messages within 1 hour. Over 95% of women found the app easy to use and compatible with their existing messaging programs; they also reported that the messages were useful and engaging and would strongly recommend the intervention to others. Nearly all women in the SS arm (39/40, 98%) had a skilled delivery compared to 78% (31/40) and 70% (28/40) of the women in the SM and control groups, respectively. All women whose social supporters were engaged on the app (SS arm: 40/40, 100%) attended ≥4 ANC visits, compared to 83% (33/40) and 50% (20/40) of the women in the SM and control groups, respectively. Fewer women (8/40, 20%) in the SS arm missed any visits due to the lack of transportation compared to 58% (23/40) and 68% (27/40) of the women in the SM and control groups, respectively. In addition, fewer maternal or fetal complications (3/40, 8%) were reported in the SS arm compared to 13% (5/40) and 25% (10/40) complications in the SM and control groups, respectively. Using the Duke-University of North Carolina (UNC) Functional Social Support scale [64], women in the SS arm reported improved SS (median 3.4, IQR 2.8-3.6) compared to 2.8 (IQR 2.6-3.2) and 2.4 (IQR 2.2-2.8) in the SM and control arms, respectively (score ranges from 1 to 4, and 4 indicates high levels of SS). In qualitative interviews, all women described the intervention as useful, actionable, and easy to use; tailored health information helped them to learn, internalize, and comprehend ANC and skilled delivery benefits, strengthening their informed decision-making as they were reportedly able to easily share and discuss information with their significant others, who in turn committed to providing them the needed support to prepare and seek help. Women also expressed that the involvement of their significant others within a friendly, trusted, and familiar environment helped them to mobilize needed support during pregnancy. Involving both health care providers (HCPs) and end users in characterizing, developing, and formulating the mHealth intervention allowed its tailoring to their preferences. Given the success in our pilot work where 78% (93/120) of the women used feature phones and promising preliminary efficacy data presented earlier [36,63], the next logical step was to assess the effectiveness, implementation, and scalability of such multiple messaging strategies to improve care access in SSA, where the contextual factors that drive successful interventions differ, but the public health impact of such interventions is likely to be the greatest [65].

Objectives

We now propose a type 1 hybrid implementation-effectiveness trial to evaluate and implement this intervention into routine care. We will test the effectiveness of the intervention in a randomized controlled trial (aim 1). We will apply the implementation outcomes framework by Proctor et al [66] to evaluate implementation, service, and client outcomes and conduct in-depth interviews with users and key stakeholders to contextualize or clarify these outcomes as well as explore implementation strategies for future scale-up using the Consolidated Framework for Implementation Research (CFIR; aim 2). We will then assess the costs and cost-effectiveness of implementing the Support-Moms intervention into routine care (aim 3). We hypothesize that implementing Support-Moms will be an effective and cost-effective strategy to improve maternity service use.

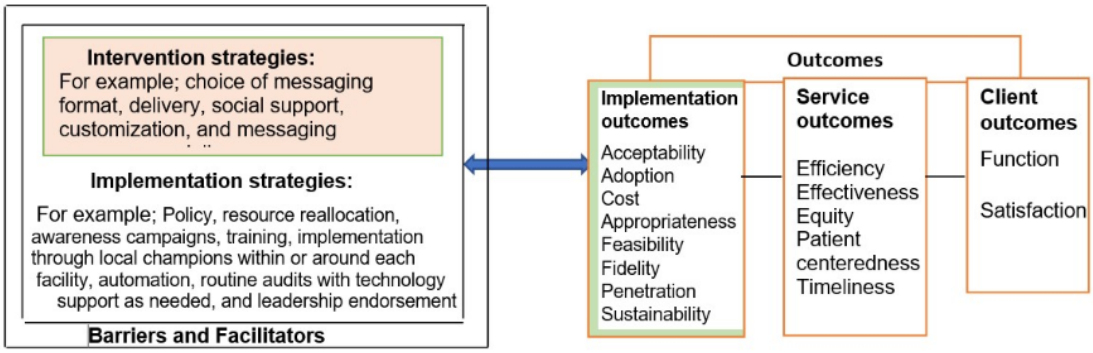
Methods

Study Overview

We propose to evaluate the effectiveness and implementation of the Support-Moms app into routine care. We hypothesize that Support-Moms will improve maternity service use and reduce the MMR when integrated into routine care. We will test the effectiveness of the Support-Moms intervention in a randomized controlled design (aim 1); evaluate intervention

implementation using the implementation outcomes framework by Proctor et al [66], as outlined in Figure 1 (aim 2); and then refine implementation strategies for future scale-up using the CFIR, as outlined in subsequent sections [67]. We will assess the cost and cost-effectiveness of implementing this intervention into routine care and its implication for sustainability (aim 3). These outcomes will serve as indicators of implementation success or necessary preconditions for attaining desired service outcomes for women in rural, resource-limited settings. This will enable us to identify practical, context-specific, and actionable strategies for achieving optimal implementation effectiveness at a low cost. The intervention strategies were developed in our pilot work together with facility HCPs. In the cost-effectiveness analysis, if Support-Moms and standard of care are found to have equivalent effectiveness, we will conduct a cost-minimization analysis where only the cost of Support-Moms per participant will be estimated and reported (no incremental cost-effectiveness ratios [ICERs] will be calculated). This alternative approach would remain informative to the policy makers and stakeholders in maternity service use. Notably, simultaneous assessment is warranted given the (1) strong preliminary evidence, (2) relatively low investment needed for costing, and (3) overall efficiency of our proposed type 1 hybrid effectiveness-implementation trial approach.

Figure 1. Modified conceptual framework by Proctor et al [66] for implementation and evaluation.



Study Setting

Uganda's public health system is organized into 7 tiers with national and regional referral hospitals, general district hospitals, and 4 levels of community HCs. Staffing and available services vary across the 4 levels; HC3 carry out vaginal deliveries, whereas HC1 and HC2 serve as low-resource referral units. HC4s and hospitals conduct normal and cesarean deliveries and have ambulances and blood transfusion services [68]. Private HCPs operate in parallel to the public health system to provide maternal health care. Mbarara District is located approximately 270 km southwest of the capital, Kampala [69]. Mbarara District hosts a regional referral hospital that serves the southwestern region (Mitooma district inclusive); most deliveries are high risk [70]. Mitooma District borders Congo and is situated approximately 370 km southwest of the capital [71]. These 2 sites were selected for this research based on their geographic, sociocultural, and institutional diversity and high maternal mortality and morbidity data (Table 1 presents more details). Both districts have publicly funded and operated facilities with an active maternity care unit. Participants may be seen at any of the maternity sites in these 2 districts or other neighboring districts (Table 1), with recruitment and follow-up organized through CHWs. This consideration, plus the diversity of the settings and the study population, has potential for generalizability to similar settings. The local economy of these 2 districts is also largely based on subsistence agriculture, with both food and water insecurity being common [72,73]; ANC attendance of ≥4 visits is still at 58%, and the skilled facility delivery rate is approximately 70%. Maternity services, including delivery, are largely provided free of charge through public HCs.

Table 1. Mbarara and Mitooma district statistics 2019.

Characteristics	Mbarara, n	Mitooma, n
Total population	Approximately 250,000	Approximately 185,000
Annual registered ANC[a] visits	31,200	18,350
Annual public facility deliveries	14,800	4450
MMR[b] per 100,000 live births	328	412
Hospital availability	5 (4 are private)	0
Publicly funded HC4s[c]	2	1
Publicly funded HC3s	10	6
VHTs[d]	246	143
Other private facilities providing maternity services	34	12
Total HCPs[e]	253	104

[a]ANC: antenatal care.

[b]MMR: maternal mortality ratio.

[c]HC: health center.

[d]VHT: village health team.

[e]HCP: health care provider.

Aim 1: Testing the Effectiveness of the Novel Support-Moms Intervention in a Randomized Controlled Trial

We will enroll a cohort of 824 adult pregnant individuals with gestational ages ≤20 weeks at enrollment (determined by last normal menstrual period or ultrasound scan where available). Consenting participants will be randomized 1:1 at enrollment to standard of care (Ministry of Health [MOH] guidelines–based routine care and information giving, n=412, 50%) versus the Support-Moms (intervention) group (n=412, 50%). We will identify, screen, and enroll people through the existing CHWs or VHT structure from areas within a 10 km radius of all publicly funded maternity centers across Mbarara and Mitooma districts, who have not yet presented for ANC by the beginning of their second trimester. We will power the study to test the superiority of the Support-Moms intervention for our primary effectiveness outcome: HCP-led skilled birth delivery. Secondary outcomes will include (1) number of ANC visits, (2) institution-based delivery, (3) SS, (4) mode of infant delivery, (5) all deaths (maternal, fetal, and newborn), (6) preterm birth, (7) birth weight, (8) breastfeeding, (9) completion of postnatal care, and (10) complications of pregnancy and childbirth (eg, obstructed labor, ruptured uterus, need for neonatal or maternal resuscitation or assisted ventilation, severe preeclampsia or eclampsia, postpartum hemorrhage, maternal or newborn sepsis, and other infections).

Recruitment and Enrollment of Study Participants

We will include individuals who (1) are in the first trimester of pregnancy and have not yet presented for ANC, (2) reside in the catchment area of a study HC, (3) are emancipated minors and adults aged ≥18 years, (4) report access to a cell phone with reception in their home, (5) are able to identify at least 2 social supporters living within the study districts, and (6) are able to provide consent. Notably in our pilot study, >95% of screened individuals had access to a cell phone, and all were able to identify at least 2 social supporters living within their communities [63]. We will track the exclusion rates to inform generalizability. CHWs will notify study research assistants (RAs) about potentially eligible participants, who will then contact and seek written informed consent and assent for emancipated minors (ie, those aged <18 years and pregnant) before enrollment into the study. Participants will be asked to identify 2 individuals from their existing SS network with whom they have had stable, long-term relationships and believe they would be available to help them during the pregnancy and study follow-up period. Eligible social supporters will include spouses, relatives, CHWs, and friends [23-25] aged ≥18 years; who are aware that the study participant is pregnant; and who own a cell phone for personal use with reported reliable reception. Potential social supporters will be excluded from the study if they are unable to use SMS or are unwilling to receive SMS notifications, as this was identified as a barrier in the pilot study. In the pilot study, one of the eligible social supporters identified by women included a spouse (75%), friend (38%), sibling (10%), parent (53%), and a CHW (25%), and we expect a similar distribution in the trial. There will be no gender exclusion criteria for social supporters. We will emphasize the selection of an existing partner, who is aware of the pregnancy, as one of the social supporters. This was not a problem in our pilot study, as most women were able to suggest a partner as a potential social supporter, alongside a friend, sibling, parent, or CHW. A few partners were excluded because they did not own a cell phone for personal use (5/40, 13%) or were not aware of the pregnancy (5/40, 13%). All other eligible social supporters that were identified by participants in the social supporter arm (80/80, 100%) were successfully enrolled and completed study procedures. RAs will contact social supporters from the intervention arm within 2 weeks of the enrollment of pregnant women to confirm an active relationship at the time of their

enrollment. Eligible social supporters will be offered an explanation of the study procedures and an opportunity to participate in informed consent. The study nurse will inform consenting social supporters about the objectives of ANC and skilled delivery as well as danger signs during pregnancy using standard MOH and WHO guidelines [9,74].

Randomization

Before the study initiation, the study statistician will generate a randomization table, inaccessible by other study team members, and lock it and store it in the REDCap (Research Electronic Data Capture; Vanderbilt University) study database. Participants will be stratified according to district and HC level and randomly assigned to either intervention or control arms in a ratio of 1:1 in blocks of 10. RAs will be informed of the arm assignment by the REDCap module after consent and at the time of enrollment. Study participants in the control group will receive MOH guidelines–based routine care and information giving. The intervention group will receive the intervention described in the next section.

Intervention Delivery and Components

The final messaging prototype that includes tailored SMS and audio health information (described earlier) will be delivered by the Support-Moms app developed through a partnership with iStreams-Uganda, an app development company based in Mbarara that developed the app, and with an existing mHealth platform [75]. The unique multimedia design allows women to be registered on the platform and be tracked throughout pregnancy and the postpartum period. Enrolled women receive automated and scheduled SMS text messages, reminders, and notifications about upcoming appointments as well as informational voice messages in their preferred language. The app includes a data collection platform and stores information submitted in real time directly from the participant's phone, thus allowing managers to access up-to-date data on process measures (eg, automated SMS text messages sent and accessed) as well as intervention delivery and health outcomes. Fixed SMS data are stored in a secure cloud, which is Health Insurance Portability and Accountability Act (HIPAA) compliant. iStreams-Uganda works in partnership with Africa's Talking, a platform that facilitates access to a telco infrastructure that uses automated SMS, voice, airtime, and other application programming interfaces—mechanisms tested and successfully used during our pilot study. This automated technology for SMS [23,25] and calls [36,63] has also been used for other studies in Uganda.

Both SMS and audio messages will be delivered at participants' preferred time and day of the week for free to optimize intervention delivery. A weekly SMS reminder on the impending ANC appointment and expected date of delivery at their preferred time and day of the week, plus a day before the scheduled ANC visit, will be sent to study participants. Social supporters will receive weekly SMS notifications to motivate the pregnant women participants to be present for scheduled ANC visits during the pregnancy as well as for delivery. Notifications to the 2 preidentified social supporters will provide information about the upcoming ANC visits and delivery due date during the study follow-up period. ANC appointment dates will automatically be generated based on the provided LNMP and MOH guidelines [74] at enrollment. Social supporters will be able to personalize the SMS content at enrollment (the default message will be "This is your reminder to assist your friend [XXX] attend her upcoming ANC visit due soon"). They will also be advised to assist study participants with problems that may affect ANC attendance or facility delivery. The intervention is designed to build on existing supportive relationships of study participants within their communities. All women and their social supporters will receive all accredited messages included in this app for at least 4 months, including the standard routine care provided at the community maternity centers.

Data Collection

Baseline participant characteristics will be collected from study participants from both arms as well as among the social supporters in the intervention arm physically (Table 2). Data collected through participant questionnaires will be conducted in the local languages, Runyankole and Rukiga. We will collect outcome data in two ways: (1) through medical record review of the routinely provided ANC cards, postnatal discharge forms (where available), and records at the relevant HCs and (2) through participant exit interviews 2 to 4 weeks following delivery to enhance data completion, particularly for people who did not deliver at a facility.

Table 2. Baseline questionnaire items for study participants and social supporters.

Topic	Details of measure
Individual level	
Individual characteristics	Age, education, employment, socioeconomic status, marital status, religion, and self-efficacy[a]
General and mental health[a]	We will assess psychological symptoms using validated Hopkins Symptoms Checklist for depression and anxiety [76,77].
Alcohol or substance use	We will assess alcohol use using the 3-item consumption subset of the AUDIT-C[b] [78,79] due to its association with adherence and health outcomes.
Reproductive history	Gravidity, parity, gestational age, prenatal and antepartum high-risk morbidities, and NCDs[c]
Pregnancy and childbirth perceptions	Health beliefs, knowledge and risk awareness, need for skilled delivery, and childbirth practices
Relationship level	
Reproductive goals and motivation	We will adopt the 6 items used in Uganda to assess personal and partner pregnancy desires [80-82], In total, 18 questions or statements reflect 6 parenthood motives [83].
Relationship power and gender-based violence[a]	We will assess gender-based violence [84] and relationship power [85-87] given its relationship with home births in Uganda [17].
Social support[a]	We will adopt and measure social support using a version of the Duke-UNC[d] Functional Social Support Scale [26], a tool that has been widely used in Uganda [64].
Community level	
Service availability[a]	Distance to the nearest health facility, availability of midwives, history of home or facility birth, community support for alternative birthing choices, and relationships with HCPs[e]
Societal level	
General health and food insecurity[a]	We will assess the general health of women, including diagnosed NCDs, and measure food insecurity using the HFIAS[f] [88]
Societal norms[a]	Beliefs about pregnancy, childbirth, birth order, twin delivery, facility delivery, and fatality
Quality of life[a]	Improved Short Form-6 Dimension version 2 survey by Brazier et al [89] to assess the quality of life

[a]Collected at exit interviews.

[b]AUDIT-C: Alcohol Use Disorders Identification Test-Consumption.

[c]NCD: noncommunicable disease.

[d]UNC: University of North Carolina.

[e]HCP: health care provider.

[f]HFIAS: Household Food Insecurity Access Scale.

To additionally reduce the risk of missing data, for participants who cannot be contacted, we will conduct home visits and interview the next of kin for those who are lost from observation or who die during the study period. These survey data will include the date and location of the birth; whether there was a skilled birth attendant present; mode of delivery (ie, vaginal vs cesarean delivery); birth outcome, including preterm birth, maternal, fetal, and newborn deaths, and any other complications of the birth (eg, obstructed labor, ruptured uterus, need for neonatal or maternal resuscitation, severe preeclampsia or eclampsia, postpartum hemorrhage, maternal or newborn sepsis, and other infections); weight and height of the newborn; number of ANC visits completed; use of breastfeeding; and attendance at postnatal care. Finally, we will administer the Duke-UNC Functional Social Support Questionnaire to measure reported SS received by women during pregnancy and childbirth.

Aim 1: Analysis Plan and Sample Size Calculations

We will first summarize health-related and sociodemographic data between arms. For our primary effectiveness outcome, HCP-led skilled birth delivery, we will fit a multivariable logistic regression model, with study arm as the predictor of interest, and age, high-risk pregnancy, and health facility at enrollment as a priori additional variables in the model, due to their strong association with the selected outcome [70,90,91]. In our primary intention-to-treat model, we will consider women with missing outcome data, after home visits and next of kin interviews, as presumed to have not received skilled birth (ie, there will be no missing outcome data in our primary analysis). In sensitivity analyses, we will (1) repeat the analysis after excluding women with missing outcome data and (2) include additional potential confounders in the model that may have persisted despite individual randomization (eg, number of previous deliveries at a facility, socioeconomic status, distance to facility, history of facility delivery, food insecurity, alcohol

use, and depression). Although not designed to detect a difference, we will also explore additional secondary outcomes, including (1) number of ANC visits completed, (2) mode of infant delivery, (3) institution-based delivery, (4) presence of one or more birth complications, (5) child mortality, (6) maternal mortality, (7) preterm birth, (8) birth weight, (9) completion of postnatal care, (10) SS, and (11) initiation of breastfeeding. Both our pilot data and other similar studies estimate that 70% of the women in Uganda deliver with a skilled attendant [15,48,49]. Finally, we will explore the role of SS as a moderating effect of the intervention through a prespecified stratified analysis among women in the upper versus lower half of SS in the cohort, as measured by the Duke-UNC Functional Social Support Scale [64]. To test our primary effectiveness hypothesis, allowing for a 2-sided type I error of 5%, 90% power, and assuming a 5% loss to follow-up, we will require 824 participants to detect a 10% difference in HCP-led skilled birth delivery between arms. Data analysis will be conducted using Stata (version 17; StataCorp LLC). The findings will be presented as descriptive statistics, scatter plots, and graphs; statistical significance will be considered at $P \leq .05$. While we will ensure completed data are collected through timely cleaning and REDCap prompts, we will still be able to detect the same effect in the primary outcome with the power of 85% in the unlikely event that we lost up to 18% of the records due to missing data.

Aim 2: Evaluating Intervention Implementation

We will evaluate intervention implementation using the framework by Proctor et al [66] (Figure 1) and plan for future scale-up per the CFIR [67] (Table 3). While the effect of the Support-Moms intervention on HCP-led skilled birth delivery, ANC attendance, and other secondary outcomes in aim 1 is critical, the translation of its potential benefit into routine care impact requires understanding the implementation process. We chose the evaluative framework by Proctor et al [66] because it consists of essential implementation science outcomes with attention to both services and clients, which will be critical for uptake and long-term use of Support-Moms in routine care (Figure 1 and Table 4). Then, we will consider and refine implementation strategies for future scale-up using the CFIR as a determinant implementation science framework (Table 3) [67].

Table 3. Consolidated Framework for Implementation Research (CFIR) constructs that will guide data collection on intervention challenges, facilitators, and potential strategies by care users, health care providers (HCPs), and payers and managers.

CFIR construct	Interview topic	Possible questions to elicit implementation strategies from users and implementers
Intervention characteristics	Intervention-setting fitness, automation, and auditing	On the basis of the reported or presented acceptability, effectiveness, patient centeredness, satisfaction, and function outcomes, how can the intervention be improved for increased implementation?
Outer setting	Existing policy, resources, and MOH[a] willingness and capacity to support increased demand for services and adopt the intervention	On the basis of the presented adoption, penetration, and other outcomes, as well as existing policies and resource commitments, what rollout strategies will be most effective in overseeing intervention implementation?
Inner setting	Facility adaptive reserve, leadership endorsement, and resource reallocation	On the basis of the identified cost-effectiveness, how can existing resources be reallocated to promote intervention uptake?
Individual characteristics	Patient centeredness, support, and community referrals	On the basis of acceptability, satisfaction, and function, what potential support will be needed for individuals using Support-Moms to improve uptake, enthusiasm, and retention?
Implementation process	Experience of HCPs on app enrollment, patient interaction, and increased demand and implementer's intention to "try," budgeting, sustainability, timing, execution, and scale-up	Explore implementers' support and satisfaction of the app to improve service use; approaches to publicizing and dissemination; engaging CHWs[b], focal HCPs, and social supporters as champions; long-term funding, potential impact; and "leading" or "lagging" indicators of the implementation success

[a]MOH: Ministry of Health.

[b]CHW: community health worker.

Table 4. Application of the framework by Proctor et al [66] to evaluate implementation, service, and client outcomes.

Outcomes and domain	Specific intervention measures	Data source
Implementation outcomes		
Acceptability	• Reported ease of use and performance expectancy, effort expectancy, social influence, facilitating conditions, self-efficacy, and behavioral intention to use the app in the future • Overall user acceptability per the tool by Weiner et al [92] • Qualitative: For example, participants: How was it for you to use these SMS, messaging, or calls? and HCP[a]: How was it for you using the messaging app?	• Exit interviews • Exit questionnaire
Adoption	• Initiation and use of the app over time • Percentage of eligible and participating social supporters	• mHealth[b] platform • Study records
Appropriateness	• Relevance (for setting) and compatibility • Overall appropriateness with the tool by Weiner et al [92] for both HCPs and end users • Qualitative: For example, participants: What happened when you received SMS or voice calls? and HCP: What happened or what did you observe when you enrolled people on the app?	• Exit interviews • Exit questionnaire
Cost	• Refer to aim 3: Evaluating the Cost and Cost-Effectiveness of Implementing the Support-Moms Intervention Into Routine Care and Its Implication for Sustainability section	• Refer to aim 3
Feasibility	• Percentage of users willing to participate; percentage of women, spouses, and social supporters meeting eligibility criteria; recruitment or participating rates, and reason for not participating. • We will use the tool by Weiner et al [92] to measure feasibility for both HCPs and end users.	• mHealth platform • Study records • Exit questionnaire
Fidelity	• Percentage of HCs[c] with capacity and integrity to deliver intended service (ANC[d], skilled deliveries, and admissions), percentage of accessible cell phones, and percentage of messages automatically sent out • Percentage of SMS or voice calls received by the participant over anticipated per protocol • Percentage of network, dead battery, phone losses, and phone functionality issues encountered	• Study records • mHealth platform • Facility audits
Penetration	• Number and type of HCs and HCPs engaging with the app • Percentage of eligible participants and social supporters enrolled	• Facility audits • Study records
Sustainability	• Use of the app over time, social supporter engagement over time, and user retention • Percentage of participants lost to follow-up and percentage of additional staff needed • Qualitative: All, for example, what challenges did you experience or face while using this app?	• Facility audits • Study records • Exit interviews
Service outcomes		
Efficiency	• Time spent on enrolling participants on the app, time spent on deliveries, timely delivery of needed supplementary or reference information, cost of delivery • Qualitative: All, for example, what do you think about this intervention?	• mHealth platform • Exit interviews
Effectiveness	• Refer to aim 1	• Refer to aim 1
Equity	• App use by facility type, participant type, and demographics	• Study records
Patient centeredness: accomplished during the formative and pilot work [36,60]		
Timeliness	• Perceived impact on ANC attendance and skilled deliveries • Qualitative: How was your experience attending ANC and preparing for birth and delivery?	• Exit interviews
Client outcomes		
Function	• Perceived quality, impact on maternity care, use, and life (survey by Brazier et al [89]) • Qualitative: How did this intervention help you in your pregnancy or work as an HCP?	• Exit questionnaire • Exit interviews

Outcomes and domain	Specific intervention measures	Data source
Satisfaction	• Satisfaction with intervention content, delivery, and credibility (Client Satisfaction Questionnaire) [93] for both HCPs and end users • Qualitative: What concerns do you have about using this technology to support you?	• Exit questionnaire • Exit interview

[a]HCP: health care provider.

[b]mHealth: mobile health.

[c]HC: health center.

[d]ANC: antenatal care.

Data Collection

Implementation Metrics

A trained RA will administer interviewer-led questionnaires at the trial exit (Table 4 presents outcomes and data sources) to (1) all intervention arm postpartum women, (2) all intervention arm social supporters, (3) all HCPs from participating facilities who enroll and deliver participants within the study sites, and (4) MOH key stakeholders and managers expected to inform rollout and adoption by the MOH. We will use a standardized checklist to conduct facility audits during implementation to document ANC visits and deliveries registered; maternity admission data; maternal mortality; disease cases managed; prescription data; laboratory data; and resource allocations at baseline, 12, 24, and 36 months following the implementation of the intervention for all study sites. A facility inventory will be done to inform our understanding of baseline conditions and set up for maternity and reproductive health services at the hospital and HC4 and HC3 public maternity centers.

We will use quantitative data on reported acceptability, appropriateness, effectiveness, function, and satisfaction to purposively select a subset of up to 15 postpartum individuals for exit in-depth interviews (or until saturation is met [94]), 15 social supporters, and up to 10 HCPs (approximately 2 for each facility level or district; refer to Table 1) involved in participant app enrollment and facility deliveries to clarify or contextualize observed outcomes based on the framework by Proctor et al [66] as outlined in Table 4. We will ask participants to describe actual events and experiences wherever possible (eg, for postpartum individuals, what worked well or poorly with receiving the messages and the challenges experienced during the study) to not only ensure coverage of specific areas but also allow unanticipated themes to emerge. We will further explore the feasibility, appropriateness, acceptability, patient centeredness, and sustainability of involving social networks in this intervention, as well as relationship dynamics, which have been shown to influence social supporter interventions [23-25] (eg, the social supporter's specific role, their relationship throughout pregnancy, routine communication, the type of voluntary and requested SS given or received during pregnancy toward improving her experience, ANC visits, birth preparedness, childbirth, and the app-related challenges and opportunities). We will schedule these interviews between 4 and 6 weeks post partum. HCPs will also be interviewed at the end of the study to clarify potential opportunities and problems that were experienced with the intervention and its delivery. These will facilitate appropriate conclusions about effectiveness and implementation success.

Implementation Strategy Development

Using CFIR, we will develop guides to further interview these postpartum individuals, social supporters, and HCPs on the intervention, individual, and inner settings to inform our implementation strategies and optimize intervention delivery (Table 3). We will develop some initial implementation strategies based on these findings and the literature (eg, awareness campaigns in the community and dissemination or publicizing the app, implementation in facilities through local champions within or around each facility to maintain enrollments, training, choice of messaging format, automation, and routine audits with technical support as needed). At the end of the implementation period, we will present data on outcomes and cost-effectiveness of the framework by Proctor et al [66] (refer to aim 3), along with the preliminary implementation strategies to the facility, district, and national MOH managers and stakeholders who have key roles in budgeting and policy or service implementation and are expected to evaluate or endorse the app. Using CFIR-informed interview guides (Table 3), we will interview 5 to 10 of these key MOH managers and stakeholders for feedback and refine our initial implementation strategies for testing in a subsequent study. All qualitative interviews will be audiotaped with the participant's permission and transcribed verbatim. RAs will be trained on the interview guides. All HCP and MOH interview guides will be piloted with 3 staff managers at Mbarara Hospital to ensure optimization, comprehension, and appropriateness.

Intervention Fidelity

Intervention fidelity plays a key role in assessing intervention effectiveness [95,96]. An RA will ensure participants know how to use the phone to retrieve information. CHWs and HCPs from the targeted public HCs will be trained to enroll participants onto the app, with technical support from the study research teams, led by ECA and GRM. We will measure the 3 elements of implementation fidelity as outlined in Table 4. Notably, 13% of the women enrolled in our pilot study missed some app messages because of lost phones or phone functionality issues. To minimize dead battery and charging issues, solar chargers will be given to study participants to charge their phones as needed during enrollment. These chargers are readily available and inexpensive, and we will be tracking their cost. Phone losses will be assessed on a case-by-case basis, replaced sparingly, and costs will be determined accordingly. Outgoing SMS and voice messages will be monitored daily by the data management team. The times and lengths of individual outgoing calls and engagements will be recorded and transmitted to the server. Message deliveries during periods of inadequate cellular reception will be stored for later transmission. Although

2-way messaging has been found to be useful in other settings [11,14], our key factors in this proposal are to provide scheduled, targeted information and catalyze SS for women seeking maternity care, a mechanism that showed promising results in our pilot preliminary data. Moreover, 2-way messaging creates a burden on the health system that may not be sustainable. However, we will assess the need for this type of feature in the exit interviews for further exploration. In addition, contact numbers of the VHT and CHWs attached to the neighboring public HC will be provided to address any questions, referrals, or emergencies that may arise. SMS and voice call delivery or reception will be considered as proxies for accessing information to alter existing predisposing factors (such as negative health beliefs and low awareness) that could enable and improve perceived need to seek care with the help of available social networks, factors that will be assessed during exit interviews (Table 2 presents more details).

All quantitative data will be collected using a web-based database that will be developed in REDCap to improve data completeness, management, and quality control monitoring. Errors or out-of-range entries are reported immediately on the website so the original interviewer can reconcile the problem in a timely manner. Data entry verification will include algorithms that automatically check completed forms for missing, out-of-range, or inconsistent values before a form can be saved on the website.

Aim 2: Quantitative Analysis Plan

We will summarize implementation outcomes for Support-Moms users and implementers using descriptive statistics. Success in the implementation survey data will be identified qualitatively and by the top tertile of relevant scales (eg, acceptability, feasibility, satisfaction, and appropriateness). We will explore similarities and differences across HCs and districts over time as well as potential associations between implementation outcomes and effectiveness at HCs and district levels. We will summarize all findings and present them through a Delphi process or technique [97], with a final meeting involving key MOH managers and stakeholders. We will describe the ranked implementation strategies selected by app users and key MOH managers and stakeholders after the dissemination process.

Aim 2: Qualitative Analysis Plan

In-depth interviews will be digitally recorded and transcribed. The first set of exit interviews will be conducted to understand participants' or stakeholders' experiences and perspectives of the Support-Moms intervention and clarify the implementation, service, and client outcomes outlined in Table 4. The goal of the CFIR-informed interviews will be to refine and inform implementation strategies for integrating the Support-Moms intervention into routine maternity care. Qualitative analysis will be inductive [98], and categories will be derived from the different study textile participants, HCPs, and MOH manager and stakeholder interviews. These responses will be transcribed into English, if needed, and coded using NVivo (version 13; Lumivero). Data analysis will be jointly performed. The study coordinator and research fellow will double code 5 sampled transcripts from each category and, together with the principal investigator, resolve any coding disagreements to ensure consistency in the codebook. Dyadic analysis will also be performed between pregnant individuals and their social supporters. Categories will then be developed and presented with illustrative quotes from data to explain experiences, challenges with the intervention, and recommendations to improve its implementation into routine maternity care.

Aim 3: Evaluating the Cost and Cost-Effectiveness of Implementing the Support-Moms Intervention Into Routine Care and Its Implication for Sustainability

The incremental cost and the cost-effectiveness of the Support-Moms intervention or program will be estimated from HCP and health system and societal perspectives to guide the decision makers on continuation, incorporation, integration, sustained use, and routinization—a method that has previously been used in a Ugandan context [99]. We will measure and record the cost of developing and implementing the intervention (program costs), the cost to HCPs from increasing demand for or use of services, and costs to users (intervention participants and their social supporters). The cost of developing and delivering the intervention will be estimated in consultation with the app developers, data from the pilot study, the maintenance team, time and motion studies conducted at representative sites over a 2-week period, as well as administrative records during implementation. The costs of maternity service use to access care will be collected from all aim 1 participants and HCPs at exit; all intervention users and HCPs will provide the cost of care seeking and intervention involvement. We will identify comprehensive tasks required by both users (eg, time used to seek care) and HCPs (eg, training and staff time) and quantify public-sector resource use during the use and provision of the HCP-led service during the 3 years of implementation. Routine and additional public-sector unit costs will be collected from the health management information system [100] and administrative records at the facility and district levels, MOH, and other safe motherhood implementing partners. Direct and indirect costs to intervention users and HCPs because of involvement in the intervention (such as trainings, time used to seek care, and time used by HCPs to enroll users on the app) will be collected from participant exit interviews and administration records. The costs of providing user phones and solar chargers will be explored.

Cost-Effectiveness Analysis

Cost analysis will include estimating program costs, costs to HCPs, and costs to users as described above. We will also develop a decision tree model to assess the potential impact of economic, clinical, or health outcomes of the Support-Moms intervention against routine care [101,102]. The model will incorporate cost items, relevant clinical probabilities, and case outcomes, allowing a cost-effectiveness evaluation. We will combine the costs and outcomes for each branch of the tree using branch possibilities to simulate the expected costs and outcomes of the intervention and routine care. We will hypothesize service users using routine maternity services or enrolled on the Support-Moms app (per trial arm) as they pass through different health states over time and within acute and chronic health states of 3 key maternal morbidities of sepsis,

postpartum hemorrhage, and hypertensive disorders [70,103-105]. Our cost-effectiveness evaluation will account for the outcomes for both the mother and the infant throughout their lifetime at the annual discounting rate of 3% [106]. The clinical and cost outcomes for the infant (eg, low birth weight and stillbirth or intrauterine fetal deaths) will be incorporated in the decision tree. We will use 1-way and probabilistic sensitivity analyses to quantify the confidence level or robustness in this model analysis output in relation to the outputs and the payer's willingness to pay thresholds [101,107]. We will estimate ICERs in terms of cost per additional HCP-led skilled birth delivery and per death averted. In addition, we will estimate ICERs per disability-adjusted life years averted and quality-adjusted life years (QALYs) gained (QALYs derived from the collected SF-6Dv2 data) as the main summary measures of cost-effectiveness [108] in line with the country's gross domestic product per capita (GDPpc) [109], to assess the value for money of adopting or providing the Support-Moms app long-term compared to routine care. If ICERs per QALY or per disability-adjusted life years <300% of GDPpc, Support-Moms will be deemed cost-effective, highly cost-effective for ICERs <100% of GDPpc, and not cost-effective otherwise. The decision tree and cost-effectiveness analyses will be programmed in TreeAge (TreeAge Software, LLC).

Ethical Considerations

The ethics approval was obtained from the Mbarara University of Science and Technology Research Ethics Committee (MUST-2022-631) and Uganda National Council for Science and Technology (HS3366ES). Study site administrative permission was obtained from the Mbarara district health officer, Mbarara City Health Officer, Mitoma District health officer, and the director of clinical services at the MOH. We are continually seeking and obtaining written informed consent from all study participants before enrolling in the study. The participants can withdraw from the study at any time. Participant data are anonymized at all times. The study was registered at ClinicalTrials.gov (NTC05940831). The research outcomes from this study will be published in international peer-reviewed journals and presented to the Ugandan MOH as policy briefs and at selected national and international conferences.

We are making firm attempts to adequately explain study purpose, schedule, expectations at the time of enrollment, and data collection and continually updating residence and phone details at each visit to minimize loss to follow-up. We are using appropriate means of contact based on participant preference and information on the best telephone network for the time of the day to telephone or send text messages, with emphasis that participation in this study is voluntary. However, reasons for decline or withdrawal from the study are being sought and documented. Participants are reimbursed for their study visits; a small compensation for their transport worth approximately UGX 20,000 (US $5.50) altogether is given at the end of each of the 2 planned baseline and exit interviews. Participating HCPs are reimbursed with US $5 as compensation for their time after every interview. The estimated time needed for interviews and other study procedures per visit is approximately 1.5 hours.

Results

This study was funded in September 2023. Ethics approval was obtained in February 2024, and actual data collection started in March 2024. As of January 2025, 75% (618/824) of all projected study participants have consented and been recruited into the study. Participants are expected to be followed up until delivery, and 15% (124/824) of the participants have exited to date. Data analysis for the trial is expected to start as soon as the last participant exits (expected in March 2026). The qualitative interviews will start in April 2025, and data will be analyzed and published as soon as data collection is done. Data collection is expected to be completed by March 2027.

We are currently recruiting at least 60 women or individuals and their social supporters per month. We have registered no loss to follow-up so far.

Discussion

We are targeting to recruit 824 pregnant women or individuals who have not yet presented for ANC by their second trimester, residing in Mitooma and Mbarara districts, with self-reported access to a cell phone with reception in their home for personal use, and are able to identify at least 2 social supporters living within the study districts. Uganda has approximately 30 million people who access mobile phones (most adult Ugandans), and 71% of users are connected using a basic feature phone [110]. Women or individuals are being identified by CHWs and VHTs, who then notify the study RAs to contact and seek written informed consent before enrollment into the study. Eligible social supporters who own a cell phone for personal use with reliable reception and know the study participant is pregnant be asked to provide consent and will be recruited within the first 2 weeks preceding enrollment of the pregnant women or individuals to ensure an ongoing relationship at the time of their enrollment. Adult HCPs who conduct deliveries within the study sites and MOH facility managers and stakeholders who participate in budgeting, procurements, or funding for facilities are being identified and offered enrollment into the study.

We developed an intervention aimed at improving communication of targeted, health-related information, motivating and mobilizing SS for pregnant women to use maternity services in rural southwestern Uganda (Support-Moms) [36]. Through an iterative approach, we (1) identified preferred key ANC topics from stakeholder interviews with 30 women and 5 HCPs and characterized a preferred messaging intervention; (2) developed content for SMS text and audio messages with 4 medical experts based on identified topics; (3) designed an app prototype through partnership with an mHealth development company (iStreams); and (4) pilot-tested the prototype and sought user experiences and feedback to refine the intervention through 3 different sets of 10 iterative exit interviews, 2 focus group discussions, and 5 cognitive interviews.

We are currently conducting a type 1 hybrid effectiveness-implementation trial [111] to test if this novel patient-centered mHealth-based SS intervention is effective and

cost-effective if implemented into routine care from individual and facility perspectives. We will simultaneously assess other implementation, service, and client outcomes per the framework by Proctor et al [66] and refine implementation strategies for future scale-up using the CFIR (individuals, intervention, inner and outer settings, and process). We hypothesize that this intervention will be an effective and cost-effective strategy to improve maternity service use for women in rural Uganda and similar settings. Data collection is underway. Our results will present the functionality of our mHealth intervention, its ability to stimulate and encourage routine health care use, and improve maternal-fetal health outcomes among all rural women, including those with limited education. The results of our work will be usable for other groups designing similar interventions to promote perinatal health in resource-poor settings. Results of this study will also provide requisite data for maternal health policy change and lay the groundwork for evaluation for a regional implementation of the intervention.

Notably, our study will have some strengths. Unlike in many studies, we used conceptual frameworks to characterize and develop patient-centered content and design aimed at making findings more relevant and generalizable to rural communities where the impact of such interventions is likely to be the greatest. This approach is often lacking in mHealth development, most of which is often led by developers and investigators, with limited input from end users [11,14,112]. While many mHealth interventions have been developed in Uganda [113-115], very few have been in the reproductive health field [114,116], and fewer have been evaluated at scale in the public sector [115,117]. Therefore, our study will be among the first ones to test mobile maternal health apps in a randomized controlled trial in Uganda, concurrently assessing effectiveness and other implementation metrics, information that is critical for guiding ultimate use and integration of this intervention in routine care. In this study, we are studying a high-risk population, in which <70% of women deliver with a skilled attendant [15], <58% attend at least 4 ANC visits (of the 8 recommended by the WHO), and thus are likely to benefit from this intervention. We believe that our grounded approach, using appropriate implementation science models and partnering with key regional stakeholders to evaluate an intervention in a rural low-resource setting, will enhance the likelihood of uptake, adoption, and integration into routine care.

We are leveraging existing CHWs, social networks, and resources to encourage uptake, retention, and adoption within a community that largely depends on family and community networks to thrive [42]. This approach is hypothesized to improve pregnancy experiences, partner involvement, support, communication, and mental health during and after pregnancy, ultimately offsetting the downstream cost of avoidable maternal morbidity and mortality [50-53]. We are also building on our pilot, promising preliminary data, and it will provide vital evidence about effectiveness, uptake, and sustained use of this tailored mHealth approach designed to address common individual, family, and community or societal barriers to health care use in Uganda.

We are building on our experience from our previous work done within a typical public health facility setting to recruit and follow up participants. Many people in Uganda move frequently in search of stable work or new settlements, including pregnant individuals [25]. In addition, some change or lose their mobile phones or phones could be inaccessible at times due to network issues. We are using our previous clinical research experience in conducting similar trials to maximize the feasibility of our mHealth intervention and retention in care. SMS distribution is controlled, and women are routinely scheduled for ANC randomly and independently. Consequently, the risk of contamination (eg, discussing and sharing information) at the facility level is minimized. To minimize potential contamination in the community, we are making an effort to clearly explain the study procedures to CHWs or HCPs and intervention women who may learn about different arm allocations through casual conversations, an approach that worked well during our pilot. We have developed and administered a quality control checklist for a few randomly selected control participants so far to assess contamination between arms every 3 months.

Acknowledgments

The authors acknowledge all the research assistants currently collecting data and all the women who have graciously accepted to participate in this study. They acknowledge the facility managers and district health officials for supporting this work. This work was funded by the National Institutes of Health-Eunice Kennedy Shriver National Institute of Child Health and Human Development (grant 1R01HD111692-01).

Data Availability

The datasets generated or analyzed during this study will also be available from the corresponding author on reasonable request.

Authors' Contributions

All authors conceptualized the project and participated in the research protocol writing. ECA wrote the first draft. All authors reviewed the manuscript and approved it for submission.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer review report from the SIHH - Science of Implementation in Health and Healthcare Study Section, Eunice Kennedy Shriver National Institute of Child Health and Human Development (National Institutes of Health, USA).
[PDF File (Adobe PDF File), 129 KB - resprot_v14i1e67049_app1.pdf]

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Abbreviations

ANC: antenatal care
CFIR: Consolidated Framework for Implementation Research
CHW: community health worker
GDPpc: gross domestic product per capita
HC: health center
HCP: health care provider
HIPAA: Health Insurance Portability and Accountability Act
ICER: incremental cost-effectiveness ratio
LMICs: low- and middle-income countries
mHealth: mobile health
MMR: maternal mortality ratio
MOH: Ministry of Health
QALY: quality-adjusted life year

RA: research assistant
REDCap: Research Electronic Data Capture
SM: scheduled messaging
SS: social support
SSA: sub-Saharan Africa
UNC: University of North Carolina
VHT: village health team
WHO: World Health Organization

Edited by A Schwartz; submitted 01.10.24; this is a non–peer-reviewed article;accepted 18.02.25; published 19.03.25.

Please cite as:
Atukunda EC, Mugyenyi GR, Haberer JE, Siedner MJ, Musiimenta A, Najjuma JN, Obua C, Matthews LT
Integration of a Patient-Centered mHealth Intervention (Support-Moms) Into Routine Antenatal Care to Improve Maternal Health Among Pregnant Women in Southwestern Uganda: Protocol for a Randomized Controlled Trial
JMIR Res Protoc 2025;14:e67049
URL: https://www.researchprotocols.org/2025/1/e67049
doi:10.2196/67049
PMID:40105879

Protocol

Unintended Prolonged Opioid Use: Protocol for a Case-Controlled Trial

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Abstract

Background: Misuse of prescription opioids remains a public health problem. Appropriate short-term use of these medications in opioid-naive patients is indicated in selected settings but can result in unintended prolonged opioid use (UPOU), defined as the continuation of opioid therapy beyond the period by which acute pain would have been expected to resolve. Clinical strategies aimed at preventing UPOU are lacking due to the absence of information about how this poorly understood clinical phenomenon actually develops.

Objective: In this research project, 3 Clinical and Translational Science Awards (CTSA) programs (Mayo Clinic, University of Michigan, and Yale University) leveraged the conceptual framework for UPOU to investigate how patient characteristics, practice environment characteristics, and opioid prescriber characteristics facilitate or impede UPOU. All data management and analyses were conducted at a fourth CTSA program (University of Minnesota). This work was accomplished by pursuing 3 specific aims.

Methods: In aim 1, opioid-naive adults receiving an initial opioid prescription were recruited for study participation. Opioid prescriptions were identified longitudinally, and patterns of use were categorized as short-term, episodic, or long-term use using established criteria. Using a prospective case-control design, patients progressing to UPOU were matched 1:1 with patients who did not develop UPOU, and differences in patient characteristics were assessed. In aim 2, clinicians who prescribed opioids to patients in aim 1 were identified and recruited for prospective assessments. Institutional and individual practice environments were assessed using a validated self-report survey. In aim 3, structural equation modeling was used to evaluate data collected in aims 1 and 2, and identified interactions were further evaluated in a large national administrative claims database.

Results: Patient recruitment began on August 1, 2019. However, due to the COVID-19 pandemic, patient recruitment was slowed and intermittently interrupted over the ensuing 3-year period. As a result of regional variations in the impact of the COVID-19 pandemic on research activities, the majority of patient and clinician recruitment occurred at the Mayo Clinic site.

Conclusions: Following complete data analyses, it is anticipated that electronic health record systems will be leveraged to help clinicians identify at risk patients and to develop direct-to-patient educational materials to raise awareness of the risk factors for developing UPOU.

Trial Registration: ClinicalTrials.gov NCT04024397; https://clinicaltrials.gov/study/NCT04024397

International Registered Report Identifier (IRRID): DERR1-10.2196/72032

(JMIR Res Protoc 2025;14:e72032) doi:10.2196/72032

KEYWORDS

opioid use; case-control; unintended opioid use; prolonged opioid use; prospective

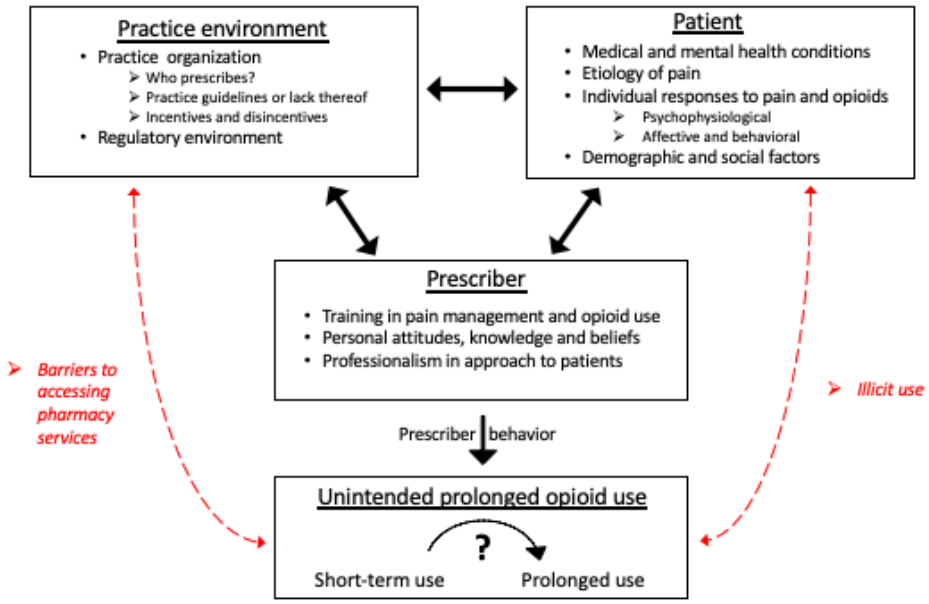
Introduction

Background

Misuse of prescription opioids remains a public health problem [1]. Appropriate short-term use of these medications in opioid-naive patients is indicated in selected settings but can result in a previously underrecognized segue to unintended prolonged opioid use (UPOU), defined as the continuation of opioid therapy beyond the period by which acute pain would have been expected to resolve [2,3]. Clinical strategies aimed at preventing UPOU are lacking due to the absence of information about how this poorly understood clinical phenomenon actually develops.

Investigators at Mayo Clinic previously organized a group of thought leaders to develop a conceptual framework for understanding the broad array of factors potentially contributing to UPOU [4]. A conceptual framework is essential both to guide the study of this clinical problem and to identify potential targets for interventions aimed at mitigating the development of UPOU. The framework is comprised of 3 domains, including patient characteristics, practice environment characteristics, and opioid prescriber characteristics that interact to either facilitate or impede UPOU (Figure 1) [4].

Figure 1. The conceptual framework for unintended prolonged opioid use.



Within each domain, potential factors, drawn from the relevant literature, moderate or mediate the influence of each domain. However, the necessary evidence within each of these domains is frequently lacking. This is critically important because 25% of patients in a population who received an initial opioid prescription proceeded to UPOU [3]. This work relied on a medical records linkage system unique to the geographically defined region, limiting the ability to perform larger studies across different patient populations. It also did not perform prospective assessment of several factors important to evaluate the proposed conceptual framework.

Study Objectives

In this research project, 3 Clinical and Translational Science Awards (CTSA) programs (Mayo Clinic, University of Michigan, and Yale University) leveraged the conceptual framework for UPOU to investigate how the patient characteristics, practice environment characteristics, and opioid prescriber characteristics facilitate or impede UPOU. All data management and analyses were conducted at a fourth CTSA program (University of Minnesota). This work was accomplished by pursuing three specific aims.

Specific Aim 1

The first aim was to identify incident cases of UPOU and prospectively assess their characteristics in comparison to new opioid users who did not progress to UPOU. At each site, opioid-naive adults receiving opioid prescriptions were enrolled. Opioid prescriptions and self-reported opioid use were followed, and patients progressing to UPOU were identified in real time. A matched sample of patients who did not develop UPOU were recruited for assessment of framework elements, including biochemical confirmation of opioid use, pain-related measures of physical and emotional functioning, and medical and social histories.

Specific Aim 2

The second aim was to assess clinicians prescribing opioids to incident cases of UPOU and new opioid users who did not progress to UPOU. Clinicians treating patients recruited in aim 1 were recruited for prospective assessment of prescriber characteristics including questions about past training in pain management, and attitudes and beliefs about pain and opioid use. The practice environment was assessed including practice organization, practice size, and estimated proportion of patients receiving pain management services.

Specific Aim 3

The third aim was to evaluate the conceptual framework. Using the information gathered in aims 1 and 2, structural equation modeling (SEM) was used to evaluate the associations between framework elements in each domain. Identified interactions were further evaluated in a large nationally representative administrative claims database.

Methods

Study Settings and Participants

Overview

In specific aim 1, opioid-naive adults receiving an opioid prescription (n=780 at each site) were identified at each clinical site (Mayo Clinic, University Michigan, Yale University) and recruited for study participation. A research coordinator assisted in activating a mobile platform on each patient's personal smartphone for purposes of providing informed consent and completion of study outcome measures. Opioid prescriptions were identified longitudinally by review of each patient's electronic health record (EHR). Patients progressing to UPOU were identified in real time, and patterns of opioid use were categorized as short-term, episodic, or long-term use using the Consortium to Study Opioid Risks and Trends (CONSORT) criteria [5]. Patients meeting criteria for episodic or long-term use were considered to have progressed to UPOU. Characteristics associated with UPOU were used to assess framework elements, including biochemical confirmation of opioid use; pain-related measures of physical and emotional functioning; and medical, surgical, psychiatric, and social histories.

In specific aim 2, clinicians who prescribed opioids to patients in aim 1 were identified and recruited for prospective assessments. Institutional and individual practice environments were assessed using a self-report survey validated in a national sample of physicians [6].

In specific aim 3, SEM was used to evaluate data collected in aims 1 and 2 to identify the associations between framework elements in each domain. Identified interactions were further evaluated in a large national administrative claims database (OptumLabs Data Warehouse [OLDW]).

Study Settings

Each CTSA clinical site leveraged established resources and clinical infrastructure.

Mayo Clinic

Olmsted County residents who previously consented to have their medical records used for research purposes were identified using the Rochester Epidemiology Project (REP) medical records linkage system [7,8]. The REP provides access to all medical records for Olmsted County residents. The indications for opioid use in these patients were both surgical and nonsurgical pain. Patients recruited from this site reflected the characteristics of UPOU as it developed in a geographically defined population.

University of Michigan

The surgical specialty clinics at the University of Michigan were used to identify opioid-naive patients receiving an initial opioid prescription following common surgical procedures, including knee and hip arthroplasty, inguinal hernia repair, intra-abdominal procedures, and thoracic and breast procedures [9]. The indication for opioid use in these patients was acute surgical pain. Patients recruited from this site reflected the characteristics of UPOU as it developed in a surgical setting.

Yale University

Yale New Haven Health is a large health care delivery system that provides services to individuals residing in the greater New Haven, Connecticut area. The EHR was leveraged to identify opioid-naive adults receiving an initial opioid prescription. These individuals were contacted using the patient communication portal of the EHR to assess their interest in participating in the research project. The indication for opioid use among these patients was surgical and nonsurgical pain. Patients recruited from this site reflected the characteristics of UPOU as it developed in a large health care delivery system.

Study Participants

A total of 780 patients were approached for recruitment at each site (N=2340), and eligibility criteria for study participation are outlined in Textbox 1. Patients meeting these eligibility criteria were further categorized based on CONSORT criteria [5]. Criteria for the long-term CONSORT category included episodes of opioid prescribing lasting longer than 90 days and including 120 or more total days of supply or 10 or more prescriptions [5]. Criteria for the episodic CONSORT category included episodes lasting 90 days or longer, with total days of supply being fewer than 120 and the total number of prescriptions filled being fewer than 10. Criteria for the short-term CONSORT category included episodes of opioid prescribing lasting 90 days or fewer [5]. Although study participation was limited to adults who own a smartphone, recent data from January 2018 demonstrated 77% of US residents own a smartphone [10].

Textbox 1. Eligibility criteria.

Inclusion criteria:

- Age ≥18 years
- No use of opioids for 6 months before the issuance of the initial opioid prescription as confirmed by review of the electronic health record and patient self-report
- Willingness to participate in all aspects of the study including use of the mobile platform on their personal smartphone

Exclusion criteria:

- Cancer-associated pain
- Concurrent treatment for cancer (eg, chemotherapy and radiation therapy)
- Residence in an extended care facility
- Any surgery or hospitalization within the past 6 months
- Mental health disorders that could impede functioning in an ambulatory care setting (eg, schizophrenia and dementia)
- Non–English-speaking individuals
- No smartphone; although study participation was limited to adults who own a smartphone, recent data from January 2018 demonstrated that 77% of US residents own a smartphone [10]

Specific Aim 1

Overview

At each of the 3 sites, a total of 780 opioid-naive adults receiving an initial opioid prescription were approached for enrollment. Subsequently issued opioid prescriptions were monitored by reviewing the EHR, and patients progressing to UPOU were identified in real time. Time-matched samples of patients who did and did not develop UPOU were recruited for assessment of outcome measures.

Participant Recruitment

Participant recruitment was site specific. For example, the Mayo Clinic site leveraged the resources of the REP to identify a population-based cohort of potential patients who had previously provided informed consent for the use of their medical records for research purposes. Since 2002, Mayo Clinic and Olmsted Medical Center have used a proprietary software system to document and manage all prescriptions including prescriptions for opioids [11]. These two institutions provide a vast majority of medical care for Olmsted County residents [7,8,12,13]. The electronic prescription system was used to identify previously opioid-naive Olmsted County residents receiving an initial opioid prescription as previously described [3]. These individuals were contacted by telephone and invited to participate in the study. The Michigan site used resources associated with the University of Michigan Analgesic Outcomes Study (AOS) [9]. The AOS is a prospective, observational cohort registry of postsurgical acute and chronic pain outcomes. Previously opioid-naive patients in the AOS registry were invited to participate in study. The Yale University site used the EHR to identify previously opioid-naive patients receiving an initial opioid prescription. More specifically, the EHR was screened by study personnel for the issuance of any opioid prescription, and previously opioid-naive patients were contacted using the EHR patient portal system and invited to participate in the study.

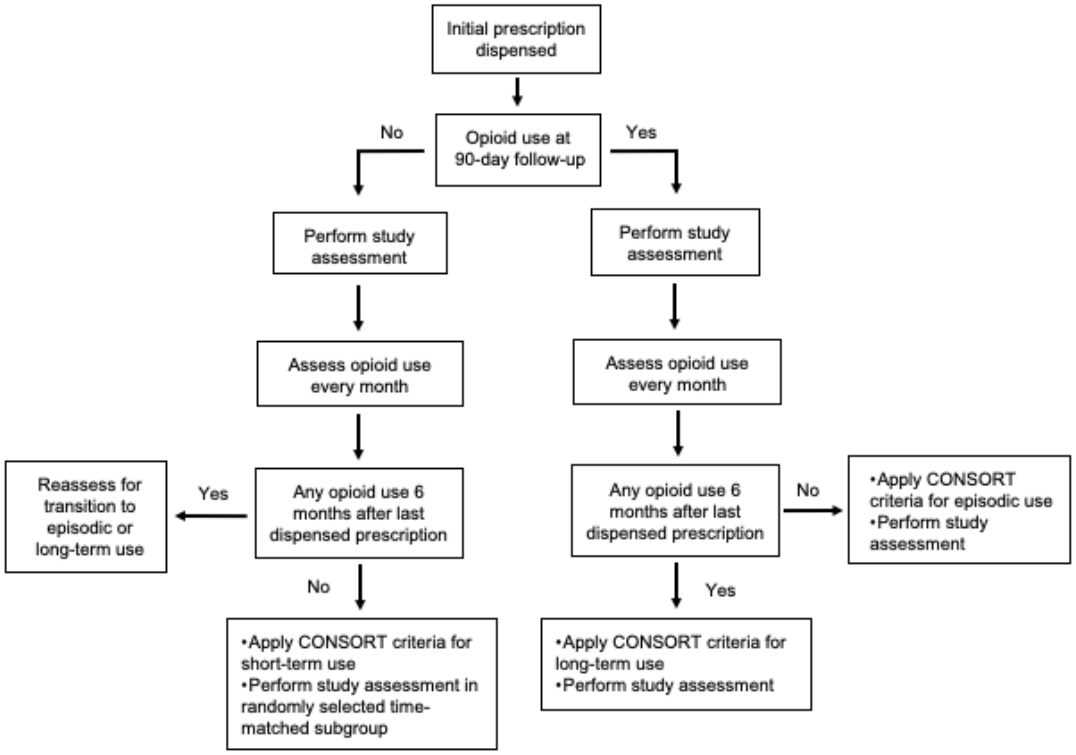
Mobile Smartphone Platform

All study participants were assisted by study personnel in downloading the smartphone platform (CareEvolution). The smartphone platform complied with the security and privacy controls defined by the National Institute of Standards and Technology SP 800 53 Rev 5 as designated by the Federal Information Security Modernization Act. The platform was granted authorization to operate by the National Institutes of Health and is Health Insurance Portability and Accountability Act compliant [14]. The smartphone platform was used to obtain informed consent and to collect all outcome measures.

Timeline for Establishing Consortium to Study Opioid Risks and Trends Criteria for Opioid Use

The timeline of the study was governed, in part, by the temporal requirements for applying CONSORT criteria (Figure 2). The beginning date of an episode of opioid use was defined as the date that the initial prescription was issued, with no previous opioid prescriptions issued for the preceding 6-month time period. The end date of an episode was the date that the last dispensed medication supply was exhausted, based on the days of supply as documented in the prescription instructions with no opioid dispensing in the ensuing 6 months. Patients who continued to use opioids on day 90 following issuance of the initial opioid prescription were invited to participate in the study assessment. Although it was not possible to accurately apply CONSORT criteria for episodic or long-term use on day 90, the study assessment was performed at this time point to ensure patients were captured at the earliest stages of episodic or long-term use. The status of opioid use in these patients was monitored every month by reviewing the EHR. This approach to follow-up limits the time interval between establishment of CONSORT criteria for episodic or long-term use and the final study assessment.

Figure 2. Flow diagram for establishing Consortium to Study Opioid Risks and Trends (CONSORT) criteria for opioid use.



A randomly selected group of patients meeting criteria for short-term use at day 90 were invited to participate in the study assessment. This group of patients was selected to be time-matched 1:1 to patients continuing to use opioids at day 90 (initial issue date ±2 weeks) Although it was not possible to accurately apply CONSORT criteria for short-term use until month 6 following issuance of the last prescription, the study assessment was performed at this time point to ensure that patients were captured in the earliest stages of short-term use. Because it was anticipated that the majority of the cohort would meet criteria for short-term use, it was not feasible to invite all patients to participate in the study assessment.

Study Assessments

Assessments were performed at 2 time points: 3 months following dispensing of the initial opioid prescription and 9 months following dispensing of the initial opioid prescription.

Demographics and Clinical Characteristics

Demographic and clinical characteristics were assessed including age, sex, ethnicity, marital status, education, employment status, BMI, and past medical and surgical histories including chronic pain.

Verification of Opioid Status and Dose

Opioid use and dose were verified by review of pharmacy and medical records. Opioid doses were converted to daily morphine equivalents using a conversion calculator as previously reported [15-17]. The opioid status was biochemically verified with a urine toxicology screen.

Occurrence and Risk of Opioid Misuse

The occurrence and risk for opioid misuse was assessed using 3 instruments. The Alcohol, Smoking, and Substance Involvement Screening Test (ASSIST) was administered. The ASSIST is validated [18] and used in the National Institute on Drug Abuse Quick Screen [19]. The Prescribed Opioid Difficulties Scale [20] was used to assess for substance use disorders associated with use of prescribed opioids [21]. The Opioid Risk Tool is a brief questionnaire that is validated [22] and was used to assess the risk of opioid misuse.

Symptoms of Opioid Withdrawal

Symptoms of opioid withdrawal were assessed using the Clinical Opiate Withdrawal Scale, which is an observer-rated instrument [23,24].

Opioid Craving

Opioid craving was assessed using responses (0 to 100 on a visual analog scale) to 3 questions: (1) How much do you crave opioids? (2) How often do you think about the next dose? and (3) How strong is your urge to take more medication than prescribed? This approach is validated [25] and was used to assess opioid craving [26-28].

Pain Intensity

Pain intensity was assessed using the 11-point verbal pain rating scale. The validity of the verbal pain rating scale is well established [29-31].

Michigan Body Map

The Michigan Body Map (MBM) is a self-report measure to assess body areas where pain is experienced. The MBM has demonstrated utility, reliability, and construct validity [32,33]. The MBM measure has been used to assess pain in a broad range of clinical settings [34-41].

Pain-Related Psychosocial Functioning

The Multidimensional Pain Inventory (MPI) measures the psychosocial impact of chronic pain [42]. The MPI has proven reliability and construct validity [43].

Negative Affect

Depressive symptoms and pain catastrophizing are key components of negative affect [44]. The Center for Epidemiologic Studies-Depression scale provides a validated measure of depressive symptoms [45] in patients with chronic pain [46,47]. The Pain Catastrophizing Scale provides a measure of negative cognitions and emotions associated with actual or anticipated pain experiences [48].

Baseline Smoking Status

Baseline smoking status was assessed using the techniques used by the Behavioral Risk Factor Surveillance System: (1) Have you ever smoked a cigarette, even a puff? (Yes or No); (2) Have you smoked at least 100 cigarettes in your entire life? (Yes, No, or Not sure); and (3) Do you now smoke cigarettes every day, some days, or not at all? (Every day, Some days, or Not at all) [49].

Quantitative Sensory Testing

Heat pain perception was quantified using the Computer Aided Sensory Evaluator IV (WR Electronics). This quantitative sensory testing device is validated [50-52], and we have used it to quantify opioid-induced hyperalgesia [15,16] and to study other pain-related states associated with altered heat pain perception [53-56].

Concomitant Treatments

Use of concomitant treatments for pain were assessed (eg, nonopioid medications, supplements, acupuncture, physical therapy, and chiropractic).

Sample Size Estimates

Based on our preliminary work [3,9,57-62], we estimated the rate of episodic opioid use would be 20% and the estimated rate of long-term use would be 7%. This would yield approximately 200 (780 × .27 = 210.6) patients developing some form of UPOU at each site. The analysis for specific aim 1 involved examining a wide variety of predictors of UPOU rather than 1 specific exposure. As a result, the minimum detectable odds ratios across a range of sample sizes were calculated. Setting the power at 0.8 and α at .05 (2-tailed), a total sample size of 1200 (600 cases and 600 controls) allowed detection of an odds ratio of 1.38 with a predictor that had a prevalence of 0.5 in controls and zero correlation in exposure between cases and controls. The detectable odds ratio (OR) goes up as the correlation between cases and controls becomes positive (detectable OR=1.48 with r=0.3), and it also increases as the prevalence of the exposure in the control group increases (detectable OR=1.55 with r=0.3 and prevalence of exposure=0.7 in controls).

Data Analysis Plan

The primary research question for specific aim 1 was to identify patient characteristics associated with UPOU. A case-control design was used with controls time matched to cases. The expectation was that multiple patient characteristics would be associated with UPOU. Descriptive statistics (means, medians, and ranges) were generated to compare cases and controls on all patient characteristics. Differences in patient characteristics between cases and controls were assessed using bivariate tests including the McNemar test for categorical variables and paired 2-tailed t tests (or Wilcoxon signed rank test, if needed) for continuous variables. The results of the bivariate analyses were used to select variables for conditional logistic regression analyses to regress UPOU on all variables identified as potentially associated with the UPOU. The regression models were constructed in stages by incorporating predictors in conceptual blocks and using standard selection methods to retain variables. All models included a fixed effect for site. ORs and 95% CI were used to evaluate the magnitude and statistical significance of the association between predictors and outcome.

Specific Aim 2

Overview

Clinicians prescribing opioids to patients in specific aim 1 were recruited for assessment of prescribing characteristics.

Clinician Recruitment

Clinician recruitment was site specific, but a similar stepped approach was used. First, an email message was sent to each clinician briefly explaining that they had issued an opioid prescription to a patient participating in the observational study. The email note contained a link to a validated self-report survey regarding clinician attitudes and beliefs about opioids, and clinicians were asked to complete the survey [6]. Clinicians who did not respond were sent a reminder email 1 week later. Clinicians who did not respond to the reminder email after an additional 1-week period were sent a final email. After a 2-week period, all clinicians not responding to the email messages were sent a paper version of the survey using each site's intracampus mail system. Clinicians not responding to the mailed survey after a 4-week period were considered nonresponders.

Study Assessment

Clinicians were assessed using the Clinicians' Attitudes and Beliefs About Opioids Survey (CAOS) [6]. The validity and test-retest reliability of the CAOS has been reported [6]. The CAOS also assesses clinician demographics and practice characteristics including sex, age, years in practice, professional training (physician surgeon, nonsurgeon physician, nurse practitioner, and physician's assistant), organization of practice (single specialty, partnership, solo, or multispecialty), practice structure (academic or university versus clinic or hospital based), proportion of weekly patient appointments involving management of chronic pain, and proportion of patients with chronic noncancer pain currently receiving opioids.

Sample Size Estimates

There was no information available to predict how many unique clinicians prescribe opioids to patients in aim 1. A 2013 meta-analysis of provider surveys estimated a survey response rate among health professionals of 53% [63]. Thus, we conservatively estimated the response rate would be between

35% to 65% and anticipated between 410 and 760 clinicians would complete the survey.

Data Analysis Plan

The primary research question for specific aim 2 was to identify clinician and practice environmental characteristics associated with UPOU. The analysis plan was similar to the plan described for specific aim 1. Descriptive statistics (means, medians, and ranges) were generated to compare cases and controls on all clinician and practice environmental characteristics. Differences in clinician characteristics between cases and controls were assessed using bivariate tests including the McNemar test for categorical variables and paired 2-tailed *t* tests (or Wilcoxon signed rank test, if needed) for continuous variables. The results of the bivariate analyses were used to select variables for conditional logistic regression analyses to regress UPOU on all variables identified as potentially associated with UPOU. The regression models were constructed in stages by incorporating predictors in conceptual blocks and using standard selection methods to retain variables. All models included a fixed effect for site. ORs and 95% CI were used to evaluate the significance of the associations between predictors and outcome.

Specific Aim 3

Overview

Using the data generated in aims 1 and 2, SEM was used to evaluate the associations between framework elements in each domain. Identified associations were further evaluated in a large national administrative claims database.

SEM Analysis

The primary goal of aim 3 was to combine the results from aims 1 and 2 and extend these by building a statistical model that synergistically integrated the three domains of the UPOU conceptual framework. The UPOU framework has a number of complexities that limit the use of regression including multiple correlated predictors and outcomes, unobserved constructs that are difficult to directly measure, and nesting of patients with clinicians who are nested within sites. SEM can estimate latent variables and include them as both exogenous and endogenous variables in the same model, use multiple observable and quantifiable indicators to estimate latent variables from the shared variability of these indicators, and accommodate multiple endogenous variables (ie, dependent variables or outcomes) in 1 model. Multilevel SEM can estimate latent variables at 1 or more levels (eg, patient and clinician levels) and appropriately test associations at and across these different levels for categorical and continuous outcomes.

The SEMs were developed in several steps. The number of measurement models were estimated for all constructs that potentially used latent variables. Descriptive statistics were examined including means, medians, SDs, ranges, measures of central tendencies, and normality of the distributions. Extensive preliminary analyses were conducted to evaluate possible inconsistencies in the data, outliers, and variations in the data, and clinically and statistically relevant cutoff points that may facilitate the analyses were identified. The primary outcome measure was UPOU, measured as a dichotomous variable of cases and time-matched controls. The predictors of interest were grouped into 3 domains: patient characteristics, practice environment, and clinician characteristics. Each of these domains contained a number of directly observable and directly unobservable constructs. Examples of directly observable variables in the patient characteristic domain included age, sex, and employment status. Examples of directly unobservable constructs in the patient characteristic domain included symptoms of opioid withdrawal, opioid craving, and the psychosocial impact of chronic pain. Analyses (eg, coefficient α, principal components analysis, and factor analysis) were conducted to determine how to optimally combine scale items into reliable measures.

After all measurement models were established, a comprehensive structural model describing the conceptual framework was developed. In the first step, models were fitted separately by domain. For example, a parsimonious model relating patient characteristics to UPOU was developed. This first step involved a model-testing approach to trim a saturated model containing all patient-level constructs to develop a final parsimonious model that maximally explained UPOU with the least number of parameters. The results from aim 1 analysis directly informed this stage, but models varied due to the use of latent variables and a different statistical model. The Akaike information criterion, Bayesian information criterion, and the root mean square error of approximation were used to guide decision model trimming and refinement. This process was conducted separately for all 3 domains. The second step combined the parsimonious, domain-specific models into an integrated model. This involved multilevel SEM with a patient-level outcome (eg, UPOU) and predictors at the patient level, the clinician level, and the practice environment level. This model started with the 3 parsimonious, domain-specific models but then was expanded to test for possible cross-level interactions. For example, the effects of pain management training on UPOU varied by patient age. The conceptual model, previous research, and empirical findings were used to guide the model-building process, particularly with regard to the direction of association and what interactions were tested. This was not a process for testing all possible interactions; rather, only specific indicated effect modifications were tested.

Missing data were evaluated to determine if the pattern was missing completely at random (MCAR) or missing at random (MAR). If missing data were MAR or MCAR, SEM techniques were used to estimate missing values using either full information maximum likelihood or multiple imputation. If missing data did not fit an MAR or MCAR pattern, other options were explored including pattern mixture models. To the extent possible, potential bias due to attrition and missing data over time were assessed. All analyses were conducted using Stata (version 15, StataCorp) or MPlus (version 7, Muthén & Muthén).

Sample Size Estimates

Common algorithms do not exist for assessing power for complex SEM; however, 3 aspects of sample size were considered. First, because of the iterative and complex nature of SEMs, it was important to verify that the sample size was

sufficiently large to produce stable model estimates. There are simulation studies suggesting that for models of the size and complexity proposed, minimum sample sizes for model stability would likely be in the hundreds [64]. Second, comparing models requires a certain sample size. Published estimates of model degrees of freedom suggest that sample sizes in the hundreds would be sufficient to discriminate competing models [64]. Finally, given a set sample size, an expected detectable effect size was estimated. Setting statistical significance at =.05 (2-sided tests) and power at 80%, a sample size of 500, for example, would allow detection effects of approximately 0.13 SD units across time (ie, considered a small effect). Even accounting for losses due to missing data, which can become an issue when combining multiple sources of data at multiple levels, the proposed sample size of 1200 patients, and the smaller number of clinician and practice environments in which they were nested, should be sufficient to estimate stable, comprehensive models and detect relatively small associations between constructs.

National Administrative Claims Database Analysis

The data collected prospectively on clinicians and patients at the 3 clinical sites provided detailed data on patients and clinicians from varied settings but were necessarily limited in sample size and derived from institutions affiliated with academic medical centers. As a result, a large national claims database was used to explore the findings of this study in a much larger and more diverse population.

The OLDW is an open, collaborative research and innovation center founded in 2013 [65]. The core linked data assets include deidentified claims data for privately insured and Medicare Advantage enrollees and deidentified EHR data from a nationwide network of provider groups. The database contains longitudinal health information on enrollees and patients, representing a diverse mixture of ages, ethnicities, and geographical regions across the United States. The EHR data are sourced from provider groups and reflects all payers, including uninsured patients.

The OLDW was used to estimate a structural model similar to that used in the analyses of clinical data from aims 1 and 2. The latent factors representing clinician, patient, and environmental factors associated with patients developing OPOU were estimated using OLDW data, and the results were compared with those estimated in the clinical data. The OLDW contains beneficiary characteristics including gender, age, race and ethnicity, household income, and geography (ie, state, county, or zip code). For beneficiaries submitting health insurance claims, a broad range of information is available including pharmacy claims (ie, prescribing clinician, drug type and date dispensed, days of supply), clinician and facility claims (ie, Current Procedural Terminology 4 codes, *International Classification of Diseases* [*ICD*]*-9* or *ICD-10* procedure codes, and *ICD-9* or *ICD-10* diagnoses), dates and place of service, cost data (ie, charges and patient and insurance amounts paid), and clinician type and specialty. In addition, OLDW includes laboratory data for 30% to 40% of patients whose clinicians have contracted with laboratories that provide data to OLDW.

Many of the concepts to be tested with clinical data were approximated using administrative claims data. Diagnostic codes were used to measure comorbidities including depression, anxiety and substance use disorders. Procedure and diagnostic codes were used to infer pain etiology from surgery, trauma, and other causes. Place of service and clinician specialty codes were used along with prescription fill information to determine the source of opioid prescriptions. Patient geographic information and prescription fill information were used to determine regulations governing the use of prescription drug monitoring programs.

Ethical Considerations

The Mayo Foundation Institutional Review Board served as the reliant international review board (IRB) of record for all participating institutions including Mayo Clinic, the University of Michigan, Yale University, and the University of Minnesota. Written informed consent, using a mobile platform, was obtained from all study participants before study participation. Use of the mobile platform to obtain informed consent and collect study outcomes was IRB approved (#18-010484). All patient-related research information was deidentified before data analysis. All patients were remunerated US $50 for the initial screening, US $150 for the first clinical assessment, and US $100 for the second clinical assessment.

Reporting Guidelines

The reporting of study methods and results adhered to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines [66].

Results

Study Recruitment

Overview

The research proposal was funded on January 3, 2019, and patient recruitment began on August 1, 2019. However, due to the COVID-19 pandemic, patient recruitment was slowed in March 2020 and halted in April 2020 for a 4-month period. Over the next 2-year period, patient recruitment was slowed or interrupted at each clinical site based on the regional impact and the individual health care system response to the COVID-19 pandemic. Compared with the more urban setting of the University of Michigan and Yale University, the impact of COVID-19 pandemic on the rural catchment area of Mayo Clinic was less disruptive and associated with fewer interruptions. As a result, the majority of patient and clinician recruitment occurred at the Mayo Clinic site. Due to the unanticipated effects of the COVID-19 pandemic on clinical research activities, two 6-month, no-cost extensions were granted by the funding agency, and all recruitment and data collection were completed by August 2024.

Patient Recruitment

Table 1 depicts the total number of cases and controls recruited at each site. The Mayo Clinic site recruited 83% (855/1030) of the cohort, the Yale University site recruited 14.3% (147/1030), and the University of Michigan site recruited 2.7% (28/1030). Data analysis of patient characteristics associated with UPOU

has been completed and the manuscript is under active development.

Table 1. Patient recruitment by study site.

Study site	Patients, n (%)		
	Total (n=1030)	Cases (n=513)	Controls (n=517)
Mayo Clinic	855 (83)	422 (82.3)	433 (83.8)
University of Michigan	28 (2.7)	15 (2.9)	13 (2.5)
Yale University	147 (14.3)	76 (14.8)	71 (13.7)

Clinician Recruitment

A total of 148 clinicians completed the CAOS survey. The Mayo Clinic site recruited 146 (98.6%) clinicians, and 2 (1.4%) clinicians were recruited at the University of Michigan site. Recruitment of unique clinicians at the Mayo Clinic site was limited, in part, by clinicians who prescribed opioids to more than 1 patient. Due to unanticipated administrative barriers at Yale University, no clinicians were recruited at this site. The data analysis of clinician characteristics associated with UPOU has been completed and the manuscript is under active development.

SEMs and National Administrative Claims Database Analysis

The SEMs are under active development, and the results of the SEMs based on the case-control data will be submitted for publication in a peer-review journal. The administrative claims database from OLDW has been successfully retrieved and is actively being prepared for data analysis using the SEMs developed from the case-control data. The results of the SEM and OLDW analysis will be submitted for publication in a peer-review journal.

Discussion

Principal Findings

The anticipated results of this prospective, case-control study should provide ample data to understand how patient, clinician, and practice environment characteristics facilitate or impede development of UPOU. More specifically, multivariate logistic regression models will elucidate the individual influence of each domain (eg, patient, clinician, and practice environment) on UPOU and multilevel SEMs will provide an estimate of latent variables and test associations at and across these different levels for categorical and continuous outcomes. Widespread dissemination will be facilitated by the results derived from the broader analysis of the OLDW.

The results of this study will further build existing knowledge about the clinical characteristics associated with UPOU. For example, in a systematic review and meta-analysis of 33 studies comprised of 1,922,743 individuals, patient-level characteristics associated with UPOU after surgery included female sex; high school level education; previous mental health diagnosis of depression, anxiety, or posttraumatic stress disorder; cocaine or alcohol use disorder; tobacco use; and preoperative use of prescription opioids, antidepressants, benzodiazepines, or antipsychotic medications [67]. In addition, a history of back and neck pain, fibromyalgia, and migraine headache were associated with UPOU after surgery [67]. However, interpretation of these findings was limited by varying definitions opioid naivety and UPOU, clinical and statistical heterogeneity, and varying approaches for establishing baseline clinical characteristics. The imprecision of the meta-analysis was due, in part, to the use of large administrative and insurance claims data by studies included in the systematic review, which limited the number of studies that were available for inclusion in the subgroup analysis of patient characteristics. The results of our study will extend these findings by including surgical and nonsurgical patients and using uniform definitions of opioid naivety and UPOU. Finally, due to imprecision associated with establishing previous psychiatric diagnoses [68,69], the severity of current depressive symptoms, the presence of positive and negative affect, and the level of pain catastrophizing were included as study outcomes.

The clinical and research implications of the study results are important for 2 reasons. First, this study leveraged a conceptual framework and a case-control design to identify patient and clinician characteristics associated with UPOU. It is anticipated that the patient characteristics will have an immediate and significant impact on the clinical care of opioid-naive adults receiving appropriately indicated opioid prescriptions for short-term use. The identified clinician characteristics will provide the opportunity to develop and deliver targeted educational content to clinicians to raise awareness of UPOU. Second, development of SEMs and secondary testing in the much larger and more diverse cohort derived from the OLDW will facilitate the design of future research projects aimed at reducing development of UPOU.

Limitations

The timeline of the research project was disrupted by the COVID-19 pandemic, but data collection was facilitated by no-cost extensions and leveraging the rural catchment area of Mayo Clinic. This produced an imbalance in the number of patients and clinicians recruited between the 3 clinical sites. While the overall target sample size was largely attained and therefore target statistical power was met, the imbalance potentially limited generalizability and precludes site-specific analyses for Yale University and University of Michigan. The opioid use status of cases and controls were based on the number of prescriptions issued by clinicians. As a result, discrepancies could exist between the number of prescriptions issued compared with the number of prescriptions dispensed by pharmacies. Finally, the CONSORT criteria were adapted to categorize opioid use 3 months following the initial prescription.

Although it is possible that the status of opioid use could change over time, all patients were followed an additional 6 months to assess the stability of the opioid use category in cases and controls.

Conclusions

Following completion of data analysis, the study results will be immediately available for widespread dissemination in clinical practice and for use in ongoing research projects. It is anticipated that EHR systems will be leveraged to identify at risk patients receiving an initial opioid prescription and to send alert messages to members of the care team. This preemptive approach could also be used to develop direct-to-patient educational materials to raise awareness of the risk factors for developing UPOU.

Acknowledgments

The authors would like to thank the research coordinators that worked on this study including Brenda Anderson, Beth Martin, and Beth Montonye. This research project was funded by the National Institutes of Health National Center for Advancing Translational Sciences (U01TR 002743).

Data Availability

The study data will be presented in the main results sections of peer-review journals and as supplemental files when indicated.

Authors' Contributions

WMH, DJE, JFW, CMB, and MMJ contributed to conceptualization. WMH, DJE, MC, NAS, and MMJ handled data curation. WMH, DJE, MC, NAS, and MMJ conducted formal analysis. WMH, DJE, JFW, CMB, and MMJ managed funding acquisition. WMH, MC, JFW, CMB, and MMJ contributed to investigation. WMH, DJE, MC, NAS, and MMJ. WMH, DJE, and NAS managed project administration. WMH, DJE, MC, JFW, CMB, and MMJ handled resources. WMH, DJE, MC, NAS, and MMJ managed software. WMH, DJE, MC. JFW, CMB, and MMJ contributed to supervision. WMH, DJE, MC, and NAS managed validation. WMH, MC, NAS, and JJM handled visualization. WMH, DJE, MC, NAS, JFW, CMB, and MMJ wrote the original draft. WMH, DJE, MC, NAS, JFW, CMB, and MMJ conducted review and editing.

Conflicts of Interest

WMH has received funding from the National Institutes of Health (NIH) and the US Food and Drug Administration (FDA). DJE, MC, and JFW have received funding from the NIH. CMB has received funding from the NIH and he has served as consultant for Merck Pharmaceuticals and Vertex Pharmaceuticals, and he has provided expert medical testimony. MMJ has received funding from the FDA, NIH, Centers for Disease Control and Prevention, American Cancer Society, and Agency for Healthcare Research and Quality.

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Abbreviations

AOS: Analgesic Outcomes Study
ASSIST: Alcohol, Smoking, and Substance Involvement Screening Test
CAOS: Clinicians' Attitudes and Beliefs About Opioids Survey
CONSORT: Consortium to Study Opioid Risks and Trends
CTSA: Clinical and Translational Science Awards
EHR: electronic health record
FDA: Food and Drug Administration
ICD: International Classification of Diseases
IRB: institutional review board
MAR: missing at random

MBM: Michigan Body Map
MCAR: missing completely at random
MPI: Multidimensional Pain Inventory
NIH: National Institutes of Health
OLDW: OptumLabs Data Warehouse
OR: odds ratio
REP: Rochester Epidemiology Project
SEM: structural equation modeling
STROBE: Strengthening the Reporting of Observational Studies in Epidemiology
UPOU: unintended prolonged opioid use

Edited by A Schwartz; submitted 02.02.25; this is a non–peer-reviewed article;accepted 24.02.25; published 24.03.25.

Please cite as:
Hooten WM, Erickson DJ, Chawarski M, Scholz NA, Waljee JF, Brummett CM, Jeffery MM
Unintended Prolonged Opioid Use: Protocol for a Case-Controlled Trial
JMIR Res Protoc 2025;14:e72032
URL: https://www.researchprotocols.org/2025/1/e72032
doi:10.2196/72032
PMID:39992690

Protocol

Examining the Efficacy of the Telehealth Assessment and Skill-Building Kit (TASK III) Intervention for Stroke Caregivers: Protocol for a Randomized Controlled Clinical Trial

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Abstract

Background: Stroke is a leading cause of serious, long-term disability and has a sudden onset. Upon discharge to the home setting, families are thrust into providing care, often without sufficient training from health care providers. Aligned with current patient and caregiver guidelines, the Telehealth Assessment and Skill-Building Kit (TASK III) is a nurse-led intervention designed to empower caregivers to address their own needs and those of the survivor using innovative skill-building strategies.

Objective: This study aims to test the short-term (immediately after the intervention at 8 wk) and long-term (12, 24, and 52 wk) efficacy of the TASK III intervention, compared with an information, support, and referral (ISR) group, to improve caregiver life changes (ie, changes in physical health, physical functioning, emotional well-being, and general health) as a result of providing care.

Methods: A randomized controlled clinical trial design will be used with baseline data collection from 296 family caregivers by telephone after the stroke survivor is discharged home. Caregivers randomly assigned to the ISR group (n=148, 50%) will receive information from the American Heart Association about stroke family caregiving. Caregivers randomly assigned to the TASK III group (n=148, 50%) will receive a TASK III resource guide and information from the American Heart Association. Both groups will receive 8 weekly calls from a nurse, with a booster call a month later. Outcomes will be assessed by blinded data collectors at 8, 12, 24, and 52 weeks. The primary outcome (at 8 wk) is caregiver life changes measured by the Bakas Caregiving Outcomes Scale. Secondary outcomes are depressive symptoms; other symptoms (eg, stress, fatigue, sleep, pain, and shortness of breath); unhealthy days; diet; exercise; and self-reported health care use. Mediators are task difficulty, threat appraisal, and self-efficacy. Program evaluation outcomes (satisfaction and technology ratings) will also be analyzed.

Results: The trial was registered on March 10, 2022. Enrollment and random assignment of the first participant was on November 30, 2022, with an anticipated completion of recruitment by November 30, 2025. Completion of the primary end point data analysis

is anticipated by August 31, 2026, with results expected to be reported on ClinicalTrials.gov by April 1, 2027. As of October 9, 2024, a total of 198 (66.9% of the proposed total sample of 296) family caregivers have been enrolled and randomly assigned to the TASK III group (n=98, 49.5%) or the ISR group (n=100, 50.5%). The last update was performed on January 25, 2024.

Conclusions: If the TASK III intervention is shown to be efficacious in the proposed randomized controlled clinical trial, our next goal will be to translate TASK III into ongoing stroke systems of care, providing a tremendous public health impact.

Trial Registration: ClinicalTrials.gov NCT05304078; https://clinicaltrials.gov/study/NCT05304078

International Registered Report Identifier (IRRID): DERR1-10.2196/67219

(JMIR Res Protoc 2025;14:e67219) doi:10.2196/67219

KEYWORDS

stroke; family caregivers; depressive symptoms; health-related quality of life; clinical trial; intervention study; protocol; nursing

Introduction

Background and Rationale

Each year, approximately 795,000 Americans experience a stroke, which is a leading cause of serious, long-term disability [1]. Because of disability, approximately 68% to 74% of stroke survivors require the care of family members [2,3], who are suddenly thrust into providing care without receiving proper training from health care providers [4-6]. The lack of training contributes to difficulty with caregiving tasks and high threat appraisal, defined as caregiver perceptions of ability to provide future care [7-10]. These stressful experiences place caregivers at risk for depressive symptoms and major life changes as a result of providing care (eg, physical health, physical functioning, emotional well-being, and general health) [7-15]. Finally, stressful caregiver experiences have been reported to impede the survivor's rehabilitation [16-18] and to increase costs from premature long-term institutionalization [11,19,20].

Major scientific and policy statements from the American Heart Association [17,21-25] and other guidelines [26-30] recommend (1) assessment of stroke family caregiver needs and concerns; (2) education on stroke-related care; (3) attention directed toward caregivers' physical and emotional health; and (4) individualized caregiver interventions that combine psychoeducational strategies with skill building (eg, problem-solving, stress management, and goal setting). Aligned with the American Heart Association recommendations and other published guidelines [17,21-30], the Telephone Assessment and Skill-Building Kit (TASK) II is a nurse-led intervention enabling caregivers to build skills based on the assessment of their own needs [31-38]. Unlike existing stroke caregiver interventions that require costly face-to-face interactions [22,23,33,39-41] and that focus primarily on the survivor's care [22,23,39-41], TASK II is delivered completely via telephone and empowers caregivers to address both their own and the survivor's needs using innovative skill-building strategies (eg, problem-solving, stress management, realistic expectations, time management, and communication with health care providers) using a mailed TASK II resource guide and calls with a nurse. Evidence has been published regarding content validity [32], treatment fidelity [36], caregiver satisfaction [32], and efficacy of the TASK II program with 254 stroke caregivers in a randomized controlled clinical trial (R01; R01NR010388; ClinicalTrials.gov ID: NCT01275495) [34]. TASK II, in comparison with an information, support, and referral (ISR) group, reduced depressive symptoms up to a year after baseline (in caregivers with mild to severe depressive symptoms) and reduced unhealthy days, a reflection of caregiver's physical and mental health at 8 weeks [34]; however, further enhancements were needed to improve caregiver life changes (ie, physical health, physical functioning, emotional well-being, and general health) and to provide additional telehealth modes of delivery based on caregiver preferences [34,38,42-44].

Through a funded R21 (R21NR016992; ClinicalTrials.gov ID: NCT03635151) feasibility study, the Telehealth Assessment and Skill-Building Kit (TASK III) version has been optimized for delivery via various modes of technology [38] and provides a stronger emphasis on caregiver self-management [37,45,46] of their own symptoms and health care needs to sustain positive life changes and health outcomes over time. Caregivers can now choose how they want to access the TASK III resource guide (mailed hard copy, e-book, USB drive, or website) and how they would like to interact with the nurse (telephone, FaceTime, or web-based videoconferencing). Our published findings demonstrate the usefulness, ease of use, convenience, feasibility, and acceptability of our new TASK III telehealth technology [38]. Our published findings have also shown content validity, accuracy, feasibility, and acceptability of our new skill-building tip sheet on goal setting to enhance caregiver self-management of symptoms and health [37]. As part of the R21 feasibility study, a pilot study with 74 stroke caregivers randomly assigned to the TASK III (n=36) or ISR (n=38) group revealed successful recruitment, retention, treatment fidelity, high satisfaction ratings, and positive data trends.

In this larger randomized controlled clinical trial (R01NR020184; ClinicalTrials.gov ID: NCT05304078), we plan to enroll 296 caregivers to test the efficacy of the TASK III program (n=148, 50%), in comparison with the ISR group (n=148, 50%) for improving stroke caregiver life changes, symptoms, and health outcomes. The TASK III group will receive the TASK III resource guide along with information from the American Heart Association about stroke family caregiving. The ISR (attention control) group will only receive information from the American Heart Association. Both groups will receive 8 weekly calls from a nurse with a booster call a month later. The nurse calls for the TASK III group to focus on assessing and addressing stroke caregiver needs and concerns using the TASK III resource guide, along with information from

the American Heart Association; support through active listening; and provide referrals to their own health care providers. The nurse calls for the ISR comparison group to focus only on information from the American Heart Association, support through active listening, and provide referrals to their own health care providers. The ISR group procedures have been used successfully as a comparator for our previous trials (eg, R01 and R21). Data will be collected at baseline and at 8, 12, 24, and 52 weeks after randomization.

Objectives

Specific Aim 1

This study aims to test the short-term (immediately after the intervention at 8 wk) and long-term (12, 24, and 52 wk) efficacy of the TASK III intervention, compared with the ISR group, in improving the *primary outcome* of caregiver life changes (ie, physical health, physical functioning, emotional well-being, and general health) as a result of providing care.

Specific Aim 2

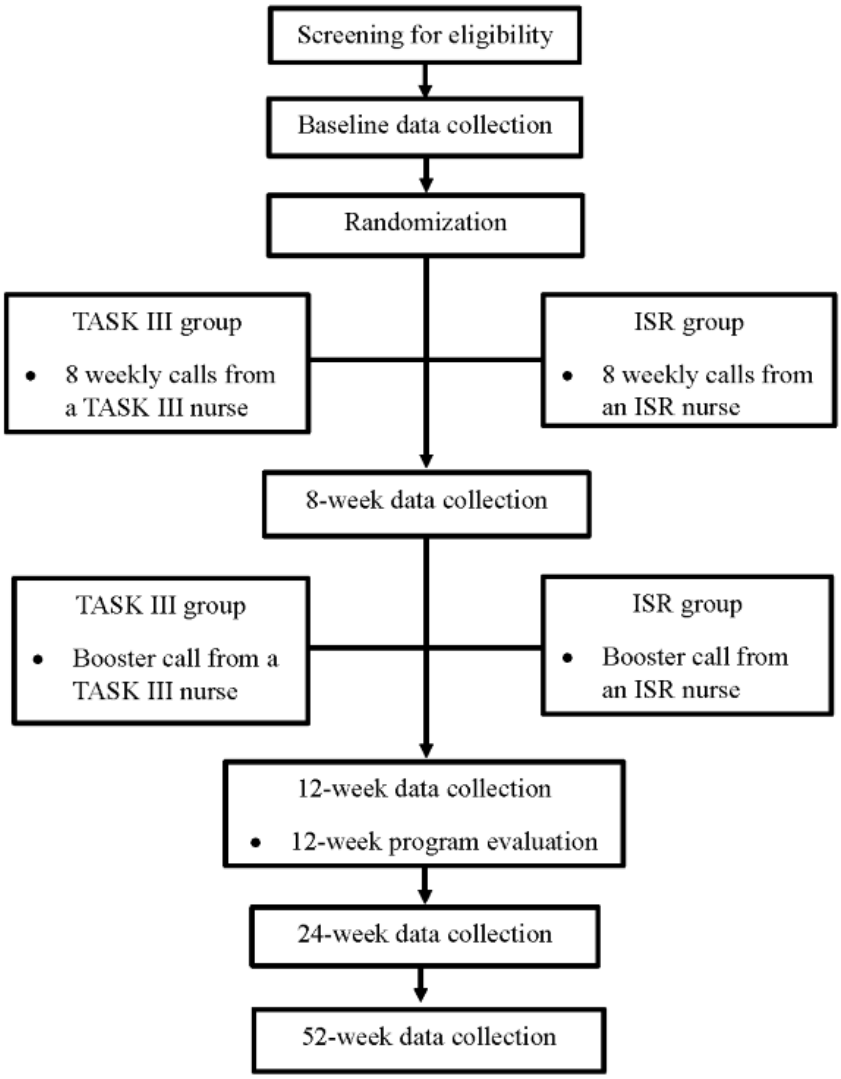
This study also aims to test the short-term (immediately after the intervention at 8 wk) and long-term (12, 24, and 52 wk) efficacy of the TASK III intervention, compared with the ISR group, in improving *secondary outcomes* including caregiver depressive symptoms (in caregivers with mild to severe depressive symptoms); other symptoms (stress, fatigue, sleep, pain, and shortness of breath); unhealthy days; self-management of diet and exercise; self-reported health care use; *mediators* (caregiver task difficulty, threat appraisal, and self-efficacy for exercise and diet); and *program evaluation outcomes* at 12 weeks (caregiver satisfaction and technology ratings).

Methods

Trial Design

An experimental, 2-group, randomized controlled clinical trial design based on a superiority framework will be used to test the efficacy of the TASK III program compared with an ISR group using an intention-to-treat design. We will randomly assign 296 stroke caregivers using a 1:1 allocation ratio to either the TASK III intervention group (n=148, 50%) or the ISR attention control group (n=148, 50%) following baseline data collection by telephone after the stroke survivor is discharged home (Figure 1). Follow-up data collection by telephone will occur by blinded data collectors after the 8 weekly TASK III or ISR calls, after the booster call at 12 weeks, and then at 24 and 52 weeks. Program evaluation by telephone will occur at 12 weeks after all the calls from the nurse have been completed while maintaining blinding of the data collectors.

Figure 1. Study flow diagram. ISR: information, support, and referral; TASK III: Telehealth Assessment and Skill-Building Kit.



Participants, Interventions, and Outcomes

Study Setting

Data will be collected from family caregivers living in the community caring for stroke survivors after discharge to the home setting. Recruitment sites are acute care and rehabilitation hospitals that provide care for stroke survivors located in the United States Midwest region. A list of our recruitment sites as of October 7, 2024, is provided in Multimedia Appendix 1. Further details regarding recruitment are provided in the *Recruitment* section.

Eligibility Criteria

Inclusion and exclusion criteria for stroke family caregivers are summarized in Textbox 1.

Eligibility criteria for the nurse interveners for both the TASK III and ISR groups include having a registered nurse license; strong interpersonal skills; and proficiency with technology, including Zoom (Zoom Communications) and Teams (Microsoft Corp) videoconferencing and basic computer skills. Blinded data collectors are required to have a high school diploma (college education preferred); strong interpersonal skills; and basic computer skills including the ability to type and enter data.

Textbox 1. Inclusion and exclusion criteria for stroke family caregivers.

Inclusion criteria

- Primary caregiver (family member or a significant other providing care for a stroke survivor at home)
- Fluent in the English language (ie, able to read, speak, and understand English)
- Access to a telephone or computer
- No difficulties hearing or talking by a telephone or computer
- Scores ≥4 on a 6-item cognitive impairment screener
- Willing to participate in 9 calls from a nurse and 5 data collection interviews (baseline, 8, 12, 24, and 52 wk)

Exclusion criteria if the following were true for the survivor

- Had not had a stroke
- Did not need help from the caregiver
- Resides in a nursing home or long-term care facility

Exclusion criteria if the following were true for the survivor or caregiver

- Aged <18 years
- Prisoner or on house arrest
- Pregnancy
- Terminal illness (eg, late-stage cancer, end-of-life condition, or renal failure requiring dialysis)
- History of Alzheimer disease, dementia, or severe mental illness (eg, suicidal tendencies, schizophrenia, severe untreated depression, or manic depressive disorder)
- History of hospitalization for alcohol or drug abuse within the past 5 years

Ethical Considerations

The study was approved by the University of Cincinnati Institutional Review Board (IRB; study 2022-0180). Lists of contact information for stroke survivors and next of kin will be obtained from each recruitment site. Approximately 1 week after study flyers and informed consent forms are mailed, stroke caregivers will be contacted via telephone by the TASK III study research staff to determine their interest in the study and to screen for eligibility. Flyers with response cards and informed consent forms may also be distributed by staff employed at each recruitment site.

The informed consent process will take place via telephone. The informed consent form is provided in Multimedia Appendix 2. The process will be explained to interested family caregivers, and if they are eligible and provide verbal consent, a baseline interview will be scheduled. All caregivers will be provided with full information about the nature, purpose, and possible risks and benefits of the study. Furthermore, caregivers will be informed that participation in the study is voluntary, and they are free to discontinue participation at any time. The principal investigator (PI) or research staff trained by the PI will obtain initial and ongoing consent. Training of research staff will include reading the informed consent and role-playing the consent process with the PI. All research staff having contact with the caregivers in the study will be trained on this process. The telephone calls to explain the consent will be scheduled at a time that is convenient for the caregiver using a telephone number provided by the caregiver. The PI or trained research staff will make the calls from a private location to protect the confidentiality of the caregiver. At the beginning of the baseline interview, the informed consent form will be reviewed again with caregivers, with verbal consent being verified before baseline data collection. Caregivers who are eligible, have provided verbal consent, and have completed baseline data collection will be enrolled and randomly assigned into either the TASK III or ISR group. Because this is a minimal risk study, the IRB has approved a waiver of written documentation of consent. We have previously conducted 4 IRB-approved studies using the same recruitment strategies as detailed in the current protocol [7,31,34,37,38]. Our procedures have not been found to be coercive by the IRB, and we have been successful in recruiting and retaining caregivers in our previous studies. In fact, we believe that approaching caregivers in person while the survivor is still hospitalized may be more coercive than requesting their participation by mail and telephone. Caregivers receiving their informed consent by mail approximately a week in advance have more time to read it and consider participation than if they were approached in person.

Only authorized study personnel will have access to the database or contact information for potential family caregivers, as well as family caregivers enrolled in the study. Study identification numbers will be generated to protect the identity of the participants. Participants will not be identified in any manner in reports or manuscripts from the study. Data from all data collection interviews and nurse calls will be audio recorded. Audio recordings will be uploaded to a secure password-protected OneDrive (Microsoft Corp) folder at the University of Cincinnati and then deleted from the digital recorders. Once the audio recordings are monitored for

adherence to the protocol or transcribed (deidentified), they will be deleted to protect the anonymity of the participants. Data entered on paper forms will be entered into REDCap (Research Electronic Data Capture; Vanderbilt University) by trained research staff using a secure log-in. Deidentified paper forms will be stored in a locked file cabinet accessible only to study personnel or shredded once data entry into REDCap is complete. REDCap is backed up nightly by the institution. Only authorized study personnel will have access to REDCap. All data collection calls to participants will be made to a telephone number provided by the participant at a time that is convenient for the participant. The TASK III and ISR group calls will be made via telephone, FaceTime, or Zoom videoconference using a secure link that is protected by the Health Insurance Portability and Accountability Act (HIPAA) based on caregiver preference. Research staff will make calls from a private location to protect confidentiality. All research staff will be trained in procedures to protect the confidentiality of the participants, including referring to caregivers using only their study ID numbers while communicating with the PI, project manager, or other approved research staff. Procedures for tracking completed interviews, determining the appropriate dates for follow-up interviews, and providing reminders for missed interviews will be specified and tracked in REDCap.

Although no compensation is provided for this study, participants are permitted to keep any study materials mailed to them, including a pedometer, Amazon Fire Tablet, USB drive, and a hard copy binder with either the TASK III or ISR content.

Interventions

Explanation for the Choice of Comparators

The comparator for this study will be the ISR program that has been used and validated as an attention control group in our previous studies testing the TASK, TASK II, and TASK III programs [31,32,34-36]. Caregivers randomly assigned to the ISR group have expressed high satisfaction ratings (ie, usefulness, ease of use, and acceptability) [32] with low attrition [31,34] and high fidelity of procedures [36]. Stroke caregivers randomly assigned to the ISR group for this study will receive a mailed copy of an American Heart Association brochure about stroke family caregiving and 8 weekly phone calls from a nurse with a booster call at 12 weeks. Calls will focus on providing ISR via the use of active listening strategies [31,32,34-36]. The ISR group can access the American Heart Association brochure through its website, which offers publicly available guidelines and web-based information for family caregivers. In addition, caregivers will receive a pedometer to track their daily steps, an Amazon Fire Tablet and a USB drive for use in the ISR program, and a unique username and password to log in to the ISR group on our TASK III website, which contains links to the American Heart Association materials for stroke family caregivers. Caregivers in the ISR group can choose to receive calls from their nurse via telephone, FaceTime, or Zoom videoconferencing. The length of each ISR session will vary based on the needs of the caregiver. As in our previous study with the TASK II program [34], our R21 feasibility trial showed that the total number of minutes on the ISR calls averaged about 17 minutes for each of the 9 ISR calls (mean 156, SD 103 min).

Intervention Description

Stroke caregivers randomly assigned to the TASK III intervention will receive a mailed copy of the TASK III resource guide, a mailed copy of an American Heart Association brochure about stroke family caregiving, a TASK III USB drive, and instructions for accessing a TASK III e-book and the TASK III interactive website. Screenshots of TASK III website are provided in Multimedia Appendix 3 [47].

TASK III Resource Guide

In a mailed binder with numbered tabs, the Caregiver Needs and Concerns Checklist (CNCC) [4] addresses 5 areas of needs: finding information about stroke, managing the survivor's emotions and behaviors, providing physical care, providing instrumental care, and dealing with personal responses to providing care (along with 35 corresponding tip sheets addressing each CNCC item) [4,32,34,35]. The Bakas Caregiving Outcomes Scale (BCOS) [7] with corresponding tip sheets addresses caregiver life changes, which is our primary outcome. Six skill-building tip sheets address the following: (1) strengthening existing skills, (2) screening for depressive symptoms, (3) maintaining realistic expectations and time management, (4) communicating with health care providers, (5) problem-solving, and (6) stress management [32,34,35]. The guide also includes (7) a new self-management skill-building tip sheet on goal setting designed for this study [37]. We will measure several key social determinants of health factors [48,49] at baseline, which will be useful in training caregivers on how to use skill-building strategies to address their needs and concerns within the context of their own social determinants of health. For example, 2 instrumental care tip sheets address managing finances and covering costs (financial strain is a key social determinant of health factors). The problem-solving skill-building tip sheet will help caregivers identify barriers and create new solutions to further mitigate financial strain. The goal-setting tip sheet helps caregivers set realistic goals to improve their own health (eg, setting a walking goal that considers neighborhood characteristics as another social determinant of health factor). Our original TASK, TASK II, and TASK III tip sheets have a large 14-point Arial font that is easily readable across all age groups. In our previous TASK II and TASK III studies, caregiver ages ranged from 21 to 83 years, representing a wide range of ages across the life span [34,38]. Our positive satisfaction data demonstrate that our materials are acceptable for a wide range of younger and older caregivers [38]. The TASK III resource guide is constructed to be appealing to both sexes. Male caregivers expressed high satisfaction ratings in our TASK II trial (>4.0 on a scale of 1 to 5), with positive qualitative comments (eg, "It's been such a help to me. It gave me an outlet that I could express my feelings."). Female caregivers also expressed high TASK II satisfaction ratings (>4.0) with positive TASK II qualitative comments (eg, "They're not just there for the person that's had the stroke, they're there for the caregiver too."). Our TASK II [34] and TASK III trials showed minority group representation consistent with the demographics of our Midwest populations, with 24.8% (63/254) in TASK II and 24% (18/74) in TASK III being Black or African American. When seeking input for the goal-setting tip sheet and technology preferences for our TASK

III program, we purposefully enrolled 50% Black or African American caregivers to ensure that our ratings and qualitative data reflected their views [34,35]. In our TASK III R21 feasibility trial, we employed a diverse research team, with our project manager, one of the TASK III nurses and one of the ISR nurses who identified as Black. We believe that these efforts enhanced the success of our TASK II and TASK III trials. Although not as well represented in our area, we will welcome other minority and ethnic group individuals.

TASK III USB Drive

A USB drive containing a searchable PDF file of the entire TASK III resource guide and separate PDF files of each of the TASK III tip sheets will be mailed to caregivers. Instructions and links to download the TASK III e-book and access the TASK III interactive website will also be provided on the USB drive.

Amazon Fire Tablet

In addition to the USB drive, we will provide all stroke family caregivers enrolled in the study with an Amazon Fire Tablet to access our materials. For the TASK III group, we will load the TASK III tip sheets as PDF files and provide links for the TASK III e-book, the TASK III website, and Zoom videoconferencing.

TASK III e-Book

An interactive multitouch e-book for the TASK III resource guide has been designed using Kotobee software [50] and tested for feasibility for use on multiple devices (eg, desktops, laptops, phones, tablets, and e-book readers). A download link automatically installs Kotobee Reader [50] and the TASK III e-book onto any Mac or PC laptop or desktop. The TASK III e-book will also be installed on the Amazon Fire tablets given to caregivers.

TASK III Interactive Website

We engaged the expertise of Oohology [51] to create in WordPress a searchable TASK III PDF library with TASK III tip sheets that appear on the website based on caregiver responses to an automated assessment process containing the CNCC and BCOS. Infrastructure for backend support of these technologies was provided during our TASK III R21 feasibility study, with continued support and ongoing hosting of the website provided by Oohology [51]. Most importantly, the tip sheets can be viewed on any laptop, tablet, or smartphone. Caregivers are instructed by research staff on how to access the TASK III interactive website through a unique username and password. *All materials created for the TASK III USB drive, e-book, and website are based on our TASK III resource guide.* Embedded within the TASK III resource guide tip sheets are links to additional resources available on the internet. We will ensure that the links are active and checked regularly during project implementation. Similar to the ISR group, the TASK III group can access the American Heart Association brochure through the American Heart Association website, which offers publicly available guidelines and web-based information for family caregivers. In addition, TASK III caregivers will receive a pedometer to track their daily steps.

TASK III Telephone Calls

The TASK III intervention calls will take place via telephone or videoconferencing using FaceTime or Zoom per caregiver preference [38]. Similar to the TASK II intervention [34-36], caregivers will receive 8 weekly calls from a nurse, with a booster call at 12 weeks. Caregivers will be assigned to a specific nurse for consistency. Nurses will train caregivers on how to assess and prioritize their needs, concerns, and life changes, then help them select corresponding content and skill-building tip sheets. The new goal-setting tip sheet will be used during each call to promote caregiver self-management of their symptoms and health.

TASK III FaceTime

Caregivers may receive calls using FaceTime [52]. Over Wi-Fi, FaceTime is accessible on iPhone 4 (Apple, Inc) or later, iPad 2 (Apple, Inc) or later, or iPad Mini (all models; Apple, Inc). Android-accessible apps such as Facebook Messenger (Meta Platforms, Inc), Google Duo (Google LLC), or Skype (Skype Technologies) will be considered.

TASK III Zoom

Caregivers can receive calls using Zoom videoconferencing [53]. Zoom unifies cloud videoconferencing, simple web-based meetings, and a software-defined solution into 1 easy-to-use platform, offering the best video, audio, and wireless screen-sharing experience across Windows, Mac, Linux, iOS, Android, and Blackberry devices [53]. Zoom allows real-time screen-sharing of TASK III resource guide materials during calls. The university has purchased secure Zoom links for research purposes to ensure the privacy of participants, which will be used in this TASK III R01 study. The length of each TASK III session will vary based on the needs of the caregiver. As in our previous study with the TASK II program [34], our R21 feasibility trial showed that the total number of minutes on the TASK III calls averaged about 43 minutes for each of the 9 TASK III calls (mean 389, SD 198 min).

Differences and Overlaps Between TASK III and ISR Groups

Both the TASK III group and the ISR group will receive the American Heart Association brochure, access to the American Heart Association website, a pedometer, an Amazon Fire Tablet, a USB drive, and 8 weekly phone calls from a nurse with a booster call at 12 weeks. Only the TASK III group will receive the TASK III resource guide that contains the CNCC and BCOS to assess caregiver needs, concerns, and life changes, as well as skill-building and content tip sheets that correspond to the CNCC and BCOS items. In the TASK III group, the nurses will train caregivers on how to assess and address their own needs, concerns, and life changes using the TASK III resource guide. This guide (containing the BCOS) informs our primary hypothesis that the TASK III group, compared with the ISR group, will have greater improvements in life changes (measured by the BCOS) from baseline to 8 weeks (after the intervention). We expect that these improvements will be sustained for a longer term from baseline to 12, 24, and 52 weeks. Including the BCOS as part of the TASK III intervention will enhance

the power to detect an effect on caregiver life changes as measured by the BCOS.

Criteria for Discontinuing or Modifying Allocated Interventions

Participation in the study is completely voluntary, and caregivers may withdraw at any time. Caregivers who ask to withdraw from the study will be given the option for a partial or full withdrawal. For example, participants may complete the rest of the calls with the nurse and withdraw from the remaining data collection interviews or participants may withdraw from the calls with the nurse and choose to complete the remaining data collection interviews. Participants may choose to completely withdraw from all study-related activities. Previously collected data from the participants will be withdrawn if specifically requested by the participant. Otherwise, collected data will be retained and analyzed, particularly for an intention-to-treat design. Participants will be withdrawn from the study if they are unable to be contacted after up to 10 attempts. A letter will be mailed to the participants notifying them that they have been withdrawn from the study.

Strategies to Improve Adherence to Interventions

Adherence to protocols for both ISR and TASK III groups will be a high priority for this study. The Treatment Fidelity Checklist [54] addressing design, training, delivery, receipt, and enactment will be used to maintain and track treatment fidelity for both TASK III and ISR procedures [36,54]. Training for the nurses will include detailed manuals and podcasts, training booster sessions, self-evaluation of recordings, evaluation by supervisors, quality checklists, and frequent team meetings [36]. TASK III nurses will attend an 8-hour training session to learn the intervention content and delivery processes and to role-play sessions with each other. The role-play sessions will be recorded and checked for competency before caregiver interaction. Beyond initial training, TASK III nurses will be monitored weekly during team meetings and asked to complete a self-evaluation of their recordings for adherence to the protocol on a monthly or bimonthly basis. Then, supervisors (ie, the PI or coinvestigator) will listen to recordings, analyze self-evaluations, and provide individualized feedback and retraining when necessary. ISR nurses will undergo a similar process, but the initial training session will last for 4 hours. Protocol adherence for the TASK II study was excellent at 80% (37.6/47) for the TASK II group and 92% (43.2/47) for the ISR group, and for common items on the checklist, 90% (42.3/47) in the TASK II group and 92% (43.2/47) in the ISR group [36]. Focus groups with nurses yielded further evidence for treatment fidelity [36]. The same procedures were used to track treatment fidelity in the TASK III R21 feasibility trial; this TASK III R01 study will follow the same rigorous treatment fidelity procedures with the nurses. Caregivers will be monitored for treatment fidelity regarding receipt (eg, the number of minutes spent on the calls with the nurse; ratings of the helpfulness of each call; the number of minutes of viewing TASK III or ISR materials; and the types of materials viewed, such as TASK III tip sheets or American Heart Association brochures or the website). Enactment will be monitored by asking caregivers whether their problems discussed with the nurse were unresolved, making progress, or resolved. In the TASK III group, the enactment will be further monitored by having caregivers evaluate their own progress on their goals to improve their own health based on our new TASK III goal-setting tip sheet [37].

Relevant Concomitant Care Permitted or Prohibited During the Trial

The trial will not interfere with any concomitant care or interventions that caregivers or their stroke survivors receive. No concomitant care or interventions are prohibited during the trial.

Provisions for Posttrial Care

There are no provisions for ancillary or posttrial care. This is a minimal risk study where the risk is not expected to be more than one would have in daily life.

Outcomes

Outcomes were selected based on a conceptual model derived from our previous research on caregiver needs and concerns [4,35]; our stroke caregiver outcomes work [8-10,31,34] informed by the transactional approach to stress proposed by Lazarus [55-57]; and our conceptual model that has empirical support from our previous research [8-10,31,34], including the original TASK and TASK II programs [31-36]. We added concepts from the self-efficacy theory based on the works by Bandura [58-60] and Lorig et al [61,62] to improve caregiver health. Our outcomes are clinically relevant, particularly our primary outcome of caregiver life changes (eg, physical health, physical functioning, emotional well-being, and general health) because of providing care [7]. Caregivers are known to neglect their own health needs while providing care [4-6,35,37], making them the hidden patients in our health care system. Difficulty with tasks threatens caregivers' ability to provide future care (ie, threat appraisal) [7-10] and is strongly associated with caregiver depressive symptoms and major life changes as a result of providing care (eg, physical health, physical functioning, emotional well-being, and general health) [7-15,17,39]. Finally, stressful caregiver experiences have been reported to impede the survivor's rehabilitation [16-18] and to increase costs from premature long-term institutionalization [8-11,19,20]. In addition to our primary outcome of caregiver life changes, we have included several secondary outcomes, such as caregiver depressive symptoms, other symptoms, unhealthy days, self-management of diet and exercise, and self-reported health care use. Further outcomes include our mediators of caregiver task difficulty, threat appraisal (ie, ability to provide future care), and self-efficacy for maintaining a healthy diet and exercise, as well as program evaluation outcomes. As listed on the ClinicalTrials.gov website (NCT05304078), Multimedia Appendix 4 [7-10,31,32,34,48,49,63-86] details measures and time points for our primary outcome, secondary outcomes, mediators, and program evaluation outcomes.

Participant Timeline

Table 1 provides the time schedule of enrollment, interventions, and data collection interviews for participants. Screening for eligibility and data collection interviews will take place via telephone. TASK III and ISR calls with the nurse will take place

via telephone or videoconference (eg, FaceTime or Zoom) based on caregiver preference. Data collection will take place at screening; baseline; and 8-week (after the 8 weekly calls with the nurse), 12-week (after the ninth booster call with the nurse), and 24- and 52- week follow-ups. Randomization will occur after the completion of the baseline interview.

Table 1. Schedule of the study period, including enrollment, interventions, and assessments.

Time point	Enrollment	Allocation	Postallocation period					Close out
	Screen	Baseline	8 weekly nurse calls	8 wk	9th nurse call	12 wk	24 wk	52 wk
Enrollment								
Eligibility screen	✓							
Informed consent	✓	✓						
Allocation		✓						
Intervention								
TASK III[a] group			✓		✓			
ISR[b] group			✓		✓			
Assessments								
Demographics, comorbidities, and other social determinants of health		✓						
Survivor impairment		✓		✓		✓	✓	✓
Primary, secondary, and other outcomes (mediators)		✓		✓		✓	✓	v
Program evaluation outcomes						✓		

[a]TASK III: Telehealth Assessment and Skill-Building Kit.

[b]ISR: information, support, and referral.

Primary, secondary, and other outcomes (ie, mediators and program outcomes) are detailed in the *Outcomes* section. Further information about these measures, as well as demographics, comorbidities, social determinants of health, and survivor impairment, is provided in Multimedia Appendix 4.

Sample Size

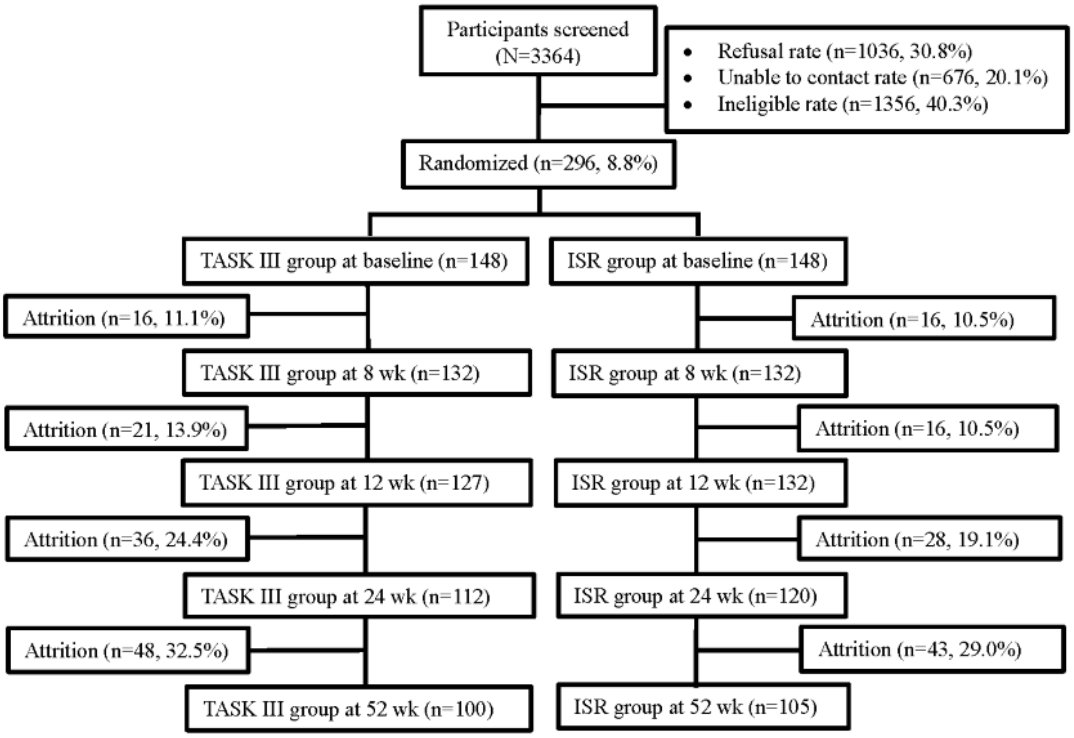
Sample size is based on the change in the total BCOS [7] scores from baseline to 8 weeks for the primary outcome of caregiver life changes because of providing care (ie, physical health, physical functioning, emotional well-being, and general health). For caregiver life changes (BCOS) [7], the sample size of 132 in each group will provide 80% power to detect a mean difference of 0.9 in the change from baseline, with the TASK III group showing a mean difference of 4.0 and ISR group showing a mean difference of 3.1 and an estimated SD of 2.6 [34]. We will also have sufficient power to address secondary outcomes. A sample size of 132 in each group will achieve 80% power to detect a mean difference of 0.20 in the change from baseline in depressive symptoms at 8 weeks between groups, with a mean difference of –0.80 in the TASK III group and –0.60 in the ISR group and an estimated SD of 0.70 in both groups using a 2-sample *t* test with a significance level of 0.05 [34]. This detectable difference is lower than the difference in depressive symptoms observed in the pilot TASK III R21 study. On the basis of pilot data, it is estimated that there will be 124 (42%) caregivers who screen positive for mild to severe depressive symptoms at baseline (ie, Patient Health Questionnaire-9 [PHQ-9] Depression Scale score >5). Because the randomization will be stratified by baseline depressive symptoms (see the *Sequence Generation* section), we estimate 62 caregivers with mild to severe depression in each group. A sample size of 62 in each group will achieve 80% power to detect a mean difference of 0.60 in the change from baseline in depression symptoms at 8 weeks between groups, with a mean difference of –2.60 in the TASK III group and −2.00 in the ISR group and an estimated SD of 1.20 in both groups, using a 2-sample *t* test with a significance level of 0.05 [34]. This detectable difference is lower than the difference in depression symptoms observed in the pilot TASK III R21 study. For unhealthy physical and mental days, the sample size will provide 80% power to detect a rate ratio of 0.85 (a 15% reduction in unhealthy days) [34]. The planned enrollment is 296 (n=148, 50% in the TASK III group and n=148, 50% in the ISR group) to account for 10.8% (16/148) attrition [34]. Power Analysis & Sample Size (version 12; NCSS LLC) was used to produce all power estimates. Power calculations were not performed for the additional secondary outcomes (ie, other symptoms, self-management steps, exercise self-management, diet self-management, and health care use).

Recruitment

Recruitment methods and retention rates were successful in our previous studies [31,34] and even better in our most recent TASK III R21 feasibility study. On the basis of our recruitment success with our TASK II and TASK III R21 feasibility studies, we plan to screen 3364 caregivers and randomly assign at least 296 caregivers to achieve our goal of 148 (50%) caregivers per

group (Figure 2). Accounting for 10.8% (16/148) attrition, this should allow us to have at least 132 (89%) caregivers per group at our primary 8-week time point.

Figure 2. Proposed participant flow diagram. The values are provided on the basis of the Telehealth Assessment and Skill-Building Kit (TASK III) R21 (R21NR016992; ClinicalTrials.gov ID: NCT03635151) feasibility study, except for the 24-week and 52-week values, which were based on the Telephone Assessment and Skill-Building Kit (TASK) II R01 (R01NR010388; ClinicalTrials.gov ID: NCT01275495) study. ISR: information, support, and referral.



Screening 3364 caregivers over 3 years (1121 per year) is feasible given our strong track record of collaboration and the large number of stroke survivors treated yearly at each recruitment site. As in our previous studies, bioinformaticians, stroke coordinators, or other employees from each recruitment site will provide us with lists of stroke survivors and their next of kin. As approved by our university IRB, study flyers signed by the stroke survivor's physician, nurse, director of the stroke team, along with copies of the informed consent form, will be mailed to caregivers of survivors receiving care from each recruitment site. A telephone number is provided for stroke caregivers to call if they do not wish to be contacted for the study. Approximately 1 week after the study flyers and informed consent forms are mailed, caregivers will be contacted via telephone by research staff to determine their interest and screen for eligibility. Flyers with response cards may also be distributed by staff employed at each recruitment site.

Assignment of Interventions: Allocation

Sequence Generation

Caregivers will be randomly assigned 1:1 to the TASK III or ISR group using a permuted block randomization stratified by type of relationship (spouse vs adult child or other) and baseline depressive symptoms (nondepressed vs depressed, with a PHQ-9 score ≥5) as in the TASK II trial [34]. Random permutations within each block within each stratum will be generated using a random number generator (SAS Proc Plan; SAS Institute).

Concealment Mechanism

The randomization scheme will be concealed in an Excel (Microsoft Corporation) document uploaded to the REDCap project site that will be accessible only to the biostatistician. Randomization will occur by logging into the REDCap project website and entering the type of relationship (spouse vs adult child or other) and baseline depressive symptoms (nondepressed vs depressed, with a PHQ-9 score ≥5) for group assignment (TASK III vs ISR).

Implementation

The biostatistician will generate the allocation sequence and upload it as an Excel file to the REDCap project site as a concealed file. The biostatistician will then program the REDCap project site to generate the group assignment once the PI or the project manager enters the type of relationship and baseline depressive symptoms. After baseline data collection, data collectors will notify the PI or the project manager that the caregiver is ready for randomization. Data collectors will not be involved in the randomization process.

Assignment of Interventions: Blinding

Who Will Be Blinded

Data collectors will be blinded to group assignment to mitigate potential bias during the 8-, 12-, 24-, and 52-week follow-up interviews. Blinding will be maintained by restricting data collector access to group assignments in REDCap. Separate weekly research team meetings will be conducted with the data

collectors. Caregiver participants will be instructed not to tell the data collectors which group they have been assigned to. Caregiver trial participants, the nurses, the project manager, the PI, and a coinvestigator will be unblinded so that the proper TASK III or ISR materials can be mailed to the participants and the correct TASK III or ISR protocol can be followed. The PI and the coinvestigator will closely monitor treatment fidelity for the TASK III and ISR groups. Separate nurses will be used for the TASK III or ISR groups to avoid treatment diffusion. We have a strong track record of keeping TASK III and ISR groups separate, including strict monitoring of treatment fidelity and adherence to protocol [36]. The lead biostatistician and her master's degree–prepared staff statistician will be unblinded to create reports, assess for missing data, and explore data trends in preparation for Data Safety and Monitoring Plan reports. While analyzing data trends for Data Safety and Monitoring Plan reports, the PI and the research team will be blinded as to which group represents each outcome variable within data tables by labeling each group by a letter rather than using the TASK III or ISR abbreviations.

Procedure for Unblinding if Needed

Only data collectors will be blinded during the trial. Unblinding the data collectors will not be permissible.

Data Collection and Management

Plans for Assessment and Collection of Outcomes

Multimedia Appendix 4 lists the study measures. Most measures were used in our previous studies [7-10,31,32,34]. All measures demonstrated acceptable evidence of reliability and validity, except the Caregiver Evaluation of Technology Scale, which was created specifically for this study. We will assess the reliability and validity of this scale, and if unacceptable, we will analyze it at the item level. Using the measures in Multimedia Appendix 4, the estimated time for telephone interviews for each time point is 60 minutes for baseline, 33 minutes for 8 weeks, 39 minutes for 12 weeks, and 33 minutes for 24 and 52 weeks. Telephone interviews of this length have not been found to be burdensome in our previous studies [7-10,31,32,34].

Plans to Promote Participant Retention and Complete Follow-Up

To promote participant retention and complete follow-up, data collection interviews and TASK III or ISR nurse calls will be made to caregivers at times that are convenient to them. Once a baseline interview is scheduled, REDCap will prepopulate a schedule for all remaining data collection interviews and nurse calls, usually on the same day of the week and time of the day. Using the calendar function in REDCap, the schedule will appear on the calendar while maintaining blinding of data collectors to group assignments. The schedule will be mailed to each caregiver, with assurance that days and times can be rescheduled as needed. A detailed calling protocol will be used by data collectors and nurses, along with call tracking entered within REDCap. To further promote retention and follow-up, caregivers who ask to withdraw from the study will be offered the option to participate in a final data collection interview that contains all the primary, secondary, mediators, and program evaluation outcomes, as specified for the 12-week time point as listed in Multimedia Appendix 4. Consistent with our intention-to-treat design, caregivers who do not complete all 8 weekly calls with the nurse or the ninth booster call with the nurse will still be asked to continue in the trial for the remaining data collection calls.

Data Management

Data management will be overseen by the PI, coinvestigator, project manager, and the lead biostatistician and staff statistician. All data collection interviews and TASK III and ISR nurse calls will be audio recorded for quality assurance. During monthly or bimonthly self-evaluations with nurses and data collectors, audio recordings will be checked for adherence to the protocol and accuracy in data entry. All study data and tracking will be entered into an electronic data system, REDCap [87], which is a secure research electronic data management system with validated data entry, audit trails for tracking data manipulation, and export procedures. It is HIPAA compliant, satisfying all local, state, and federal regulations for the capture and storage of private health information for research purposes. The biostatistician will run quarterly reports assessing for missing data and range checks for data values. Any missing data or suspected errors in data entry will be discussed with the PI and the project manager, who can then access the audio recordings to resolve any issues with data entry.

Statistical Methods

Recruitment, Attrition, and Fidelity Ratings of Data Collection and Intervention Procedures

Using procedures similar to the TASK II study and our TASK III feasibility study, we will monitor screening and recruitment rates, attrition rates, and fidelity ratings of all data collection and intervention procedures [34,36,54,88]. We will compute the number of participants screened and enrolled per month, the proportion of screened eligible participants who enroll, intervention assignment–specific retention rates at each follow-up visit, and the proportion of outcome measures completed. For fidelity ratings, we will use an itemized checklist to monitor adherence to the unique components of the TASK III study [36]. Adherence will be scored with dichotomous responses for the presence or absence of each item. Frequencies and percentages will be calculated for each item by group. Intervention dosage will be calculated for nurse call duration (min) and the time caregivers spend reading study materials (min) for each group. Descriptive statistics for intervention dosage will be computed by group, and between-group mean differences will be evaluated using 2-sample t tests or nonparametric alternatives if the normality assumption is violated.

Assessment of Scales and Descriptive Statistics

After initial data verification, cleaning, and scale scoring, the coefficient alpha will be calculated as a measure of internal consistency reliability on all multiple-item scales. Descriptive statistics (frequencies, measures of central tendency, and variability) will be produced for all variables. Data will be screened for outliers, multicollinearity, and statistical model assumptions.

Baseline Equivalence and Possible Covariates

Baseline differences in caregiver and survivor characteristics and social determinants of health will be explored to identify potential covariates for our analyses. As in our TASK II trial, stratified random assignment using the type of relationship and baseline depressive symptoms will ensure a balance between the 2 groups for those 2 factors [34]. Baseline differences between the 2 groups will be evaluated using 2-sample *t* tests or Wilcoxon rank sum tests, chi-square tests, or Fisher exact test as appropriate. Baseline variables that are significantly different between the 2 groups at the .05 level will be controlled for in all analyses. In our previous TASK II trial, the ISR calls, on average, were significantly shorter than TASK II calls ($P<.01$) [34]. As in our previous studies [31,34], the number of minutes on TASK III and ISR calls with the nurse may serve as a covariate in our analyses.

Primary Analyses for Specific Aims 1 and 2

Overview

The general modeling strategy for the analyses in aims 1 and 2 will be repeated measures regression modeling using the generalized liner mixed model (GLMM) framework. In GLMM, it is possible to use data from participants when some of the data are missing under the assumption of missing at random. In addition, this modeling strategy allows for time-varying covariates, flexible covariance structures, and participant-specific effects and thus will be able to accommodate the analyses proposed. Our primary goal will be to assess the overall intervention effects on the change from baseline. All primary analyses conducted will be based on the intention-to-treat principle. Analyses will be done using SAS software (version 9.4 or higher).

Specific Aim 1

The *primary outcome* is caregiver life changes as a result of providing care (ie, physical health, physical functioning, emotional well-being, and general health). Life changes are measured using the BCOS total score [7]. The explanatory variables used in the specific aim 1 model will be the intervention group, time, and the intervention group–by–time interaction. Covariates (including social determinants of health) identified using the process described above will be included as appropriate. The number of minutes spent on calls with the nurse in both TASK III and ISR groups will potentially be used as a covariate as well. The model examined will be a 2 (intervention: ISR and TASK III) by 5 (time: baseline and 8, 12, 24, and 52 wk) mixed factorial model, along with covariates. In the GLMM framework, an appropriate link function will be specified depending on the distribution of the dependent variable. Hypotheses related to the immediate postintervention time point at 8 weeks and long-term, sustained efficacy at 12, 24, and 52 weeks will be tested using relevant least square mean contrasts and simple effects constructed within SAS PROC GLIMMIX.

Specific Aim 2

S*econdary caregiver outcomes* are depressive symptoms; other symptoms (stress, fatigue, sleep, pain, and shortness of breath); unhealthy days; self-management of diet and exercise; and self-reported health care use. In the analyses for depressive symptoms, we will look at both overall and subgroup analyses for caregivers who screen positive for depressive symptoms (PHQ-9 score >5) [34]. *Mediators* are task difficulty, threat appraisal, and self-efficacy for exercise and diet. Each of these outcomes will be modeled separately. The models for secondary caregiver outcomes and mediators used in specific aim 2 are similar to those for life changes tested for aim 1 and will include the intervention group, time, and the intervention group–by–time interaction. Covariates (including social determinants of health) identified using the process described above will be included as appropriate, as well as potentially the number of minutes spent on the calls with the nurse in both TASK III and ISR groups. The full model consists of a 2 (intervention: ISR and TASK III) by 5 (time: baseline and 8, 12, 24, and 52 wk) mixed factorial, along with covariates. In the GLMM framework, an appropriate link function will be specified depending on the distribution of the dependent variable. Hypotheses related to immediate postintervention time point at 8 weeks and long-term, sustained efficacy at 12, 24, and 52 weeks will be tested using relevant least squares mean contrasts and simple effects constructed within SAS PROC GLIMMIX. *Program evaluation outcomes* consist of caregiver satisfaction and evaluation of technology ratings. Satisfaction ratings from the Caregiver Satisfaction Scale [32] (usability, ease of use, and acceptability) and evaluation of technology ratings will be summarized at the item and scale levels by intervention group using descriptive statistics, including mean and 95% CI. Caregiver Satisfaction Scale scores, total, and subscales will be compared between groups using 2-sample *t* tests or nonparametric alternatives if the normality assumption appears violated.

Interim Analyses

There are no plans for interim efficacy or futility analysis. There is little chance that we would find harm from the intervention, thus rendering interim efficacy and futility analysis inappropriate.

Methods for Additional Analyses, Including Subgroup Analyses

Age Across the Life Span

We will compare caregiver age between TASK III and ISR groups using 2-sample *t* tests and control for age as a covariate in our analyses if significant age differences are noted.

Sex as a Biological Factor

We will explore sex differences by careful description of subgroup effects.

Minority Group Representation

We will also explore racial differences (ie, Black or African American vs White individuals) by careful description of subgroup effects.

Methods to Handle Protocol Nonadherence and Statistical Methods to Handle Missing Data

We will make every effort to avoid missing data. If missing data are identified, the PI or the project manager will access the corresponding audio recording to determine whether missing

data were due to an error in data entry. We will assess the reasons, patterns, and distribution of missing data, allowing us to assess whether an assumption of missing completely at random is reasonable or whether missingness is conditional on another variable in the dataset (ie, missing at random). Descriptive statistics will compare the characteristics of patients with and without missing data. If missing at random, we will incorporate variables that are identified to be related to the missingness in the analysis using multiple imputations if the amount of missing data affects the study results. Missing data have been minimal for our original TASK study [31], TASK II randomized controlled clinical trial [34], and TASK III feasibility study; we will use the same procedures to avoid missing data in this study. As mentioned previously, we will use an intention-to-treat design and rigorous treatment fidelity procedures [36] to monitor all research staff for adherence to protocol.

Plans to Give Access to the Full Protocol, Participant-Level Data, and Statistical Code

We will make the full protocol, participant-level data, and statistical code available to others. Data will be shared with undergraduate honors students, graduate students, postdoctoral students, and interested faculty members at our university and other institutions. Special measures will be taken to ensure that family caregivers and stroke survivors are not identified by any data that are shared. Close collaboration with the PI and her research team will be necessary for the use of shared data. Project-generated resources will include our finalized REDCap database, intervention materials, and training manuals for the project manager, TASK III study nurses, ISR study nurses, data collectors, and screening and recruitment staff. Close collaboration with the PI and her research team will be necessary for the use of shared resources by other investigators.

Oversight and Monitoring

General Composition of the Research and Intervention Delivery Team

Overview

The study team will consist of TB (PI and nurse), who will lead the interdisciplinary team of coinvestigators, consultants, TASK III and ISR nurse interveners, project coordinators, and data collectors to successfully achieve the aims of the study. EM (coinvestigator and nurse) will help to guide and train the TASK III and ISR nurses, especially with respect to tracking and maintaining treatment fidelity throughout the intervention period. NK (coinvestigator and physician) will provide valuable expertise on stroke, facilitate recruitment of participants, and provide guidance on future implementation of TASK III intervention into stroke systems of care. BH (coinvestigator and biomedical informatics specialist) will facilitate accessing Epic medical records to obtain lists of stroke survivors and their next of kin for recruitment. HS (coinvestigator and biostatistician) will work with investigators and a staff statistician to develop and implement the statistical analysis plan and dissemination of results. MR (coinvestigator and IT and instructional designer specialist) will oversee the TASK III telehealth technologies and work with an information technologist and website or digital designer for ongoing support and hosting of the TASK III website. KD (coinvestigator and physical therapist) will help promote physical activity in caregivers, provide oversight and interpretation, and assist with the dissemination of physical activity–related data. BB (consultant and dietician) will provide ongoing expertise for study methods and materials related to the caregivers' dietary habits, as well as oversight of the interpretation and dissemination of nutrition-related data. MM (consultant and social worker) will consult on updating and maintaining equitable and accessible community resources and support for both TASK III and ISR. HJ (consultant and nurse) will provide consultation on culturally sensitive approaches for recruiting and interacting with diverse family caregivers. JKA and PHM (consultants and nurses) will be available for consultation as needed for the overall study design and methods.

In addition to the PI, coinvestigators, and consultants, the team will consist of the following staff.

Project Manager

The person selected for this role has a master's degree in public health and will coordinate all aspects of the study including all day-to-day project operations, first-line supervision of research staff, coordination of communication with all study personnel, research team meetings, preparation of agendas and minutes, assistance in the preparation of the training manuals and protocols, maintenance of study files, budget management, scheduling and coordination of all family caregiver calls and mailings, and study coordination with recruitment sites. Furthermore, they will conduct caregiver and stroke survivor screenings and informed consent procedures. Under the direction of the biostatistician and the PI, they will also assist in the development, testing, and maintenance of the REDCap database; conduct the query management process; provide data management documentation, such as the data management plan; and ensure that data are being entered and cleaned in a timely and appropriate manner.

Nurse Interveners

A total of 3 hourly nurse interveners will be hired and trained to deliver the 9 TASK III intervention calls to 148 stroke caregivers randomly assigned to the TASK III intervention group. Three additional hourly nurse interveners will be hired and trained to deliver the 9 ISR group calls to 148 stroke caregivers randomly assigned to the ISR group. Nurses will be required to have a current registered nurse license and excellent interpersonal skills. In addition to making caregiver calls, the nurses will be responsible for self-evaluation of their own audiotapes, further retraining procedures, and documentation of TASK III intervention or ISR content delivered to caregivers. They will also attend weekly research team meetings.

Research Assistants

A total of 4 hourly research assistants will be hired and trained to conduct participant screening and collect data via telephone for 296 stroke caregivers at the 5 time points specified for the project (baseline and 8, 12, 24, and 52 wk). The hourly research assistants will provide coverage for each other in the event of illness or time off, cover a wide range of availability times for caregiver data collection calls, and attend weekly research team

meetings while remaining blinded to group assignment of caregivers throughout the study.

Informatics Support Person

The informatics support person for this study is a data analyst from the Center for Health Informatics at the University of Cincinnati Department of Biomedical Informatics. The data analyst will be supervised by BH to extract lists of stroke survivors and their next of kin from Epic electronic medical records from the University of Cincinnati Health and University of Cincinnati Health West Chester Hospitals for recruitment.

IT Support and Website or Digital Designer

This person will be supervised by MR and will work closely with TB and her interdisciplinary team to refine and maintain the TASK III telehealth technologies for the TASK III resource guide (ie, mailed hard copy, USB drive, Amazon Fire Tablets, e-book, and TASK III website) and the technologies for nurse calls (ie, telephone, Zoom videoconferencing, and FaceTime on iOS devices). The IT support and website or digital designer will work with Kotobee [50] on the TASK III e-book and Oohology [51] for ongoing support and hosting of the TASK III website. He will also help to train TASK III and ISR nurses on the use of the TASK III telehealth technologies and provide ongoing IT support throughout the project.

Staff Biostatistician

The staff biostatistician will work with HS to carry out the statistical analysis plan to address the study aims.

Composition of the Data Monitoring Committee, Its Role, and Reporting Structure

This study was approved by the university IRB as "no greater than minimal risk." According to the funder's policy (ie, National Institute of Nursing Research; NINR), "Monitoring by the PI or designee may be appropriate for protocols involving minimal risk or no more than a minor increase over minimal risk which are conducted at a single site." For this study, the IRB- and NINR-approved data and safety monitoring plan will be the responsibility of TB (the PI). Members of the research team will provide input, particularly HS, the statistician coinvestigator; EM, the nurse coinvestigator; and NK, the physician coinvestigator. The PI (TB) and research team members (HS, EM, and NK) are well-qualified and will meet quarterly (and more frequently as needed) to review data and the safety of the study procedures and involvement of participants. TB (the PI) will consult with the research team members (HS, EM, and NK), but she will be the monitoring entity for this study. She will collaborate closely with our local IRB throughout the study and will submit the approved IRB-continuing review, including the dates and summarized reports generated from data and safety monitoring meetings with the research team to the National Institutes of Health (NIH) along with the yearly NIH progress report. There are no conflicts of interest with or financial stakes in the research outcome with the PI (TB) or any members of the research team.

Adverse Event Reporting and Harms

The PI (TB) will be seeking input from members of the research team (HS, EM, and NK), and will meet quarterly (and more frequently as needed) with them to (1) review any deviations in the study protocol; (2) review any adverse events; (3) track any negative trends in data that may indicate harmful effects of the study procedures; (4) review study recruitment and retention; and (5) review data management procedures, particularly those designed to protect the privacy of participants. All protocol deviations, adverse events, and unanticipated problems will be reported by the PI (TB) to the local IRB and NINR yearly or more frequently as needed. At the time of the yearly IRB-continuing review, a summary of the frequency and dates of the data and safety monitoring meetings with the PI (TB) and the research team (HS, EM, and NK) will be provided, along with reviews and reports generated from each meeting. The approved IRB-continuing review, including the dates and summarized reports generated from the data and safety monitoring meetings with the PI and the research team, will be submitted to the NINR along with the yearly NINR progress report. The PI (TB) will provide a report of the following to IRB and NINR within 48 hours: (1) unanticipated problems or unexpected serious adverse events that may be related to study protocol; (2) IRB-approved revisions to the study protocol that indicate a change in risk for participants; (3) a summary of recommendations made by the PI and the research team as appropriate and, if applicable, the action plan for response; and (4) notice of any actions taken by the IRB or regulatory bodies regarding the research and any responses to those actions. All personal identifiers will be removed from any documents sent to the NINR. Identifiable data will be stored in locked file cabinets and within our secure, password-protected, HIPAA-compliant REDCap database.

Frequency and Plans for Auditing Trial Conduct

The PI (TB), with inputs from the research team (HS, EM, and NK), will provide auditing of at least 50% of all cases for compliance with IRB requirements, conformance with informed consent requirements, verification of source documents, and investigator compliance. Recommendations concerning the continuation or conclusion of the trial will be made during each quarterly meeting, based on the results of monitoring. The process will involve both the investigators and the sponsor (NINR).

Plans for Communicating Important Protocol Amendments to Relevant Parties

The PI will communicate important protocol modifications with the coinvestigators, consultants, project manager, and research staff as appropriate. All modifications will be approved by the local IRB before implementation and reported to the NINR on the yearly NIH progress report.

Dissemination Plans

This clinical trial is registered (ClinicalTrials.gov ID: NCT05304078), and information about the results will be submitted to ClinicalTrials.gov, which is available to the public. The IRB-approved informed consent form will include the following statement: "A description of this clinical trial will be available on ClinicalTrials.gov, as required by the US Law. This website will not include information that can identify you. At most, the website will include a summary of the results. You

can search this website at any time." Participants will be encouraged to check back with the ClinicalTrials.gov site for a lay summary of the results after completion of the study. Participants contacting the PI for results will be referred to the ClinicalTrials.gov website. We anticipate that there will be manuscripts, not only from the findings addressing specific aims 1 and 2 but also from secondary analyses of data generated from this study. We will disseminate results from specific aims 1 and 2, as well as results from secondary analyses, in peer-reviewed journals. We will make the data available to others as detailed in the Plans to Provide Access to the *Full Protocol, Participant-Level Data, and Statistical Code* section.

Results

Enrollment and random assignment of the first participant was on November 30, 2022, with an anticipated completion of recruitment by November 30, 2025. The primary end point data analysis is anticipated to be completed by August 31, 2026, with reporting of results in ClinicalTrials.gov anticipated to be by April 1, 2027. As of October 9, 2024, a total of 198 (66.9% of the proposed total sample of N=296) family caregivers have been enrolled and randomly assigned to the TASK III group (n=98, 49.5%) or the ISR group (n=100, 50.5%). On the basis of reviewer comments during the funding process, the exclusion criteria were changed from caregivers or survivors aged <21 years to those aged <18 years. An IRB modification was added to remove the word "unpaid" from the inclusion criteria for family caregivers because some states provide financial resources to family caregivers. Additional IRB-approved recruitment sites have been added, including the use of social media (eg, Facebook; Meta Platforms, Inc) for recruitment [89]. The protocol reported in this paper is protocol version 5, as approved by the IRB on May 9, 2024.

Discussion

Anticipated Results and Interpretation

This study protocol builds upon our findings from our previous studies with both the TASK [31,32] and TASK II R01 programs [34-36], as well as our most recent refinement and feasibility testing of the TASK III R21 program [37,38]. In caregivers with mild to severe depressive symptoms, the TASK II (in comparison with ISR) intervention was found to reduce depressive symptoms up to a year after baseline; however, improvement in caregiver life changes (ie, physical health, physical functioning, emotional well-being, and general health) occurred only from baseline to 12 weeks in this subsample [34]. Furthermore, TASK II caregivers typically waited until nurse calls 5 through 9 to address their own physical and emotional health needs [36]. To strengthen our findings regarding caregiver life changes, we refined the TASK III intervention to include an assessment of life changes using the BCOS [7], starting with nurse call 2, and added a goal-setting tip sheet to improve caregiver health [37]. Promising data trends indicating stronger caregiver life changes in the TASK III R21 intervention compared to the ISR intervention were reported on the ClinicalTrials.gov website. In this proposed trial, relative to the ISR group, we anticipate that caregivers randomly assigned to the TASK III group will show greater improvements in our primary outcome of caregiver life changes from baseline to 8 weeks (immediately after the intervention) in the total sample, which is sustained for a long term from baseline to 12, 24, and 52 weeks. This study will enable us to (1) successfully conduct a large efficacy trial of the TASK III intervention and (2) further refine the TASK III intervention via program evaluation data (satisfaction and technology ratings) for future implementation. Findings will provide evidence of efficacy for the TASK III program, which is a necessary step toward implementing the TASK III program into stroke systems of care.

Potential Pitfalls, Alternative Approaches, and Future Directions

We have a strong track record of recruitment and retention in our previous TASK, TASK II, and TASK III studies [31,34]. Nevertheless, we will closely monitor recruitment and retention and will secure additional recruitment sites if needed. Our study does not require face-to-face interactions with caregivers; therefore, we are not limited by geographic boundaries for recruitment. Some caregivers might be reluctant to try the new technologically enhanced TASK III resource guide (TASK III USB drive, e-book, and interactive TASK III website) or use videoconferencing (FaceTime and Zoom) for calls with the nurse. During the first TASK III session, we will instruct and demonstrate how to use the new Amazon Fire Tablet; how to connect with the nurse via FaceTime (if they have an iOS device); how to connect with the nurse via Zoom; and how to use each TASK III resource guide delivery mode (TASK III USB drive, e-book, and interactive TASK III website) and the American Heart Association website. We will encourage caregivers to explore these newer technologies during each call from the nurse but respect their preferences [38] and suggest that they call us if they have difficulties. We will have IT support available for caregivers. For the ISR group, during the first call, we will instruct and demonstrate how to use the new Amazon Fire Tablet, how to connect with the nurse via FaceTime (if they have an iOS device), how to connect with the nurse via Zoom, and how to access the American Heart Association website.

Our future directions include procedures detailed in the *Dissemination Plans* section that include reporting our findings in ClinicalTrials.gov (ID NCT05304078) and peer-reviewed journals and making our data available to others. Once we are able to demonstrate that TASK III intervention is efficacious, our next goal is to translate the optimized TASK III intervention into stroke systems of care to meet recommendations and guidelines for follow-up care for survivors and caregivers.

Acknowledgments

Research reported in this publication was supported by the National Institute of Nursing Research of the National Institutes of Health (NIH) under award number R01NR020184. The Center for Clinical and Translational Science and Training at the University of Cincinnati is funded by the NIH Clinical and Translational Science Award program, grant UL1TR001425. This program is led by the NIH's National Center for Advancing Translational Science. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH. NIH was not involved in the design of the study; the collection, analysis, and interpretation of data; or writing the manuscript.

Data Availability

The datasets generated or analyzed during this study are available from the corresponding author on reasonable request. The SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) checklist based on the SPIRIT guidelines [89-91] and the CONSORT-EHEALTH (Consolidated Standards of Reporting Trials of Electronic and Mobile Health Applications and Online Telehealth) checklist [92] based on the CONSORT (Consolidated Standards of Reporting Trials) guidelines [88] are available upon request.

Authors' Contributions

All authors have contributed to the planning and designing of the trial and writing, reading, and editing of the manuscript. All authors have read and approved the submitted version and agree to be personally accountable for their own contributions, as well as those in which they were not personally involved.

TB, JKA, and PHM contributed to the conception of the study. All authors contributed to the design of the work. TB, NK, JI, and BH were involved in the acquisition of data. TB, HS, and KD analyzed the data, and TB, EM, HS, NK, and KD were involved in the interpretation of data. All authors drafted and substantially revised the work.

Conflicts of Interest

NK was associated with the Astra Zeneca Speaker Bureau (this conflict has ended) and is a National Football League unaffiliated neurotrauma consultant. All other authors declare no other conflicts of interest.

Multimedia Appendix 1
List of recruitment sites.
[PDF File (Adobe PDF File), 93 KB - resprot_v14i1e67219_app1.pdf]

Multimedia Appendix 2
The study informed consent statement.
[PDF File (Adobe PDF File), 206 KB - resprot_v14i1e67219_app2.pdf]

Multimedia Appendix 3
Screenshots of the Telehealth Assessment and Skill-Building Kit III website.
[PDF File (Adobe PDF File), 479 KB - resprot_v14i1e67219_app3.pdf]

Multimedia Appendix 4
Measures for primary and secondary outcomes, mediators, program evaluation outcomes, and sample characteristics.
[PDF File (Adobe PDF File), 104 KB - resprot_v14i1e67219_app4.pdf]

Multimedia Appendix 5
Peer review report from the CMGC - Clinical Management in General Care Settings Study Section (National Institutes of Health, USA).
[PDF File (Adobe PDF File), 87 KB - resprot_v14i1e67219_app5.pdf]

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Abbreviations

BCOS: Bakas Caregiving Outcomes Scale
CNCC: Caregiver Needs and Concerns Checklist
GLMM: generalized liner mixed model
HIPAA: Health Insurance Portability and Accountability Act
IRB: institutional review board
ISR: information, support, and referral
NIH: National Institutes of Health
NINR: National Institute of Nursing Research
PHQ-9: Patient Health Questionnaire-9
PI: principal investigator
R01: R01NR010388; ClinicalTrials.gov ID: NCT01275495
R21: R21NR016992; ClinicalTrials.gov ID: NCT03635151
REDCap: Research Electronic Data Capture
TASK III: Telehealth Assessment and Skill-Building Kit
TASK: Telephone Assessment and Skill-Building Kit

Edited by A Schwartz; submitted 10.10.24; this is a non–peer-reviewed article;accepted 05.02.25; published 25.03.25.

Please cite as:
Bakas T, Miller E, Sucharew H, Kreitzer N, Israel J, Rota M, Harnett B, Dunning K, Jones H, McCarthy M, Brehm B, Austin JK, Mitchell PH
Examining the Efficacy of the Telehealth Assessment and Skill-Building Kit (TASK III) Intervention for Stroke Caregivers: Protocol for a Randomized Controlled Clinical Trial
JMIR Res Protoc 2025;14:e67219
URL: https://www.researchprotocols.org/2025/1/e67219
doi:10.2196/67219
PMID:39937971

Protocol

Evaluation of the Tu'Washindi Na PrEP Intervention to Reduce Gender-Based Violence and Increase Preexposure Prophylaxis Uptake and Adherence Among Kenyan Adolescent Girls and Young Women: Protocol for a Cluster Randomized Controlled Trial

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Abstract

Background: Adolescent girls and young women constitute a priority population disproportionately affected by HIV, accounting for 25% of annual HIV incidence among people older than 15 years in Kenya. Although oral preexposure prophylaxis (PrEP) is effective in reducing HIV acquisition, its protective benefit has been limited among adolescent girls and young women in sub-Saharan Africa because of low uptake, adherence, and persistence. Intimate partner violence (IPV) and relationship power inequities are widespread among adolescent girls and young women and contribute to higher HIV incidence and lower PrEP use. Interventions are needed to support sustained PrEP use among adolescent girls and young women by addressing IPV and relationship dynamics.

Objective: This study aims to test the effectiveness of Tu'Washindi na PrEP ("We are Winners with PrEP"), a multilevel community-based intervention, to increase uptake and adherence to PrEP and reduce IPV among adolescent girls and young women in Siaya County, Kenya.

Methods: The Tu'Washindi na PrEP intervention was co-designed by our team and adolescent girls and young women using participatory methods and includes 3 components delivered over 6 months: an 8-session, empowerment-based support club for adolescent girls and young women, community sensitization targeted toward male partners, and PrEP education events for couples. The intervention will be evaluated using a cluster randomized controlled trial across 22 administrative wards in Siaya County, Kenya, enrolling 72 adolescent girls and young women per ward (total N=1584). The primary objectives are to test the effectiveness of the intervention on PrEP uptake and adherence immediately after delivery (month 6 after enrollment) and 6 months later (month 12). As secondary objectives, we will test the intervention effect on IPV. A rigorous process evaluation will explore mechanisms of change, contextual factors, and implementation considerations to inform future refinement and scale-up, using programmatic data, participant questionnaires, and qualitative interviews with participants and intervention providers.

Results: Data collection started in September 2022. As of December 2024, enrollment has been completed in 16 of the 22 study wards, with 72.6% (1150/1584) of participants enrolled. We anticipate that data collection will be completed in May 2026 and results will be available by mid-2027.

Conclusions: The study builds directly on our promising formative and pilot research to develop the evidence base for this youth-designed, multilevel HIV prevention intervention. If effective, Tu'Washindi will be ideally positioned for sustainable integration into existing youth-focused programming to expand and support PrEP use in this priority population.

Trial Registration: ClinicalTrials.gov NCT05599581; https://www.clinicaltrials.gov/study/NCT05599581

International Registered Report Identifier (IRRID): DERR1-10.2196/55931

(JMIR Res Protoc 2025;14:e55931) doi:10.2196/55931

KEYWORDS

adolescent girls and young women; HIV prevention; preexposure prophylaxis; PrEP; adherence; Kenya; intimate partner violence

Introduction

Background

Optimizing the effectiveness of proven biomedical prevention interventions is critical to decreasing the high incidence of HIV among adolescent girls and young women aged 15 to 24 in sub-Saharan Africa, a priority population for HIV prevention. More than 1 in 4 new HIV infections in this region are among adolescent girls and young women [1], who are over twice as likely to acquire HIV as their male counterparts [2]. Oral preexposure prophylaxis (PrEP) is an effective, female-initiated biomedical HIV prevention intervention, but its protective benefit has been limited among adolescent girls and young women across sub-Saharan Africa by challenges to uptake, adherence, and persistence [3-17]. In western Kenya, a study of adolescent girls and young women attending family planning clinics found that 76% met PrEP eligibility criteria, but only 4% initiated PrEP [16], and the proportion of adolescent girls and young women persisting with PrEP for 3 months postinitiation ranged from 5% to 37% across studies [7,10,11,15,17]. In samples of PrEP users at an average of 6 months postinitiation, only 4% to 8% had tenofovir diphosphate (TFVdp) levels suggesting high adherence [4-6]. The public health impact of PrEP will be determined by concurrent interventions that address critical barriers to uptake and adherence.

Adolescent girls and young women who live in a context of heightened gender inequality and risk of intimate partner violence (IPV) represent a large subpopulation who are uniquely vulnerable to HIV infection. IPV is widespread among adolescent girls and young women in western Kenya: 19% reported experience of sexual IPV in the past year, 25% reported physical IPV, and 34% reported emotional IPV [18-20]. Experience or fear of IPV in sexual relationships is associated with having limited relationship power [20,21] and with 28% to 55% higher HIV incidence in adolescent girls, young women, and adult women [21-23]. Studies have found that IPV and other partner-related social harms are associated with 1.5- to 2.5-fold higher risk of poor adherence to oral PrEP and the dapivirine ring for HIV prevention. Similar to HIV treatment and contraception [19,20,24-29], IPV and relationship inequality introduce barriers to uptake of and adherence to PrEP at multiple levels. At the individual-level, restricted access to information and health services, poor negotiation skills, low self-efficacy, and fear of violence or relationship dissolution hinder adoption of health-promoting behaviors [30-32]. Dynamics at the partner level, such as poor communication and low decision-making power, limit disclosure about PrEP use and reduce partner support, which can impact adherence [33-35]. These challenges are further compounded at the community level by a lack of PrEP awareness, inequitable gender norms, and stigma associated with taking PrEP, which contribute to partner and community opposition to female PrEP use [36-39]. A multilevel context-specific intervention to address barriers to PrEP use is needed to ensure that adolescent girls and young women experiencing relationship inequality and IPV benefit from this effective biomedical prevention strategy.

In response, our intervention, Tu'Washindi na PrEP (We are winners with PrEP), was designed in close partnership with local adolescent girls and young women and incorporates strategies targeted to address relationship dynamics and IPV at multiple levels [40,41]. This intervention has 3 components: an empowerment-based support club for adolescent girls and young women, PrEP education events for couples offered in the context of a health fair (Buddy Days), and community sensitization about PrEP targeted toward adolescent girls and young women's partners [40]. The pilot cluster randomized controlled trial (cRCT) of Tu'Washindi at 6 Determined, Resilient, Empowered, AIDS-free, Mentored and Safe (DREAMS) spaces demonstrated feasibility, high acceptability, implementation with fidelity, and promising effects on PrEP and IPV outcomes [42]. PrEP uptake and adherence were both approximately twice as high in the intervention arm as in the control arm ($P<.05$) [43]. Although the adherence was still lower than desired in the intervention arm, with Wisepill openings on 25% of days on PrEP, they still represented substantial improvement over programmatic outcomes [6,17]. We also observed less frequent or severe IPV among intervention arm participants [43].

Because our pilot findings suggested that Tu'Washindi shows promise as an acceptable intervention that can be implemented with fidelity to promote PrEP uptake and adherence among adolescent girls and young women without concomitant increases in IPV, we designed a fully powered effectiveness trial to determine whether these gains translate to increases in biomarker measures of PrEP adherence and whether the intervention can reduce IPV risk.

Study Objectives

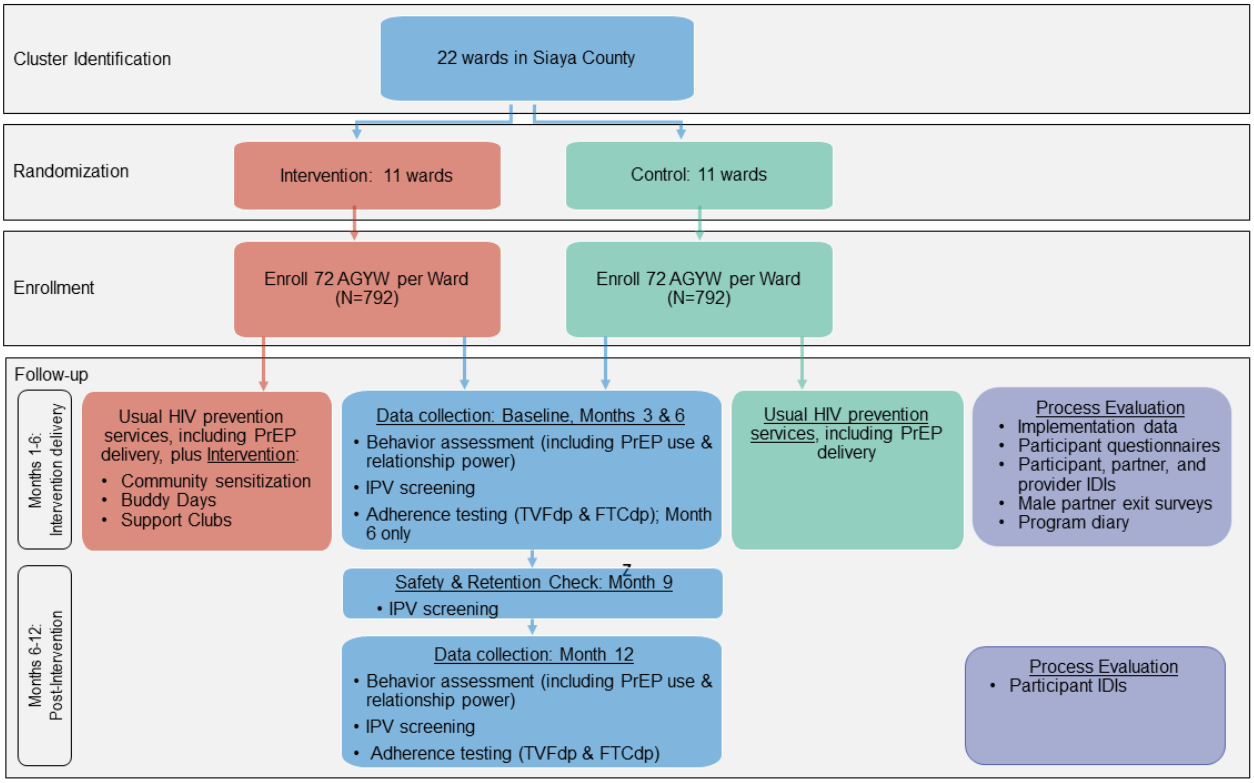
The objective of this study is to test the effectiveness of the multilevel Tu'Washindi intervention to increase effective PrEP use and reduce IPV among Kenyan adolescent girls and young women by addressing relationship dynamics and partner opposition to PrEP. A process evaluation will assess the implementation processes and theorized mechanisms of change influencing intervention effectiveness and identify implementation challenges and strategies to facilitate future scale-up in programmatic settings to maximize public health impact. Study findings will contribute to the limited evidence base for effective PrEP adherence interventions to reduce HIV acquisition in this priority population.

Methods

Design

This study has a 2-arm parallel cRCT design (Figure 1). We have randomized 22 administrative wards in a 1:1 ratio and aim to enroll about 72 adolescent girls and young women from each (total N=about 1584) to receive either the Tu'Washindi intervention plus usual HIV prevention services, or usual HIV prevention services alone. Because of the urgent need for interventions to support PrEP use among adolescent girls and young women in a real-world context, the intervention is delivered outside of DREAMS to evaluate its impact on adolescent girls and young women accessing PrEP from Ministry of Health (MoH) facilities. This pragmatic study design enables us to determine effectiveness of the intervention when layered onto ongoing county-wide HIV prevention programming [44]. After informed consent and baseline data collection, the Tu'Washindi intervention is implemented in each intervention cluster while the control cluster continues with usual HIV prevention services. The duration of study participation is 12 months, with data collection visits at intervention midline (study month 3), intervention endline (study month 6), and at 6 months postintervention (study month 12). A prospective process evaluation is being conducted to characterize intervention implementation, explore theorized mechanisms of change, and capture contextual factors influencing study outcomes. The protocol was written following the 2013 SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) guidelines (Multimedia Appendix 1).

Figure 1. An overview of the study design. AGYW: adolescent girls and young women; FTCtp: emtricitabine triphosphate; IDI: in-depth interview; IPV: intimate partner violence; PrEP: preexposure prophylaxis; TFVdp: tenofovir diphosphate.



Study Setting

Siaya County is located in the former Nyanza Province in western Kenya, along the shores of Lake Victoria. The county is primarily periurban and rural, and agriculture and fishing are the main economic activities [45]. Siaya County has the second highest HIV incidence in Kenya (2.5% per year); it is the site of 12% of new HIV infections but comprises just 2% of the national population [46]. In addition, the former Nyanza Province has the highest prevalence of gender-based violence in Kenya: 22% of women aged 15 to 49 have reported sexual violence and 56% have reported physical violence at least once since the age of 15 [18].

Study Organization

The Tu'Washindi study leadership is comprised of investigators from RTI International and Impact Research and Development Organization (IRDO) and meets monthly. This group is

ultimately responsible for the design and conduct of the trial, including intervention updates, protocol preparations and revisions, and protocol and safety monitoring. The trial management committee meets weekly, and it is responsible for the day-to-day conduct of the trial. It includes the principal investigator (PI) and site PI, project director and project coordinator, intervention leads, and quantitative and qualitative data management teams. The University of North Carolina Center for AIDS Research Clinical Pharmacology and Analytical Chemistry Core is responsible for analysis of the dried blood spot (DBS) samples. The study is further supported by a 5-member national-level technical advisory committee who meet annually and advise on design considerations to ensure a smooth transition from research to implementation if the intervention is effective; a 15-member youth advisory board that meets quarterly and provides feedback on study design and methods, data collection tools, and recruitment and retention of study participants; and a 12-member stakeholder advisory board made up of PrEP technical staff from MoH and other delivery partners, IPV referral agency representatives, and other community leaders that meets twice yearly to advise on effective integration of the study into existing structures and on linkage to PrEP and other referral services.

cRCT Component

Site Selection and Randomization

The study clusters comprise 22 of the 30 administrative wards in the county. The 30 wards were categorized into 5 strata based on community type (ie, periurban, rural fishing, or rural nonfishing) and whether the proportion of girls on PrEP is above or below the median, using MoH programmatic data. (Although the geography and PrEP use criteria define 6 strata, only 1 ward in the county fell within the urban, low PrEP use stratum. Because it was not possible to create a pair of intervention and control wards in this stratum, it was excluded.) The 22 study wards were purposively selected to ensure an even number of wards within each stratum and a balanced distribution of wards across strata. Randomization was completed by RTI statisticians once the 22 study wards are selected and placed into strata. Within each stratum, wards were randomly allocated to the intervention or control arms in a 1:1 ratio. After randomization, we created pairs of intervention and control wards within each stratum and determined the order in which they would be enrolled in the study based on the location of each ward, to minimize the risk of contamination while ensuring the feasibility of implementation. Subsequently, one intervention and control site pair were randomly selected from each stratum for inclusion in the qualitative component. Allocation was revealed to the investigators before community mapping (see the Recruitment and Screening section) and to the participants after their enrollment into the study.

Eligibility Criteria

To be eligible, potential participants must be females aged 15 to 24, currently in a sexual relationship with a male partner for at least 1 month, and vulnerable to HIV per a modified version of the DREAMS eligibility screening tool. To reflect the population most likely to participate in this intervention in a programmatic setting, they must be either taking PrEP or interested in taking PrEP (ie, she thinks that she would benefit from PrEP but is not currently taking it). In addition, they must be residents of the applicable study ward; willing and able to attend support clubs; willing and able to provide adequate contact information; fluent in English, Dholuo, or Kiswahili; and able and willing to provide informed consent (or assent and parental consent for nonmature minor participants aged 15 to 17). Potential participants are excluded if they are living with HIV (by self-report); planning any long-term travel or relocation in the next 12 months; or have any condition that the site PI or designee determines would preclude participation.

Individuals who do not meet the criteria for participation in this trial (ie, screen failure) because of criteria that are likely to change over time may be rescreened. Examples include not being resident of the ward or not being interested in taking PrEP.

Recruitment and Screening

Recruitment occurs simultaneously in each pair of wards before moving on to the next pair and focuses on the catchment areas of 2 to 4 health facilities in each ward. Before recruitment, community mapping is conducted to identify key stakeholders, referral resources, locations where adolescent girls and young women gather, and locations where men gather. Recruitment takes place at venues identified through community mapping, including health facilities, schools, churches, DREAMS Safe Spaces, youth groups, and community markets. To ensure that the study findings are generalizable to adolescent girls and young women across the 15- to 24-year age range, we aim to enroll at least 25% of the study participants from the 15- to 19-year age group who have lower rates of PrEP use but have similar HIV incidence to the 20- to 24-year age group [47,48]. Attendees interested in the study are invited to meet with the research assistant after the recruitment meeting to discuss questions, obtain additional information, and schedule an appointment for informed consent, eligibility screening, and, if eligible, for enrollment.

Retention

Once a participant is enrolled in the study, the study team makes every reasonable effort to retain her to minimize bias associated with loss to follow-up. To ensure high retention, IRDO tracks retention rates and follows standard study operating procedures detailing strategies, such as clear explanation of the visit schedule at all visits, collection of detailed locator information with multiple means to contact participants, appropriate and timely visit reminders, offering weekend hours for study visits, and conducting immediate follow-up on missed visits through phone, home or other off-site visits.

Intervention and Control Conditions

Intervention Design

Tu'Washindi was developed by our team using a participatory process with adolescent girls and young women and service providers in Siaya County to ensure that it was responsive to adolescent girls and young women's stated needs for PrEP support in the context of their relationships [40]. The intervention components are informed by social cognitive theory [49] in combination with a socioecologic framework for PrEP

introduction [50] to address factors at the individual, partnership, and community levels that influence adolescent girls and young women's response to IPV and their PrEP use (Figure 2 [50,51]).

Social cognitive theory informs support club activities to enhance individual-level behavioral capability (eg, knowledge and skills to use PrEP and IPV safety planning), improve outcomes expectations (eg, that PrEP use will prevent HIV without threats to safety or relationship security), and increase self-efficacy to use PrEP safely and consistently. At the partnership level, support clubs also aim to develop skills for healthy communication and PrEP disclosure. Drama activities are integrated into each session to allow participants to practice these skills and build self-efficacy. Adolescent girls and young women follow suggested storylines from the intervention manual, developed by youth in the formative phase [40], to create and enact plays about overcoming partner-related barriers to PrEP use, including one to be performed at the Buddy Days. Buddy Days also work at this level to facilitate disclosure and build male partner support for PrEP use by engaging couples in discussions about PrEP, healthy relationships, and promoting HIV prevention as part of family well-being. To increase men's receptiveness to information provided at the Buddy Days or from their female partners, community sensitization events deliver accurate information about PrEP (eg, safety, effectiveness, and eligibility), discuss common myths and misperceptions, and encourage men to support their partners' PrEP use [53]. At the community level, the community sensitization activities aim to increase PrEP knowledge, reduce PrEP stigma, and reduce the acceptability or normalization of IPV as a response to adolescent girls and young women's PrEP use. Support clubs aim to increase social assets, including peer support for PrEP use and access to IPV resources in the community. Table 1 illustrates the intervention's alignment with the conceptual framework.

Figure 2. The conceptual framework; adapted from Pettifor et al [51] and Mathur et al [50]. IPV: intimate partner violence; PrEP: preexposure prophylaxis.

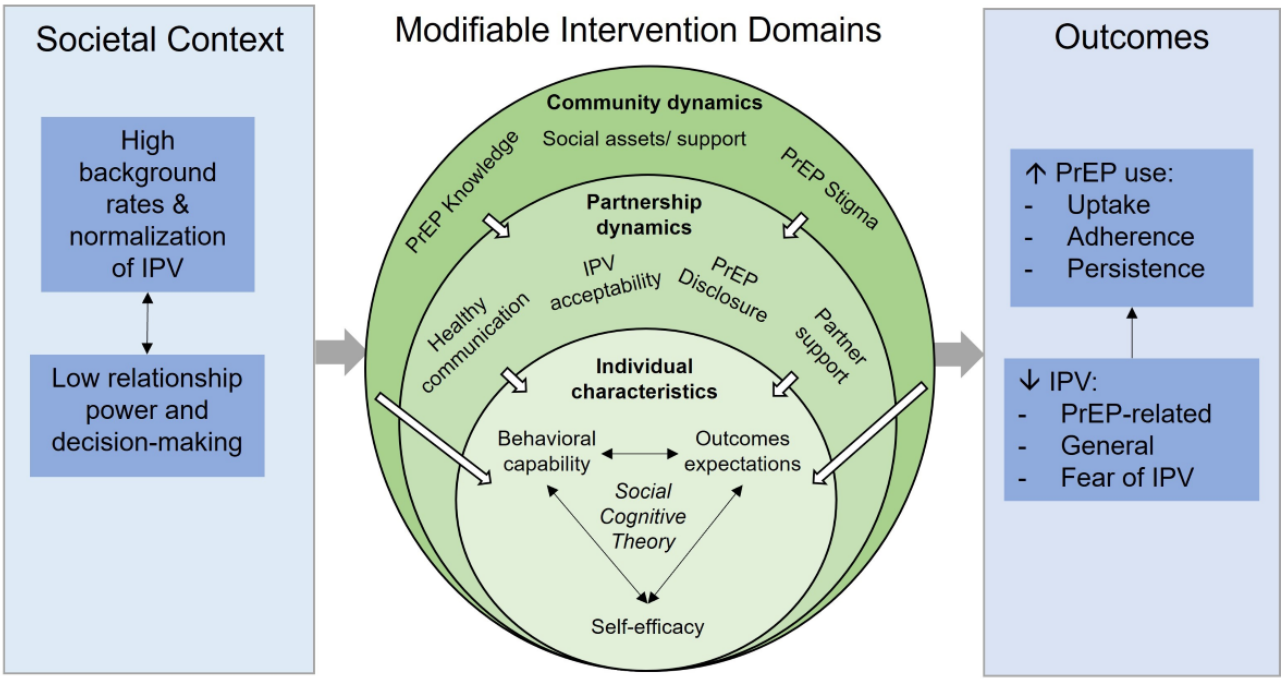


Table 1. Mapping of intervention components to conceptual framework.

Level and domain	Community sensitization	Buddy Days	Support clubs
Individual			
Behavioral capability			✓
Outcomes expectations		✓	✓
Self-efficacy			✓
Partnership			
Healthy communication		✓	✓
Reduce intimate partner violence acceptability	✓	✓	✓
Disclosure of preexposure prophylaxis use		✓	✓
Partner support or acceptance	✓	✓	
Community			
Preexposure prophylaxis knowledge	✓	✓	
Stigma	✓		
Social assets			✓

Intervention Delivery

Before delivery, the intervention manual and training tools were updated to reflect lessons learned during the pilot and the change to implementation outside of DREAMS. Because age restrictions on PrEP in DREAMS did not permit us to pilot the intervention with adolescent girls aged 15 to 17 years, we pretested the activities with 12 to 15 adolescent girls in this age range over a 1-month period to obtain feedback on comprehension and relevance of the content and how best to support participation.

Delivery takes place in 4 phases, with activities occurring concurrently in 2 wards during phase 1 and in 3 wards during phases 2 to 4. In each ward, the intervention is conducted over a 6-month period with intervention implementation beginning about 1 week after enrollment concludes. Each new phase of the intervention commences immediately after the activities in the previous phase are concluded. This phased approach minimizes staff burden and allows for close monitoring of implementation to identify and correct problems early on.

The intervention activities include sensitization of MoH clinics, intervention staffing and training, community sensitization sessions, Buddy Days, support clubs, and monitoring and quality assurance.

For sensitization of MoH clinics, before study initiation in each intervention ward, we collaborate with the facility in-charges from each of the 2 to 4 health facilities selected for study recruitment to identify PrEP delivery staff and schedule a half to one day training to introduce the study and discuss relationship-related challenges to PrEP use, with the goal of ensuring that the counseling support offered at the clinics complements the messages provided through the intervention. We also review PrEP adherence and couples' counseling and disclosure approaches to more comprehensively address adherence challenges commonly experienced by adolescent girls and young women.

Intervention staffing and training within each ward is delivered by a set of 2 to 4 mentors (ie, women slightly older than the participants who have completed at least some secondary education and are rooted in their communities), an experienced male community organizer, and clinicians and counselors with experience in PrEP provision to adolescent girls and young women (hereafter "intervention providers"). Staff supervisors train each cadre over 1 to 3 days to review the intervention manual and to practice the required activities.

Community sensitization sessions are conducted by the community organizer approximately weekly over the first 3 months of the intervention period, lasting about 60 minutes to 90 minutes each. Sessions occur in places where adolescent girls and young women's male partners are known to gather [54]. Content focuses on PrEP information and dispelling myths and rumors. When time allows, additional content on healthy relationship communication is also included. Clinicians may attend larger sessions to support the organizer.

Buddy Days take place around month 3 of the intervention period, with about 2 to 3 events per ward to maximize participation. The sessions are cofacilitated by the community organizer and clinician and include provision of information about PrEP; facilitated discussion of reasons to support adolescent girls and young women's PrEP use, healthy relationship communication, and acceptability of IPV; and an interactive drama, designed and performed by volunteer Tu'Washindi participants based on story guides in the intervention manual, to illustrate real-world partner-related challenges to PrEP use. The cofacilitators foster audience engagement both during and after the performance by soliciting reflections on the drama, discussions of alternate storylines, and experiences from audience members [55]. To encourage and destigmatize participation, Buddy Days are open to all community members and offer health services, such as HIV testing services and screening for hypertension and diabetes. In addition, all adolescent girls and young women and their

partners who attend the Buddy Days together as a couple receive a small basket of foodstuffs worth about US $5 as an incentive.

Support clubs meet for approximately eight 2-hour sessions over the 6-month intervention period, facilitated by the mentor or by 1 or more participants with mentor support. About 3 to 4 support clubs are offered at varying times and locations to maximize convenience and maintain a small enough number of attendees (18-24) to build community and trust. The support clubs aim to be youth-friendly and nonjudgmental, with an emphasis on ground rules and confidentiality, and support for PrEP uptake and adherence are integrated throughout. Each interactive, participatory session follows the same basic format: a check-in and activity to build community; recap of the previous session; a new topic related to PrEP and relationships, led by the mentor, clinician, or counselor (Table 2); drama activities; and a closing activity to reflect on lessons learned and build confidence and support.

Table 2. Sample support club topics and coleaders.

Session and topic	Leaders
Session 1: PrEP[a] information	Mentor and clinician
Session 2: disclosure	Mentor and counselor
Session 3: undisclosed PrEP use	Mentor and clinician
Session 4: healthy relationships	Mentor and counselor
Session 5: IPV[b] and PrEP use	Mentor and counselor
Session 6: open session[c]	Mentor
Session 7: open session[c]	Mentor
Session 8: future goals and closing ceremony	Mentor

[a]PrEP: preexposure prophylaxis.

[b]IPV: intimate partner violence.

[c]Participants' choice of topics.

Monitoring and quality assurance involves closely monitoring intervention delivery for quality and fidelity. Staff supervisors will observe at least 15% of community sensitization activities, 100% of Buddy Days, and at least 20% of support clubs using activity-specific observation forms to document assessments of fidelity (ie, adherence to the intervention manual), quality of facilitation (eg, facilitator maintains focus and nonjudgmental delivery), participant engagement, and any factors that may have affected implementation. Intervention staff receive feedback and coaching after each observed session. Findings will inform staff retraining and implementation refinement for subsequent phases. For example, training of intervention providers may be bolstered if gaps are identified.

Usual Care Services

Participants in the intervention and control clusters will have access to a range of evidence-based HIV prevention services offered in the county, including Global Fund–supported services, such as HIV testing services, syndromic management of sexually transmitted infections, family planning and postviolence care services; ongoing DREAMS programming; and PrEP [56]. Participants in both arms receive information about available services and are referred to these services upon request. PrEP is available to adolescent girls and young women aged ≥15 at >100 MoH facilities throughout the county [57], and all the participants who choose to use PrEP in the study can access it through these MoH facilities. In keeping with our study design, this choice of usual services as the comparator condition is realistic, ethical, and relevant [58] because it represents a wide range of evidence-based services to reduce HIV risk. However, PrEP uptake and persistence have been suboptimal in this context, indicating that the intervention is warranted, and that the comparator condition is not sufficiently robust to preclude our ability to detect an effect [59].

Data Collection

Data collection visits occur simultaneously in each pair of wards at enrollment, and months 3, 6, and 12 (Table 3). At enrollment, interviewer-administered questionnaires are used to assess sociodemographics, relationship characteristics, IPV, behavioral HIV risk factors, and history of PrEP use. Measures are repeated in follow-up questionnaires to document changes in relevant characteristics, attitudes, and behaviors.

DBS samples are collected via fingerprick at months 6 and 12 from all participants who report initiation or continuation of PrEP since the last visit. For participants who report discontinuation of PrEP, reasons for discontinuation are recorded, but DBSs are not collected. Due to storage and transport challenges, DBS samples are also not collected for participants who have relocated outside the county and have follow-up visits conducted by phone or at a remote location. DBS samples are stored in freezers at the IRDO laboratory and then shipped to the laboratory at the University of North Carolina Center for AIDS Research Clinical Pharmacology and Analytical Chemistry Core for quantification of drug concentrations by liquid chromatography-tandem mass spectrometry technology [60].

Table 3. Participant timeline.

Procedures	Month 0 (BL[a])	Month 1	Month 2	Month 3 (3 MFU[b])	Month 4	Month 5	Month 6 (6 MFU)	Month 7	Month 8	Month 9	Month 10	Month 11	Month 12 (12 MFU)
Assess and confirm eligibility	✓												
Informed consent	✓												
Enrollment	✓												
Locator information and update	✓			✓			✓			✓			✓
Quantitative data collection													
Sociodemographic and behavioral characteristics	✓			✓			✓						✓
PrEP[c] use history	✓			✓			✓						✓
IPV[d] history	✓			✓			✓						✓
Hypothesized mechanisms of action[e]	✓			✓			✓						✓
Laboratory assessment (dried blood spots)							✓						✓
Tu'Washindi intervention													
Community sensitization session (weekly)		✓	✓	✓									
Buddy Days				✓									
Support clubs (once or twice per month)		✓✓[f]	✓✓[f]	✓	✓	✓	✓						
Qualitative data collection													
In-depth interviews (subset of participants)							✓						✓
Safety monitoring													
Standardized assessments				✓			✓						✓
Short in-person or telephone contact visit										✓			
Reporting of IPV, injuries, social harms, or other relevant concerns		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

[a]BL: baseline appointment.

[b]MFU: month follow-up appointment.

[c]PrEP: preexposure prophylaxis.

[d]IPV: intimate partner violence.

[e]Also part of process evaluation.

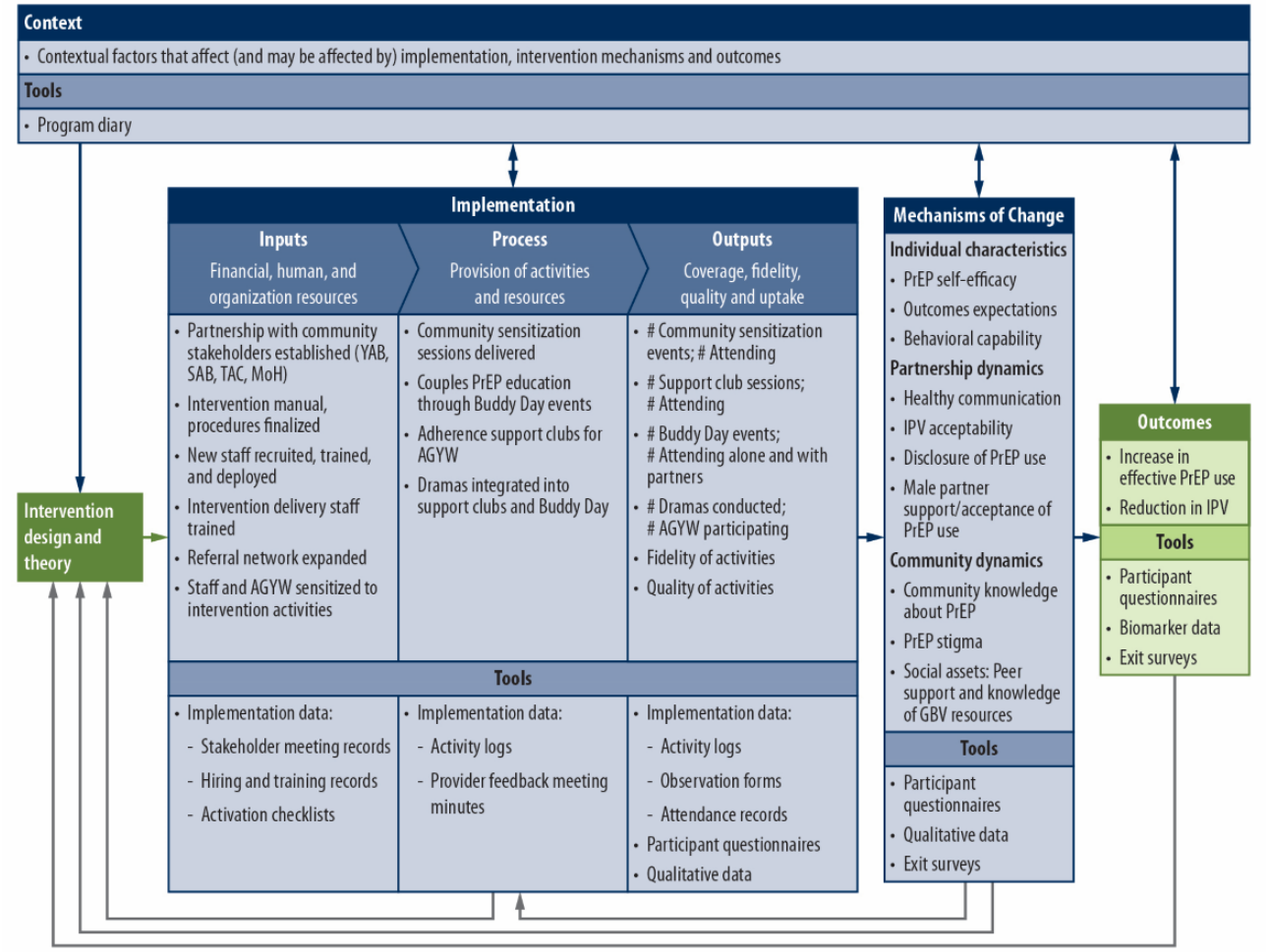
[f]Two support clubs per month.

Process Evaluation Component

Overview

The mixed methods process evaluation uses implementation data; quantitative adolescent girls and young women participant questionnaires; exit surveys with men who attend intervention activities; qualitative in-depth interviews (IDIs) with adolescent girls and young women participants, their male partners, and intervention providers; and a project diary. Our process evaluation framework (Figure 3 [61]) highlights the key evaluation components, relationships between them, and key measures and data sources [62-65].

Figure 3. Process evaluation framework and key measures. Adapted from the Medical Research Council guidelines for process evaluation of complex interventions [60]. IPV: intimate partner violence; MoH: Ministry of Health; PrEP: preexposure prophylaxis; SAB: Stakeholder Advisory Board; TAC: Technical Advisory Committee; YAB: Youth Advisory Board.



Participants and Eligibility

Eligibility criteria for adolescent girls and young women participants are described in the Eligibility Criteria section. Participants in exit surveys or male partner IDIs must be males aged ≥15 years. In addition, the exit survey participants must have attended a study Buddy Days or community sensitization event and have been present for at least half of the event, while IDI participants must be a sexual partner of the adolescent girls and young women clinical trial participant and that adolescent girls and young women participant must have provided permission for the study staff to contact the male partner. Intervention providers must be aged ≥18 years and have been involved in delivering Tu'Washindi intervention activities. In addition, all participants must be fluent in English, Dholuo, or Kiswahili; willing and able to provide informed consent; and not have any condition that the site PI or designee determines would preclude participation.

Participant Selection and Recruitment

Exit Surveys

At all intervention sites, all men who attend a Buddy Days event as a couple are approached while waiting for incentive distribution and asked to complete a survey. A research assistant approaches about 20% of men who attend community sensitization events and asks them to complete survey after the event.

In-Depth Interviews

For each of the 5 intervention and control ward pairs randomly selected for qualitative research, we use data captured at month 3 to purposively select a subset of adolescent girls and young women participants (n=30; 4 per intervention ward and 2 per control ward) who are behaviorally eligible for PrEP, per self-report, and have attended at least one support club meeting (intervention wards only). We aim to ensure representation of

PrEP users and nonusers and those with and without a history of IPV. Participants who are selected for IDIs are contacted by a research assistant before their month 6 visit, informed that they have been selected, and invited to participate in the IDI.

On the basis of the information provided by the adolescent girls and young women at the month 6 visit, we purposively select male partners (n=20; 4 per intervention ward) for IDIs to represent a range of exposure to the Buddy Days and community sensitization activities.

Male partners are only contacted with the permission of the adolescent girls and young women participants, who provide contact information. A research assistant then contacts the male partner and invites him to participate in the IDI. Study staff do not disclose the PrEP use status of adolescent girls and young women participants to any partner whom they recruit for the IDIs.

Intervention providers are purposively selected for IDIs by the study coordinator to represent a variety of job functions, including mentors, community organizers, counselors, and clinicians (n=20, 4 per intervention ward).

Data Collection

Implementation data includes staff hiring and training records; minutes from youth advisory board, stakeholder advisory board, and technical advisory committee meetings; and study activation checklists to track activities, materials, and systems required for successful implementation, such as community introductions, final intervention manuals, and vetted lists of referral agencies. Providers maintain activity logs and attendance records for each meeting or event, and supervisors record minutes from feedback and coaching meetings. Quality and fidelity of intervention activities is documented on observation forms as described above.

Participant questionnaires are administered to adolescent girls and young women participants at each visit to assess mechanisms of change (for all participants) and perceived intervention quality (intervention arm) or potential contamination (control arm). The hypothesized mechanisms of change include PrEP self-efficacy and outcome expectations, PrEP knowledge, healthy communication, disclosure of PrEP use to male partner and partner reaction, community knowledge of PrEP, PrEP stigma, and social assets.

Exit surveys are brief, anonymous, quantitative, interviewer-administered questionnaires that gather information on men's views of PrEP, their willingness to support their partner's PrEP use, and feedback on intervention activities.

IDIs are conducted in a private location and facilitated by trained female interviewers following a semistructured guide as follows:

- Serial IDIs with adolescent girls and young women participants are conducted at 2 time points (months 6 and 12). Key topics include relationship quality and experiences of IPV, patterns of PrEP use and barriers and facilitators to PrEP access and use, experiences with the intervention, and perceptions of how the intervention has affected the hypothesized mechanisms of change and study outcomes.
- Male partner IDIs take place at the end of the intervention period and explore men's experiences with the intervention. Interviews also aim to identify mechanisms through which their attitudes toward PrEP were shifted, or reasons why they were not.
- Intervention provider IDIs are conducted at the end of intervention delivery to elicit their perceptions of the adequacy of inputs (eg, training and resources), fidelity and quality of delivery, and challenges and perceived benefits to delivering each intervention component.

A program diary is maintained by the study coordinator to record external events (eg, elections, police activity, festivities, and health campaigns) and internal events (eg, increased funding or supply shortages) that may affect intervention delivery or study outcomes. Before intervention implementation in each ward, the study coordinator identifies a set of sources, including study staff, health facility personnel, community members or others who are well-positioned to provide this contextual information, and contacts them at regular intervals to record any updates.

Data Management

Most questionnaire data are collected on tablets using REDCap (Research Electronic Data Capture; Vanderbilt University) or collected on paper forms and entered into REDCap at the study offices, with hard copies securely stored at the field site [66,67]. RTI implements a quality assurance plan, including routine generation of quality control reports by the data manager and communication of findings for resolution. IDIs are audio-recorded, with debriefing reports completed immediately after each interview and quickly shared with the study team to highlight preliminary findings. Interviews are translated and transcribed at the study site. Electronic copies of forms are securely transmitted to RTI and reviewed for quality control, with weekly query resolutions.

Sample Size Considerations

The study is powered to identify an absolute difference of 15% between intervention and control arms for the primary outcomes: the proportion with effective PrEP use at month 6 and month 12. Power calculations are conducted using simulations based on the logistic model with normally distributed ward (cluster) effects and assuming 11 wards per treatment arm with type 1 error of 0.025 to account for separate analyses at each of 2 time points. With 60 participants per ward, we will have ≥80% power to detect a 15% difference in the outcome as long as the SD for ward variation is ≤10% and the level of effective PrEP use in control wards remains <50% (far higher than observed in recent trials and demonstration projects). To allow for up to 20% loss to follow-up, our total sample size will be 1584 participants: 72 adolescent girls and young women in each of the 22 wards (11 wards per arm).

Data Analysis: Clinical Trial

Outcomes and Hypotheses

The primary outcomes of the study will be the proportion of study participants with effective PrEP use, defined in Table 4, evaluated immediately postintervention, at month 6, and at

month 12 to gauge the persistence of intervention effect. TFVdp levels will be dichotomized by Clinical Pharmacology and Analytical Chemistry Core laboratory specialists to delineate between consistent (≥4 doses per week) versus inconsistent (<4 doses per week) adherence [68]. The aim 1 hypothesis is that the proportion of participants with effective PrEP use at (a) month 6 and (b) month 12 will be *higher* in the intervention versus control arm.

Table 4. An overview of key measures for the cluster randomized controlled trial, collected at enrollment and months 3, 6, and 12, unless otherwise noted.

Measure	Method
Primary outcomes	
Effective PrEP[a] use (biomarker assessment)	Percentage of all study participants with biomarker TFVdp[b] levels indicating consistent PrEP use (≥4 doses per week) for the past 2 months. [68,69]. Represents a composite outcome of PrEP initiation and high execution to capture these key steps in the HIV prevention continuum. Collected at months 6 and 12 only.
Secondary outcomes	
IPV[c] prevalence	Percentage of participants reporting IPV since the last study visit, measured with the WHO VAWI[d] [70] and classified by the STRIVE consortium definition [71]: any act of severe physical or sexual violence or ≥2 acts of moderate physical violence.
IPV severity	Percentage of participants reporting any sexual or severe physical IPV since the last study visit, measured with WHO VAWI [70].
IPV intensity	Continuous score calculated from the number of specific violent acts reported and the reported frequency of each act (0=never; 1=once; 2=a few times; and 3=often) since the last study visit, measured with WHO VAWI [70].
Exploratory outcomes (subcomponents or alternate measures of primary and secondary outcomes)	
PrEP uptake	Percentage of participants initiating PrEP *among those not on PrEP at baseline*, self-reported and validated by Ministry of Health records.
PrEP execution	Percentage of participants with TFVdp levels indicating consistent use *among those reporting current PrEP use.*
PrEP persistence	Percentage of participants with any detectable TFVdp *among those who ever initiated PrEP.* Participants who self-report discontinuation will be categorized as having undetectable TFVdp levels.
Recent PrEP use (biomarker)	Percentage of all study participants with biomarker FTCtp[e] levels indicating consistent PrEP use (≥4 doses per week) for the past 2 wk. Collected at months 6 and 12 only.
IPV type	Percentage of participants reporting each IPV type (physical, sexual, emotional, and economic) since the last visit, per WHO VAWI [70].

[a]PrEP; preexposure prophylaxis.

[b]TFVdp: tenofovir diphosphate.

[c]IPV: intimate partner violence.

[d]WHO VAWI: World Health Organization's Violence Against Women instrument.

[e]FTCtp: emtricitabine triphosphate.

The secondary outcomes of the study will be the proportion of participants reporting any IPV and severe IPV (Table 4) between enrollment and month 6, and between month 6 and month 12, and the difference in IPV intensity scores at months 6 and 12. The aim 2 hypothesis is that the proportion of participants reporting any IPV and severe IPV and IPV severity scores will all be *lower* at both time points in the intervention arm versus control arm.

In exploratory analyses, we will first explore effect modification by age (15-19 vs 20-24) and DREAMS participation (current, former, or never) for the primary and secondary outcomes. Second, we will break down the primary outcome into steps along the continuum (PrEP uptake, execution, and persistence) and IPV outcomes by type—physical, sexual, emotional, and economic—to understand where the intervention had its strongest effects. Third, we will compare the proportion of participants per arm with emtricitabine triphosphate (FTCtp) levels indicating consistent PrEP adherence over the past 2 weeks. Comparing TFVdp and FTCtp levels will yield insights on adherence patterns over both a long and short window of time before collection. We will also analyze the alignment of adherence measures with HIV risk perception and behavior to better understand adherence patterns.

Analysis Approach

Descriptive and bivariate statistics will be used to compare participant characteristics in the intervention and control arms and those who completed the study versus those lost to follow-up. Outcomes will be modeled using an intent-to-treat approach with mixed effect logistic and linear regression models. Model predictors will include treatment assignments, randomization strata, and a random effect for ward (cluster) within stratum that is assumed to be independent and normally distributed with mean 0. If the cluster randomization does not adequately balance baseline characteristics across arms, we will conduct exploratory analyses controlling for those characteristics. We will analyze the data from each of the 2 time

points separately and the primary outcomes analyses will use a type I error rate of 0.025 at each time point.

Missing Data

In any situation with missing data, we will perform appropriate secondary analyses adjusting for variables that may be related to the missingness mechanism. If missing data rates are higher than anticipated (>10%), we will include covariates that are related to missingness in regression models. We will also perform sensitivity analyses to assess the potential impact of the missing data.

Data Analysis: Process Evaluation

Quantitative Data

Implementation inputs, processes, and outputs will be analyzed descriptively, and we will draw comparisons across intervention wards. Intervention effects on each mechanism of change will be modeled individually following the approach described for the cRCT. We will regress each mechanism on the exposure (intervention arm assignment), controlling for baseline levels of the mechanism. If the primary analyses show no effect of the intervention on PrEP or IPV outcomes, the results will inform our interpretation of whether the intervention failed to affect the intended mechanism or whether the change in mechanism did not lead to the hypothesized outcome. If the primary analyses suggest a positive intervention effect on PrEP or IPV outcomes, we will conduct causal mediation analysis [72,73]. Coverage, uptake, and exit survey data on perceived impact will also be evaluated as moderators of intervention effectiveness at the site level in exploratory analyses of mechanisms of change.

Qualitative Data

The coding process will involve a core group of about 2 to 5 analysts from IRDO and RTI who will develop one or more codebooks and establish qualitative coding procedures. Data will be coded using a qualitative software package, such as Dedoose (SocioCultural Research Consultants, LLC). A set of preliminary codes will be developed based on key themes or topics identified a priori and the findings highlighted in the debriefing reports for each of the 3 datasets (eg, adolescent girls and young women, male partners, and providers). Each group member will apply the initial set of thematic codes to a common transcript, discuss their coding experiences, and agree on expanding and modifying code names and definitions when necessary. We will continue with an iterative process of revising the codebooks as we continue to read and code the data. Once finalized, the codebooks will be used for a final recoding of all transcripts.

A preselected number of transcripts will be double-coded by 2 coders to establish intracoder and intercoder reliability. Following this process, the coding team will discuss discrepancies, which will ultimately be resolved through consensus. This process will continue until the intercoder reliability is at least 80%. Thereafter the remaining texts will primarily be coded by 1 analyst only, with one or more rounds of consistency checks and regular discussions among the coding team to ensure that coding remains standardized and reliable.

Comprehensive listings of all coded quotations for every code or code “family” will be generated in the qualitative analysis software. Coding memos will be used to summarize and explore the relationship between the constructs of the evaluation framework (eg, the relationship between implementation processes and hypothesized mechanisms of change, or between mechanisms of change and outcomes). Analysts will also review and analyze coded serial IDI content within each participant’s dataset to look specifically for patterns over time. The findings and interpretations of the data will be critically discussed until there is group consensus on the dominant themes and meanings contained in the data [74].

Integrated Synthesis of Quantitative and Qualitative Data

For each construct of the evaluation framework, findings from the qualitative and quantitative analyses will be integrated to build a more comprehensive picture of whether the target intervention inputs, processes, and outputs were achieved, whether these resulted in the hypothesized changes in mechanisms of action, whether these changes resulted in the intended outcomes, and how external contextual factors influenced implementation, thereby both evaluating the success of study implementation and testing the theory of change.

Study Monitoring

Protocol Oversight

The study team continuously reviews recruitment and follow-up data to ensure compliance with the protocol and ethical standards. The IRDO study coordinator regularly monitors protocol compliance at study sites. The IRDO internal research monitor conducts quarterly spot checks of 100% of informed consent forms and 10% of data files. Any issues are documented in quality control logs and reviewed with the study staff. Protocol deviations or violations are reported to the study leadership and institutional review board (IRB) within 5 business days.

Data and Safety Monitoring Board

The trial is monitored by a data and safety monitoring board (DSMB) composed of 4 members: a statistician, a medical physician, a researcher with content expertise in IPV, and a researcher with expertise in PrEP use among adolescent girls and young women. All DSMB members are independent from any professional or financial conflict of interest with the research project, study investigators, and study institutions. The DSMB established a charter that outlines their responsibilities and meets approximately semiannually to review data quality and integrity, protocol adherence, participant safety, study conduct, and progress. On the basis of their review, they make recommendations on study continuation and modifications.

Safety Monitoring

This study adheres to the World Health Organization Ethical and Safety Recommendations for Intervention Research on Violence Against Women [75]. All data collection staff receive training on IPV assessment, recognizing warning signs of immediate danger, discussing sensitive topics with participants, managing distressed participants, legal reporting requirements,

and referral protocols. We aim to ensure that all communication with participants protects against unintentional disclosure of PrEP use, study participation, or reported IPV and does not place participants at additional risk of harm. To increase confidentiality, the study is presented to the community and to the participants as a study on HIV prevention methods in young women, and the focus on IPV is not advertised.

The MoH clinics conduct clinical safety monitoring for PrEP according to Kenyan guidelines. This study focuses on monitoring for adverse events that could be associated with the intervention, including IPV, social harms, serious adverse events, and unanticipated problems. All instances of these events are recorded on case report forms and followed up until resolution or 30 days after the participant exits from the study. These adverse events are reviewed monthly by the protocol team and reported to the IRB and DSMB according to their established protocols.

All staff have been trained to respond to any reports on IPV and social harms using the World Health Organization's Listen, Inquire, Validate, Enhance Safety, and Support (LIVES) approach through referrals [76]. Staff follow up by phone or during subsequent visits to check on referral uptake and provide additional assistance if needed. Participants who report being in immediate danger or feeling unsafe returning home are offered an immediate escorted referral to vetted rescue or shelter services, and study staff follow up with the participant weekly until their situation is resolved or stabilized, or until 30 days after their exit from the study. If staff have concerns about the safety of a participant's enrollment, they alert the site PI or designee to make a final determination about eligibility.

Ethical Considerations

The trial is being carried out in accordance with International Council on Harmonization Good Clinical Practice and the United States Code of Federal Regulations applicable to clinical studies (45 CFR part 46).

Ethics Approval

The study protocol and associated documents have been reviewed and approved by the Maseno University Ethical Review Committee (MUERC; MSU/DRPI/MUERC/00991/21). The RTI International Committee for Human Subjects Research established a reliance on MUERC for the study under a signed IRB authorization agreement. No amendment to the protocol or informed consent forms is implemented without prior ethics committee approval. Protocol violations are reported in writing to MUERC in accordance with their policy.

Informed Consent Process

IRDO study staff obtain informed consent or assent from all participants taking part in the cRCT or IDIs. Study staff explain the study purpose and procedures, risks and benefits to the eligible participants, and compensation for their participation. They emphasize that their participation is voluntary and that there is no penalty if the individual decides not to participate. Participants aged ≥18 years provide written consent in English, Kiswahili, or Dholuo. The IRB has granted a waiver of parental consent for adolescent girls and young women participants who meet the criteria for "mature minors" outlined in MoH guidelines for Conducting Adolescent HIV Sexual and Reproductive Health Research in Kenya [77], and for male partners aged 15 to 17 years to take part in IDIs, because they constitute a minimal-risk research activity. All minor participants may choose to involve their parent in the consent process. For minor participants not meeting the above criteria, or who involve their parents, we obtain parental consent and child assent. The IRB has also granted a waiver of written consent for the brief and anonymous exit interviews focused on program acceptability.

Confidentiality

All study procedures occur in private settings. Each participant receives a unique study identification number, and personally identifiable information does not appear on study data. All electronic data and study records are stored on secure, password-protected devices and uploaded to a secure RTI project server. Access to the system is restricted to trained study staff. Hard-copy data, consent and contact information forms with personally identifiable information are kept in separate double-locked files at the site and not transmitted to RTI.

To minimize confidentiality risks during the follow-up visits, we use contact methods agreed to by the participants, including aliases for study staff. To protect confidentiality during group activities, participants are asked to follow ground rules and pledge not to disclose others' personal details outside the group. At each session's start and end, participants are reminded to respect confidentiality and that there is a risk that others may disclose what they say.

Participants' study information will not be released without their written permission, except as required by law or as necessary for review, monitoring, and auditing by the following:

1. Representatives of the US federal government, including the United States Office of Human Research Protections, the National Institutes of Health (NIH) and contractors of the NIH, and other local, United States, and international regulatory entities
2. Representatives of RTI
3. Study staff
4. Site IRBs

Criteria for Early Termination of Study Participation

Participants can withdraw from the study at any time for any reason. The PI, site PI, or designee may also withdraw participants for safety or noncompliance reasons, with the DSMB notified of such terminations. Efforts are made to complete a final evaluation for participants who withdraw. Staff document withdrawal reasons in study records. Participants who withdraw may rejoin and resume intervention or follow-up visits up to their original exit date, with PI and DSMB consultation.

Study Discontinuation

The study may be suspended or terminated at any time by the NIH, RTI, site IRBs, or other authorities due to funding issues or substantial concerns, such as DSMB recommendations. If this occurs, the PI will be notified in writing with the reasons, and will inform participants, the IRB, and the sponsor. The

study may resume if safety, protocol compliance, and data quality issues are resolved and approved by the relevant parties.

Dissemination and Use of Findings

Study findings will be disseminated to the study communities, the scientific community, and HIV service and advocacy organizations via peer review publications, professional meetings, research briefs, and stakeholder meetings. All media, presentations, and publications resulting from data collected during this study will be collaborative in nature but require approval from the study leadership. All publications will be submitted to PubMed Central, in accordance with NIH Public Access Policy.

Results

The study was funded in August 2021, and data collection started in September 2022. As of December 2024, enrollment has been completed in 16 of the 22 study wards, with 72.6% (1150/1584) participants enrolled. We anticipate that data collection will be completed in May 2026 and results will be available by mid-2027.

Discussion

Innovations and Future Application

This study offers 4 key innovations. First, it offers the opportunity to address the lack of evidence-based interventions that explicitly confront the role of IPV and relationship dynamics in supporting PrEP use among adolescent girls and young women. Current interventions have focused largely on instrumental adherence support (eg, pill-taking reminders and strategies), motivational interviewing, and peer support, with limited evidence of success [4,5,78-83]. If found effective, the Tu'Washindi intervention will be one of the first to successfully address critical partner-related barriers to uptake and adherence and to directly involve male partners to build their support for PrEP use among adolescent girls and young women. Second, our intervention approach is youth-designed and tailored to meet the specific needs of adolescent girls and young women, qualities that have been specifically called for in recent literature to address shortcomings in existing interventions [84,85]. The intervention components of male engagement and couples' education were added to the design in direct response to the formative research findings, and our participatory design methods resulted in high intervention acceptability and uptake among adolescent girls and young women and high ratings for relevance and perceived effectiveness. Third, our multilevel approach recognizes that IPV and relationship power create barriers to HIV prevention at the individual, partnership, and community levels. Tu'Washindi supports adolescent girls and young women to respond to experienced or anticipated IPV at each level by fostering self-efficacy, improving relationship communication, developing support systems, and encouraging action to maintain safety and HIV prevention adherence [86-88]. Fourth, we assess short- and long-term adherence with biomarker measurements of 2 active PrEP metabolites, TFVdp and FTCtp to gain a more thorough understanding of adolescent girls and young women adherence behavior. Although the field has focused on TFVdp levels to classify long-term (ie, previous 1-3 months) PrEP adherence [89], FTCtp concentrations can delineate between consistent (≥4 doses/week) versus inconsistent (<4 doses/week) PrEP adherence over 2 weeks before sample collection with ≥89% accuracy [90]. Thus, we will have the ability to classify adolescent girls and young women by short-term (2 weeks) adherence in addition to the long-term (2 months) adherence measured by TFVdp levels.

Our intervention and evaluation have been designed from the start to facilitate scalability, sustainability, and rapid adoption. Tu'Washindi was designed to be delivered by trained community members with support from clinicians and counselors, and to integrate into ongoing national or donor-funded youth-focused programs prioritizing HIV prevention. The proposed study uses a pragmatic, rather than exploratory, design to maximize generalizability and ensure results are applicable to real-world settings [44,91]. In addition, our design includes a rigorous process evaluation to document implementation process, quality and fidelity of delivery, resource requirements, and contextual factors to provide valuable guidance to program and policy stakeholders who wish to replicate or adapt the intervention outside of the research setting. In combination, the intervention design and process evaluation approach will reduce the "know-do gap" [92] and accelerate Tu'Washindi's translation from research to practice.

Limitations

Several limitations to this study should be noted. First, there is a risk of PrEP and HIV test kit shortages in MoH clinics, which could interfere with adherence and complicate interpretation of results. We will carefully document shortages as part of the program diary, and study staff will help link participants to other sources of PrEP provision if necessary. Second, cluster randomized studies carry a risk that individual participant characteristics may differ at baseline in important ways. Our design stratifies on 2 important community characteristics (ie, geographic type and baseline PrEP use) to reduce this risk, and our analysis plan incorporates exploratory analyses to control for baseline differences between randomization arms.

Conclusions

Tu'Washindi has demonstrated feasibility and acceptability in pilot research and shows promise to promote PrEP use and reduce IPV among adolescent girls and young women. The proposed study builds directly on our intervention development work to conduct a rigorous effectiveness trial, a critical step in developing the evidence base for this youth-designed, multilevel HIV prevention intervention. Our rigorous process evaluation will clarify mechanisms of change, and implementation considerations to inform policy and practice. If effective, Tu'Washindi will be ideally positioned for sustainable integration into existing youth-focused HIV prevention programming to expand and support PrEP uptake and adherence in this priority population.

Acknowledgments

Research reported in this publication was supported by the National Institute of Mental Health of the National Institutes of Health under award number R01MH125671. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health. The funder did not have and will not have any role in the study design, collection, management, analysis, and interpretation of data; writing of the report; or the decision to submit the protocol or results for publication.

The authors would like to thank Miriam Hartmann and Donald Brambilla for their contributions to protocol development; Rosemary Achieng Onyango, Joseph Okore Onyango, Daniel Okello Adede, Jacob Onyango, and Mark Ayallo for their contributions to intervention design and study implementation; and Lyndsey Shafiei, Brittany Thomas, and Alice Litavecz for their role in data management and quality control.

Data Availability

The research tools, protocols, standard operating procedures, analytic code, codebooks, and deidentified data generated in this study will be available from the corresponding author upon reasonable request. Before access to deidentified participant data is granted, a data sharing agreement will be implemented to ensure that the data will be used for the proposed purpose and that no attempts will be made to identify participants.

Authors' Contributions

STR was involved in conceptualization, methodology, writing original draft, supervision, project administration, and funding acquisition. AMM was involved in conceptualization, methodology, writing original draft, and supervision; ENB was involved in methodology, software, formal analysis, data curation, and writing original draft. SN was involved in conceptualization, methodology, investigation, supervision, and writing original draft. ETM was involved in conceptualization, methodology, supervision, and writing original draft; LD was involved in methodology, writing review, and editing. MLC was involved in methodology, resources, investigation, writing review, and editing. JN was involved in methodology, supervision, project administration, writing review, and editing, JB was involved in investigation, supervision, writing, reviewing, and editing. KA was involved in conceptualization, methodology, supervision, resources, writing original draft, and project administration.

Conflicts of Interest

None declared.

Multimedia Appendix 1
SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) 2013 checklist: recommended items to address in a clinical trial protocol and related documents.
[PDF File (Adobe PDF File), 124 KB - resprot_v14i1e55931_app1.pdf]

Multimedia Appendix 2
Peer-review report by the Center for Scientific Review HIV/AIDS Intra- and Inter-personal Determinants and Behavioral Interventions Study Section (National Institutes of Health, USA).
[PDF File (Adobe PDF File), 99 KB - resprot_v14i1e55931_app2.pdf]

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Abbreviations

cRCT: cluster randomized controlled trial
DBS: dried blood spot
DREAMS: Determined, Resilient, Empowered, AIDS-free, Mentored and Safe
DSMB: data and safety monitoring board
FTCtp: emtricitabine triphosphate
IDI: in-depth interview
IPV: intimate partner violence
IRB: institutional review board
IRDO: Impact Research and Development Organization
LIVES: Listen, Inquire, Validate, Enhance Safety, and Support
MoH: Ministry of Health
MUERC: Maseno University Ethical Review Committee
NIH: National Institutes of Health
PI: principal investigator
PrEP: preexposure prophylaxis
REDCap: Research Electronic Data Capture
TFVdp: tenofovir diphosphate

Edited by A Schwartz; submitted 30.12.24; this is a non–peer-reviewed article;accepted 12.02.25; published 01.04.25.

Please cite as:
Roberts ST, Minnis AM, Napierala S, Montgomery ET, Digolo L, Cottrell ML, Browne EN, Ndirangu J, Boke J, Agot K
Evaluation of the Tu'Washindi Na PrEP Intervention to Reduce Gender-Based Violence and Increase Preexposure Prophylaxis Uptake and Adherence Among Kenyan Adolescent Girls and Young Women: Protocol for a Cluster Randomized Controlled Trial
JMIR Res Protoc 2025;14:e55931
URL: https://www.researchprotocols.org/2025/1/e55931
doi:10.2196/55931
PMID:

Protocol

Racial Disparities in Parkinson Disease Clinical Phenotype, Management, and Genetics: Protocol for a Prospective Observational Study

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Abstract

Background: Parkinson disease (PD) has been described and studied extensively in White populations, with little known about how the disease manifests and progresses in patients from the Black community. Studies investigating disease features in Black populations are uncommon, with some suggesting that the Black population with PD is more disabled and has greater disease severity and different clinical features compared with the White population with PD. These health disparities are likely to influence the quality of care for Black patients with PD.

Objective: This study aimed to investigate the motor and nonmotor symptoms and quality of life in Black and White participants with PD in a case-case design.

Methods: This is an observational, prospective, multicenter, case-case design study. Other aims will investigate the management of PD in Black individuals and the presence of shared or unique genetic risk factors among the Black PD population. A total of 400 Black and 200 White participants with PD will be recruited. Data will be collected at 7 US sites and entered into a Research Electronic Data Capture database. Linear multivariate regression analysis will be used, except for comparing PD management, which will be analyzed using the chi-square test or Fisher exact test. Bonferroni correction will be applied. This protocol also describes plans for educational programming for clinicians and patients at the end of the study in partnership with national PD organizations.

Results: The Rush Institutional Review Board approved the project as the single-site institutional review board in February 2022, and it was funded by the National Institute of Neurological Disorders and Stroke in April 2022. Recruitment began in July 2022. At the time of submission of this manuscript, 131 participants had been recruited.

Conclusions: To our knowledge, this is the largest study of PD phenotype and management in Black patients in the United States. The planned collaboration with the Global Parkinson's Genetics Program and PD GENEration will enhance our understanding of genetic risk factors for PD in this understudied population.

International Registered Report Identifier (IRRID): DERR1-10.2196/60587

(JMIR Res Protoc 2025;14:e60587) doi:10.2196/60587

KEYWORDS

Parkinson disease; racial disparities; clinical protocol; health disparities; genetic risk factors; quality of life; quality of care

Introduction

Background

Parkinson disease (PD) is a progressive and incurable neurodegenerative disorder affecting 1 million people in the United States [1]. Health care resource usage costs for patients with PD in the United States are high and rise 2 to 3-fold in individuals with advanced disease [2]. Our current understanding of PD is disproportionately based on studying populations of European ancestry, leading to a significant gap in our knowledge about the clinical characteristics, life experiences, functional outcomes, and pathophysiology in individuals of African descent. The cumulative incidence of PD in African Americans has been estimated at 23/100,000, compared with 54/100,000 in European Americans [3]. Direct comparison of Black and White patients suggests greater disability and disease severity in Black individuals [4], and our data suggest that quantitative measures may be more sensitive in detecting these differences [5]. Factors proposed to account for phenotypic differences include barriers to access to care and methodological confounds due to inconsistent diagnostic criteria or ascertainment bias [6-8]. It is also possible that population-specific genetic variation modifies PD risk and clinical manifestations of PD in Black individuals. Approximately 90 common susceptibility loci for PD and a growing number of rare gene variants are now well-established in White populations [9]. Still, the impact of these factors on the Black population is largely unknown.

In our pilot work, Black and White patients with PD participated in a clinical phenotyping study, and the results showed no significant differences between the groups in sex, education, disease duration, Hoehn and Yahr stage, or Movement Disorder Society-Unified PD Rating Scale (MDS-UPDRS) part III Motor scores [10]. However, quantitative NIH Toolbox performance measures detected differences in gait and balance between Black and White participants with PD: gait speed (0.8±0.3 vs 1.1±0.2, $P<.001$), pegboard (41.4±15.6 vs 33.2±10.9, $P=.04$, and standing balance (32.7±13.1 vs 47±12, $P<.01$) [5]. In the nonmotor assessments, the Montreal Cognitive Assessment (23.4±3.1 vs 27±2.1, $P<.005$) and Symbol Digits Modalities Test (39.4±14.1 vs 49.6±9.1, $P=.01$) scores were worse in Black participants after correcting for education level. Hamilton Depression scale scores were worse in Black participants with PD compared with White participants (7±5.6 vs 4±3.5, $P=.04$), but other neuropsychiatric scales were similar between groups. The PD Quality of Life (PDQ-39) scores were higher (worse) in Black participants with worse ratings in participation in social roles and activities.

In summary, this pilot data showed differences in the motor examination, nonmotor features, and quality of life of Black patients with PD that warranted the current larger study. In our previous work and this protocol, race is self-identified by the patient as Black or White. Traditionally in the Chicago metropolitan area, this includes Black patients who are African, Afro-Caribbean, African American, or who report a mixture of races.

Racial disparities in the clinical management of PD include inequitable access to care and disparities in therapeutic interventions. Previous studies show that Black individuals with parkinsonism are less likely to see a neurologist, have less access to telemedicine, and are less likely to receive treatment, including antiparkinsonian medication, surgical procedures, and rehabilitation therapy. Black patients are 30% less likely to see an outpatient neurologist for neurologic conditions [11], and both Black persons and those with lower socioeconomic status are less likely to receive specialized care for PD [4]. Compared with White persons with PD, Black patients with PD were 40% less likely to receive any rehabilitation therapy (physical therapy, occupational therapy, and speech therapy). Black persons with parkinsonism were less likely to be receiving any antiparkinsonian medication on their initial visit to a movement disorders center [12]. They were half as likely to receive newer antiparkinsonian medications but twice as likely to be on antipsychotic medication. African Americans were 4 times less likely to receive any treatment for PD (medication or physical therapy) in a cohort with the same health care insurance (Medicaid) [13], and White persons were nearly twice as likely to be prescribed medications for PD in a study of racial disparities in stroke (National Institute of Neurological Disorders and Stroke [NINDS] Reasons for Geographic and Racial Differences in Stroke study) [14]. African Americans were also found to be 5 to 8 times less likely to undergo deep brain stimulation surgery for PD than White patients [15,16]. Notably, racial disparities in access to care and clinical management are likely to be associated with adverse outcomes, including greater severity of Parkinsonian symptoms and greater disability [4].

Genetic susceptibility loci and genetic variants causing monogenic PD have been explored in populations of European, Latino, and Asian ancestry [17]. Based on preliminary work, it appears that the cumulative genetic risk for Black and African American patients with PD shows significantly different distributions compared with European populations when applying the genetic risk score composed of the 90 risk loci previously linked to European populations [17].

More recent work from the Global Parkinson's Genetics Program confirms this differential risk, identifying a novel genetic risk factor in *GBA1* in patients with PD of African ancestry [18]. This supports the need for additional work in this area.

Objective

The overall objectives of this study are to perform comprehensive phenotyping, compare Black and White persons with PD, and investigate causes of racial disparities, including differences in clinical management and responsible genetic risk factors. The study is partnering with the ongoing Global PD Genetics Program (GP2) [19], which contributes samples and granular phenotypic data from the enrolled participants to enhance our understanding of the genetic architecture of PD in

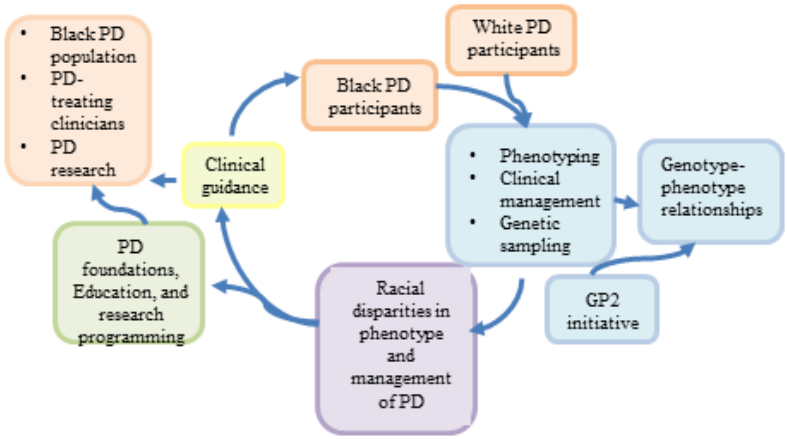
the Black population. The long-term goal of this application is to address the critical gap in knowledge of PD in this underserved population to improve diagnosis, optimize treatment, and plan for clinical trials. The central hypothesis is: PD is phenotypically and genetically different in Black versus White populations, and Black patients receive different and suboptimal clinical management. The research questions this study hopes to answer are as follows: (1) whether Black participants with PD have worse quantitative motor function and cognition, higher levels of depression and disability, and reduced quality of life compared with White participants with PD; (2) whether pharmacological, surgical, rehabilitation, mental health, and telehealth interventions differ by race with underuse of newer or more costly interventions in Black participants with PD; and (3) whether the contribution of genetic factors to PD risk and heterogeneity differs by race.

Methods

Overview

The overall strategy is to describe clinical phenotypes, genetic risk profiles, and treatment disparities in the American Black PD population and use the results to develop guidance for educating Black patients and their treating clinicians on how to prevent racial disparities in PD and foster future research opportunities in racial disparities and improve management (Figure 1). This is a multicenter, cross-sectional, case-case, nonrandomized, observational study.

Figure 1. Conceptual model. GP2: Global Parkinson's Genetic Program; PD: Parkinson disease.



Study Setting and Design

The 7 study sites are Rush University, University of Maryland, University of Cincinnati, University of Pennsylvania, University of Chicago, Emory University, and Morehouse University (Figure 2). The sites were chosen based on US census data showing higher populations of Black persons in these geographic regions. A total of 400 Black patients with PD and 200 White patients with PD will be recruited. Patients who consent to enroll will have a single study visit encompassing data and sample collection for all 3 aims. A virtual option can also be used to complete questionnaires, followed by an in-person visit for the remaining measures.

Figure 2. Overview of the organizational structure. GP2: Global Parkinson's Genetic Program; PD: Parkinson disease.

Eligibility Criteria

The eligibility criteria are intentionally broad to facilitate the inclusion of diverse samples and ensure the achievement of enrollment targets. Inclusion criteria include age >18 years and fulfilling the Movement Disorder Society Clinical Diagnostic Criteria for Parkinson's Disease [20]. Patients must self-identify as being Black or White race. Patients must also be able to sign an evaluation to sign consent [21] or have a legally authorized representative (LAR) sign on their behalf. Exclusion criteria include insufficient English to complete study activities or inability to meet idiopathic PD criteria. Eligibility criteria are broad to include representative samples and ensure meeting enrollment targets.

Recruitment and Screening Strategies

Recruitment will occur in the outpatient movement disorder clinics at the 7 study sites. Treatment clinicians or study coordinators will approach potential participants to discuss participation. Potential participants will be identified by prescreening medical records or by referral to the treating provider. Each White participant was initially matched to be within 5 years of age of the mean age of every 2 Black participants enrolled at the same site. Each time 2 Black

participants were enrolled at a site, the study statistician would contact the site with the age range of the next White participant. Part-way through the study, propensity matching replaced this manual process. Potential participants will be interviewed to determine if they meet the eligibility criteria for enrollment.

Black patients with PD have been underrepresented in clinical research [22]. Therefore, study planning includes targeted strategies to facilitate recruitment and foster participant satisfaction with research participation. An advisory board of 6 individuals comprised of Black individuals with PD and family members of affected individuals assists in developing outreach strategies and providing feedback on their study visit experience, with protocol modifications as needed. The patient advisory board members will have participated in the study at 1 of the study sites. Educational strategies include initiatives for both study participants and study staff. A brief video and flip charts with culturally appropriate information are used to improve understanding of participation in research, including the informed consent process [23]. Participation of Black study coordinators is encouraged to foster rapport and cultural sensitivity. Teaching cross-cultural sensitivity is part of the prestudy and annual activities for all site investigators and coordinators [24]. Barriers to recruitment and enrollment will be explored, with each enrolled participant completing a Participations in Clinical Trials Questionnaire that includes a question on barriers to research participation [25]. During quarterly Steering Committee meetings with all site investigators, recent publications on minority recruitment and research are reviewed with the study author.

Study Assessments and Outcome Measures

Study participants will have a single visit with the site investigator and coordinator after obtaining consent or a hybrid combination of in-person and virtual visits. Recommendations of the NINDS PD CDE Working Group informed the choice of measures, scales, and questionnaires. Data will be collected and entered into a REDCap (Research Electronic Data Capture) system that uses electronic data entry forms. General assessments include demographic data (age, sex, education, and income), medical history, and a confirmatory neurological examination. The remaining assessments fall into 3 categories, namely motor and nonmotor symptoms (Table 1), quality of life and social determinants of health (Table 2), and management of PD (Table 3, Multimedia Appendix 1).

Table 1. Motor and nonmotor measures for phenotyping.

Data type or domain and measure or instrument	Description
Parkinson disease severity	
MDS-UPDRS[a] parts I to IV[b]	Revised, improved version of the MDS-UPDRS for use in PD[c] studies [26]
Hoehn and Yahr stages	Common system for staging PD [27]
Physical function	
2-minute walk, 4-meter gait speed, 9-hole pegboard, grip strength, and balance test[b]	To quantitate physical performance relative to available age and gender norms [28]
Functional reach	A single-item assessment of balance [29]
Schwab and England Activities of Daily Living Scale	A single-item rating of independent function [30]
PROMIS Profile-29 Physical Function version 2.0 4a[b]	Measure of disability [31,32]
Cognitive function	
Montreal Cognitive Assessment version 8.3[b]	Detects mild cognitive impairment in PD [33,34]
Benton Judgment of Line Orientation 15-items	Measure of spatial perception and orientation [35,36]
Hopkins Verbal Learning Test	Test of verbal short-term memory requiring rapid encoding of information [37]
Digit span	Measure of verbal working memory [38]
Semantic fluency	Measures semantic fluency using animal categories [39]
Symbol Digit Modalities Test[b]	Screens for cognitive impairment [40]
Mental health	
PROMIS Profile-29 depression, anxiety	Measures depression and anxiety
Pain	
PROMIS Profile-29 Pain Interference version 1.1	Measures pain interference with daily life [41]
PROMIS Profile-29 Pain Intensity version 1.0	Measures severity of pain
Sleep	
Epworth Sleepiness Scale	Measures daytime sleepiness in adults [42]
PROMIS Profile-29 version 1.0 Sleep Disturbance 4a, PROMIS Profile-29 version 1.0 Fatigue 4a	Measures sleep disturbance and fatigue [43,44]
Autonomic	
Scales for Outcomes-PD Autonomic[b]	Measures autonomic function [45]

[a]MDS-UPDRS: Movement Disorder Society Unified Parkinson's Disease Rating Scale.

[b]Minimum dataset.

[c]PD: Parkinson disease.

Table 2. Quality of life and patient health expectations measures.

Data type or domain and measure or instrument	Description
Health-related quality of life	
The Parkinson's Disease Questionnaire-8[a]	PD[b]-specific quality of life scale [46]
Patient health expectations	
Expectations Regarding Movement Scale	Expectations regarding movement with aging [6]
Participation in medical research	
Trust in Medical Researchers Scale	Likelihood of participation in medical research [47]
Social determinants	
PROMIS Informational Support version 2.0 4a	Measures access to information and resources [48]
Health Stressors Rush Survey	Covers food security, utilities, insurance, transportation, and housing instability
PROMIS Profile-29 Ability to Participate in Social Roles and Activities version 2.0 4a	Measures satisfaction with social roles and activities [48]

[a]Minimum dataset.

[b]PD: Parkinson disease.

Table 3. Study assessments for management of Parkinson disease.

Data type or domain and measure or instrument	Description
Pharmacological management	
Parkinson's Disease Medications Questionnaire[a]	Antiparkinsonian drugs[a]
Prescribed Non-Parkinson's Medications Questionnaire[a]	Non-Parkinson drugs
Unprescribed Drugs Questionnaire	Vitamins, dietary supplements, alternative therapies, recreational drugs, drugs of abuse
Surgical management	
Surgical Questionnaire[a]	DBS[b], FUS[c]
Rehabilitation therapy	
Rehabilitation Referral Questionnaire[a]	Physical, occupational, speech therapy
Godin Leisure-Time Exercise Questionnaire, Activity Questionnaire	Exercise and activity [49]
Mental health and social services	
Mental Health and Social Services Referral Questionnaires[a]	Psychiatrist, psychologist, social worker
Telehealth use and acceptance	
Telehealth Use and Acceptance Questionnaire[a]	Perceived usefulness and ease of use [50]
Participation in clinical trials	
Participation in Clinical Trials Questionnaire	Clinical trial participation and barriers to participation
History of treating clinicians for PD	
History of treating clinicians for Parkinson's disease[a]	Number and types of clinicians, medical visit frequency
Medical comorbidities	
Cumulative Illness Rating Scale-Geriatrics (CIRS-G)[a]	Medical comorbidities [51]
Self-efficacy	
PROMIS Self-Efficacy for Management of Chronic Conditions	Self-efficacy for managing daily activities, symptoms, medications, and emotions [52]
Health literacy	
Rapid Estimate of Adult Literacy in Medicine	Health literacy [53]
eHealth Literacy Scale	eHealth literacy [54]

[a]Minimum dataset.

[b]DBS: deep brain stimulation.

[c]FUS: focused ultrasound.

Participants who used a LAR for consent can complete assessments with assistance from a research assistant or proxy (care partner). All scales and questionnaires include a check box to document proxy assistance. The scales are administered by the neurologist (site investigator), study coordinator, or other staff as appropriate. The investigator completes the following assessments: MDS-UPDRS [26], Hoehn and Yahr Staging [27], Schwab and England Activities of Daily Living Scale [55], and the Cumulative Illness Rating Scale [51]. The investigator will also complete a questionnaire for the GP2 study that includes demographic and disease-specific information, such as disease duration. The study coordinator administers the rest of the study assessments.

Participants have blood samples drawn and sent to the National Institutes of Health for genetic studies. All participants are also offered enrollment into the Parkinson's Foundation PD GENEration study in which seven PD genes are examined and results are disclosed to the participant. If the participant consents, an additional blood sample is shipped to the PD GENEration sequencing vendor (Fulgent Genetics). For these participants, genetic counseling, including results disclosure, is performed by either a PD GENEration genetic counselor from Indiana University or the genetic counselor at the Rush University site (either live or through telemedicine).

To optimize recruitment, all Black patients with PD are eligible for enrollment regardless of physical or cognitive impairment level. Therefore, not all patients can complete all study assessments. A minimum dataset, including the primary outcome measures, must be completed, as well as the sample collected for all study participants. The recommended order of study assessments prioritizes outcome measures such that primary outcome measures are completed first, cognitive measures are

completed early, and the minimum dataset for all study aims is collected. When a participant cannot complete all study assessments, the site investigator must be contacted. The investigator and coordinator should arrive at a consensus about what assessments will be omitted, and coordinators should record the omitted assessments. The patient can only complete selected study assessments (no proxy assistance permitted), including the cognitive assessments and the "Rapid Estimate of Adult Literacy in Medicine" [25].

Outcome Measures

The primary outcome measures to characterize PD phenotypes include the NIH Toolbox Motor assessments (2-minute walk, 4-meter walk, balance test, pegboard test, and grip strength) [28]; the Montreal Cognitive Assessment (MoCA), Symbol Digit Modalities Test (SDMT), PROMIS Profile-29 Physical Function, Parkinson's Disease Questionnaire-8 (PDQ-8), and the MDS-UPDRS. The primary outcome measures to assess PD clinical management include the proportion of participants with antiparkinsonian medications prescribed at the initial visit to the neurologist, the proportion of participants with initial treatment of depression, and the proportion of participants with PD surgical interventions. To characterize genetic risk variants in our sample, the frequencies of the 90 established common PD genetic risk variants based on published genome-wide association studies in a predominantly White population will initially be examined. The study team will also aggregate and summarize sequencing results from PD GENEration, including potential rare variants among 7 established PD genes. The proportion of LRRK2- and GBA-PD will be summarized based on either PD GENEration, which permits comprehensive detection of potential pathogenic alleles, or GP2 genotyping, which can detect many of the most common, recurrent pathogenic variants. Finally, exploratory genotype–phenotype analyses will determine whether established PD risk variants modify clinical manifestations in Black individuals.

Sample Size

The sample size was calculated for each primary outcome measure described above with 80% power and a 2-sided test to detect a similar effect size observed from our pilot data (Table 4). Bonferroni correction was applied to control the overall significance level at .05. The minimal sample size for these analyses requires 365 Black and 183 White participants to complete this aim. The data observed in 3 studies guided the sample size calculation for PD clinical management (White vs non-White or Black: 78% vs 62% for measure 1 [4], 92% vs 80% for measure 2 [56], and 10% vs 0.4% for measure 3 [57]). The sample size was calculated using 90% power and a 2-sided test for each primary measure. Bonferroni correction was applied to control the overall significance level at .05. With a 1:2 ratio, the largest sample size required among all 3 measures is 173 White patients with PD and 346 Black patients with PD. For the genetic studies, our sample size will permit exploratory analyses, and all data will be contributed to GP2 for fully-powered meta-analysis.

Table 4. Pilot data effect sizes for sample size calculation.

Primary measures	White patients with PD[a] (n=25), mean (SD)	Black patients with PD (n=25), mean (SD)
4-meter walk computed score	1.1 (0.2)	0.8 (0.3)
Balance *t* test score	47 (12)	32.7 (13.1)
Pegboard dominant score	33.2 (10.9)	41.4 (15.6)
MoCA[b]	27 (2)	23.3 (3.1)
SDMT[c]	49.6 (9.1)	39.4 (14.1)
PDQ-39[d]	12.8 (7.9)	22.5 (12.3)

[a]PD: Parkinson disease.

[b]MoCA: Montreal Cognitive Assessment.

[c]SDMT: Symbol Digit Modalities Test.

[d]PDQ-39: Parkinson's Disease Questionnaire.

Data Collection and Monitoring

The co-principal investigators (DH and LS), core administrative, and coordinating personnel meet weekly to identify potential issues with consent or assessment procedures, manage any reported adverse events, and monitor the sites' progress. The REDCap database created to house the data is audited weekly to ensure fidelity. All study data are directly entered into the REDCap database in real time unless internet connectivity is an issue at the site.

Statistical Analysis

Each primary outcome measure will be compared between Black and White patients with PD. Bonferroni correction will be applied. The primary outcome measures are a 4-meter walk computed score, Balance test *t* score, Pegboard dominant *t* score, MDS-UPDRS motor score [26], MoCA [33], SDMT [58], PROMIS Profile-29 Physical Function, and PDQ-8 [46]. For significant measures, linear regression analysis will be performed to examine further the difference between the 2 groups with adjustment for age, sex, and disease duration. The interaction effects of race with these 3 variables will be explored. Regression analysis for cognitive measures will adjust for depression and anxiety scales in addition to these demographics. Regression will also be adjusted for comorbidities using the Cumulative Illness Rating Scale-Geriatrics score. The study site effect will be controlled as a random effect in the model. All analyses will be done using SAS (version 9.4).

For the PD management analysis, each primary outcome measure will be compared between Black PD and White PD groups using the chi-square test or Fisher exact test. Bonferroni correction will be applied. A hierarchical logistic regression analysis will assess the determinants of racial disparities in management. Besides race, age, sex, and education, income, symptom severity, and comorbidities will be included in the model. The interaction effect of race with those variables will be explored. The study site effect will be controlled as a random effect in the model. Secondary analyses will investigate differences between White PD and Black PD groups in other clinical management measures, including telehealth, participation in clinical trials, and rehabilitation therapy.

Genetic Analysis

This study will leverage a quality control and analysis pipeline established for the GP2 program. After standard quality control of raw genotyped data, data will be imputed to the most recent build of the multiethnic 1000 genomes reference panel using the default settings of miniMac2. This will yield ~15 million variants to test after additional quality control. These data will be contributed to GP2 for genome-wide association meta-analysis and admixture mapping. Within the RaDPD sample, ~90 currently established common PD risk variants to examine frequencies will be extracted. For analyses of PD genetic modifiers, linear regression—with an initial focus on outcome phenotypes with established evidence from the published literature, including age of onset, motor progression, and cognition—will be performed [59-65]. These outcomes will be supplemented with the most promising outcomes based on the results from aim 1 analyses identifying clinical features that differentiate PD in Black versus White patients. Sequencing results will be available for participants in PD GENEneration for 7 genes associated with PD: *GBA*, *LRRK2*, *PRKN*, *SNCA*, *PINK1*,*PARK7*, and *VPS35*. Comprehensive genome sequencing of all samples is planned for a future project.

Ethical Considerations

This study was approved by the Rush Institutional Review Board (IRB; ORA 20121005), which serves as the single-site IRB for this study. Each participant will sign a consent form, which includes blood and genetic analysis, before participation. Each participant also signs permission for the DNA results from sequencing to be housed in the PDGeneration database and the National Institutes of Health (deidentified) through GP2. If the participant requests genetic results, they are identifiable to PDGeneration, facilitating the return of results. Potentially vulnerable study populations are patients with cognitive impairment and socioeconomic disadvantages. Given the study aims to investigate racial disparities in the phenotype–genotype differences between Black and White patients with PD, it is necessary to include these populations. Study participants must be able to provide informed consent as determined by the Evaluation to Sign Consent to confirm they understand the risks and benefits and can provide their informed consent. This low-risk study does not present a greater risk to potentially vulnerable populations. Given the short duration of this study (1 study visit), it is not expected that significant cognitive decline will occur throughout the study to impact a participant's ability to provide ongoing consent. Participants unable to achieve a passing score on the Evaluation to Sign Consent will be excluded unless a LAR is present to provide consent.

A human subjects research ethics review will occur at the time of IRB approval. The informed consent process occurs with the study team live during the study visit. Data are entered directly into a password-protected, Health Insurance Portability and Accountability Act–compliant REDCaP database, with the participant having an assigned site-specific study ID. Participants are compensated US $100 for the study visit plus US $25 for travel expenses, and some sites arrange transportation with established institutional programs.

Results

The Rush IRB approved the project as the single-site IRB in February 2022 and funded by NINDS in April 2022. Recruitment began in July 2022. At the time of submission of this manuscript, 131 participants had been enrolled. One of the original study sites has been replaced by a new site due to issues with regulatory approval. Other activities have included quarterly steering committee and monthly coordinator meetings. Steering committee meetings include discussing recent publications and speakers focused on racial disparities.

Discussion

Study Rationale

The study rationale is that the knowledge gained will improve clinical diagnosis and management for Black persons with PD, drive programming to improve access to care and management, and inform research strategies in PD in the Black community. It is anticipated that the main findings of this study will be that Black patients with PD will have more gait abnormalities and higher rates of genetic variants for PD specifically seen in the Black population. It is also anticipated that Black individuals with PD will be less likely to have been referred or have access to specialized care for PD, including surgical treatments and nonmedication therapies. This protocol was structured as a one-time visit to encourage participation and to optimize the likelihood of full data collection. Aim 3 is a collaborative effort with the Global Parkinson's Genetics Program (GP2), a worldwide consortium funded by the Aligning Science Across Parkinson's initiative to understand the genetic architecture of PD. This collaboration enables samples collected in this study to be part of a larger gene discovery effort with investigators from African and Afro-Caribbean patients with PD to foster a greater understanding of genetic variation specific to the Black population [17]. This study fills a unique niche by performing deep phenotyping to study racial disparities and analyze genotype–phenotype relationships in PD.

The recruitment of Black patients into research studies is historically much lower than White patients [22]. Contributory factors include distrust owing to historical research abuse and institutional racism, lack of information and understanding of research studies and informed consent, insufficient recruitment efforts by researchers, social stigma, and financial considerations [66]. In 1993, the National Institutes of Health established the

Revitalization Act, which mandated minority inclusion in randomized clinical trials. An important strategy to promote study recruitment in both Black and White patients with PD is raising awareness of previous studies showing evidence of racial disparities in access to care, disease features, and clinical management.

A potential barrier to participation in PD research is motor and cognitive impairments, present in patients with PD of all racial and ethnic backgrounds. To accommodate the needs of patients with more severe motor and cognitive impairment, the protocol was designed to allow for the collection of a "minimum dataset." The goal is to complete as many study assessments as possible. However, implementing more limited data collection will enable the successful completion of enrollment targets and ensure the inclusion of a representative range of disease severity. The typical time of the study visit is between 3 to 6 hours, and more limited data collection, focused on the primary outcome measures for each of the study aims, reduces the visit time to 1 to 2 hours.

Conclusions

Many unique challenges arise in clinical research in the Black PD community, but the importance of understanding racial disparities warrants focus on this population. Given what little is known about how PD manifests in Black patients, this will be the most comprehensive study of the phenotype and management of PD in the US Black population, with the potential to improve clinical diagnosis and management and to foster future research directions. It is not clear what the true implications of the study will be, but improvement of study recruitment in this population, education of patients, caregivers, and clinicians on disparities, and ultimately, changes in practice will drive the final impact of the study and drive health policy recommendations at a national level.

Acknowledgments

The authors thank all the patients and caregivers participating in the RaDPD study and colleagues at the collaborating sites for recruitment. This research is supported by the National Institutes of Health/National Institute of Neurological Disorders and Stroke R01 NS125294. The authors would like to acknowledge RaDPD study group members: DH, Bichun Ouyang PhD, MHST, Sharlet Anderson PhD, David Gonzalez PhD, Jacob Hawkins MS, Staci Davis BS (Rush University); LS, Rebecca Weimer BS, Christina Griffin MS (University of Maryland); Alberto Espay MD, Emily J Hill MD, Kelly DeLano MS, Lauren Wingler BS, Ayesha Shaik (University of Cincinnati); Nabila Dahodwala MD, Whitley Aamodt MD MPH MSCE, Amanda Cruz BS, Ritikha Vengadesh BE (University of Pennsylvania); Stewart Factor DO, Elaine Sperin LPN (Emory University); Tao Xie MD PhD, Tomas Mercado BS, Crystal Mercardo BS (University of Chicago), Chantale Branson MD, Tamiko Durham MS (Morehouse University); Josh Shulman MD PhD (Baylor University); SBC, and AS (National Institutes of Health).

Data Availability

The datasets generated and analyzed during this study will be available upon reasonable request. These will be distributed to individual investigators on approval of the principal investigators (distribution costs covered by the requesting investigator). The study teams will use common data elements and a REDCap system to maximize the ability to share these data. Other products of the blood samples (serum, etc) may be shared if there are remaining samples. Research results will be disseminated publicly through publication in scientific journals and in the context of scientific meetings at which project findings will be reported. Such data publication will occur during the term of the project or after its conclusion, as appropriate and in keeping with normal scientific practices for reporting results.

Authors' Contributions

DH and LS conceived the program and wrote the protocol with JH's help. JS, SBC, AS, and RaDPD study group members provided ongoing critical review. BO aided in sample size calculation and analyses. DH and MHST drafted the manuscript, and all authors reviewed and approved the final version.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Instruments, measures, and scale information.
[DOCX File , 22 KB - resprot_v14i1e60587_app1.docx]

Multimedia Appendix 2
Peer-review report from the Clinical Neuroscience and Neurodegeneration Study Section (CNN) - Brain Disorders and Clinical Neuroscience Integrated Review Group - Center for Scientific Review (National Institutes of Health, USA).
[PDF File (Adobe PDF File), 78 KB - resprot_v14i1e60587_app2.pdf]

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Abbreviations

GP2: Global Parkinson’s Genetic Program
IRB: Institutional Review Board

LAR: legally authorized representative
MOCA: Montreal Cognitive Assessment
NINDS: National Institute of Neurological Disorders and Stroke
PD: Parkinson disease
PDQ-39: Parkinson's Disease Quality of Life
REDCap: Research Electronic Data Capture
SDMT: Symbol Digit Modalities Test

Edited by T Leung, D Khajeei; submitted 15.05.24; this is a non–peer-reviewed article;accepted 30.09.24; published 07.04.25.

Please cite as:
Hall DA, Shulman JM, Singleton A, Bandres Ciga S, S Tosin MH, Ouyang B, Shulman L
Racial Disparities in Parkinson Disease Clinical Phenotype, Management, and Genetics: Protocol for a Prospective Observational Study
JMIR Res Protoc 2025;14:e60587
URL: https://www.researchprotocols.org/2025/1/e60587
doi:10.2196/60587
PMID:

Protocol

Methadone Patient Access to Collaborative Treatment: Protocol for a Pilot and a Randomized Controlled Trial to Establish Feasibility of Adoption and Impact on Methadone Treatment Delivery and Patient Outcomes

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Abstract

Background: Access to methadone treatment can reduce opioid overdose death by up to 60%, but US patient outcomes are suboptimal. Federally allowed methadone treatment accommodations during the COVID-19 public health emergency were not widely adopted. It is likely that staff-level characteristics such as trauma symptoms influence the adoption of treatment innovation.

Objective: Methadone Patient Access to Collaborative Treatment (MPACT) is a 2-phased project (pilot and field trial) to develop and test a staff-level, multimodal intervention to increase staff adoption of low-barrier, patient-centered methadone treatment practices and ultimately improve treatment retention and patient outcomes.

Methods: A pilot and national trial will measure implementation feasibility, acceptability, and effects of the MPACT intervention on treatment practice change, clinic culture, patient retention, and patient posttraumatic stress symptoms (PTSS). The pilot will be a single-arm 5.5-month pilot study of MPACT conducted in 2 Arizona methadone treatment clinics (rural and urban) among 100 patients and 22 staff. The national trial will be a 20-month cluster randomized trial conducted among 30 clinics, 600 patients (20 per clinic), and 480 staff (18 per clinic). Data will be gathered by staff and patient surveys and patient chart review. The primary study outcome is increased patient methadone treatment retention measured as (1) time to first treatment interruption from study enrollment; (2) active in treatment at enrollment, day 30, 60, 90, and 120; and (3) continuous days in treatment during

the study period. Secondary study outcomes include reductions in vicarious trauma and PTSS among enrolled opioid treatment program staff and PTSS among enrolled patients.

Results: The pilot study was funded by the National Institute on Drug Abuse (award R61DA059889, funded September 2023), and the field trial will be funded under the associated R33 mechanism in September 2025. The pilot study was completed in March 2025. The randomized controlled trial will begin in December 2025. Both the pilot and trial have been approved by the University of Arizona Human Subjects Protection Program and have been registered with the clinical trials network.

Conclusions: The MPACT study will provide a foundation for an evidence-based, staff-level intervention aimed at improving patient retention in methadone treatment. Future studies should examine the individual components of MPACT to determine their differential contributions to the primary outcome of patient methadone treatment retention and to secondary outcomes of staff and patient reduction in stress symptoms.

Trial Registration: ClinicalTrials.gov NCT06513728; https://clinicaltrials.gov/study/NCT06513728 and ClinicalTrials.gov NCT06556602; https://clinicaltrials.gov/study/NCT06556602

International Registered Report Identifier (IRRID): DERR1-10.2196/69829

(JMIR Res Protoc 2025;14:e69829) doi:10.2196/69829

KEYWORDS

methadone; implementation; patient-centered treatment; opioid use disorder; posttraumatic stress symptoms; vicarious trauma

Introduction

Background

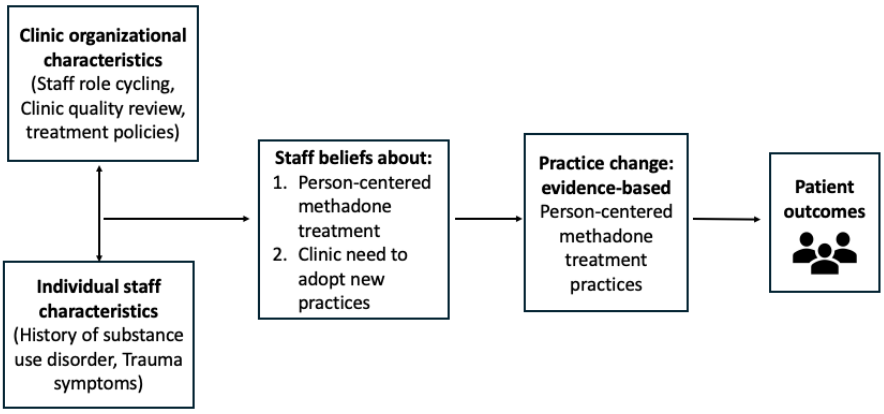
Methadone is one of the most essential tools available to reduce opioid overdose deaths because it is safe, effective, and patient-preferred for the treatment of opioid use disorder (OUD) [1-3]. Access to methadone, one of 2 safe and effective OUD treatments, can reduce overdose mortality by up to 60% [4,5]. However, the promise of methadone is significantly diminished by geographic maldistribution of clinics and variations in the delivery of methadone maintenance treatment (MMT) across the country [6-8]. Treatment variations likely produce the observed wide-ranging MMT retention rates (30%-84%) [9,10].

MMT in the United States is delivered only by opioid treatment programs (OTPs; "methadone clinics") certified and accredited by the federal government [11]. Variation in treatment quality and access maldistribution means that the impact of poor MMT outcomes is felt most acutely in rural communities as well as among populations who are Black, Hispanic, or Indigenous [12]. Unlike other health care environments, OTPs serve a daily average of more than 100 people in a narrow time window [13] and have been described as feeling "like bus stations" [14] rather than medical clinics. OTPs have been criticized as being unresponsive to patient need for treatment flexibility [15] and are not equipped to address what we know to be higher rates of patient trauma exposure and posttraumatic stress symptoms (PTSS) compared to the general population [16,17]. While MMT outcomes can be impeded by patient trauma [18], it is also possible that poor MMT outcomes and patient trauma are exacerbated by OTP practice and culture [19,20]. Patients report disenfranchisement from treatment decision-making through language referring to dosing as "privileges," staff behavior described as "carceral" [21], and being tied to the OTP by "liquid handcuffs" due to daily required in-clinic supervised dosing [22].

Policy and systems evolution is occurring to improve the way MMT is delivered in the United States. Unprecedented US regulatory change during the COVID-19 public health emergency [23] and again in February 2024 [11] permitted and then further clarified methadone dosing and delivery flexibility so that treatment was more individualized and patient-centered. However, as has been observed, policy changes during the COVID-19 public health emergency were insufficient to ensure sustained changes [24-26]. This is likely the result of multiple factors hindering the implementation of MMT innovation. Implementation science suggests that in addition to the outer setting factor of federal policy, there are inner setting factors that likely influence the adoption of MMT treatment innovation [27]. These include clinic organizational characteristics and culture as well as staff characteristics and staff beliefs. Figure 1 displays our current thinking about hypothesized relationships between and among inner setting factors, adoption of innovation, and patient outcomes.

Staff trauma is one particular inner setting factor that is linked to the adoption of innovation and quality of treatment delivery. A preliminary study by several authors here suggests that OTP staff trauma may play a central role in shaping clinic culture and methadone treatment practice changes [14]. Evidence from studies among other types of health professionals demonstrates that vicarious trauma (VT), or work-related trauma (ie, coexperiencing patient distress and change in worldviews because of ongoing distress), is associated with reduced staff empathy and increased PTSS [28]. VT outcomes include burnout, reduced patient empathy and compassion satisfaction, low morale, impaired clinical decision-making, and compromised patient care [29-31]. The only extant study of OTP staff trauma histories and symptoms found that 63% of staff exhibited PTSS at clinical levels, indicating a need for treatment [32]. Therefore, a potential strategy to facilitate the adoption of MMT innovation is to implement staff-level interventions aimed at reducing PTSS and VT while providing training about low-barrier, patient-centered methadone treatment.

Figure 1. Potential inner setting factors impacting methadone treatment outcomes.



To this end, we developed Methadone Patient Access to Collaborative Treatment (MPACT): a multimodal intervention to increase staff awareness of and readiness to adopt MMT treatment innovation. MPACT promotes treatment flexibilities allowed by federal regulators and patient-centered, trauma-informed MMT and seeks to empower OTP staff and clinic groups to adopt these treatment flexibilities by addressing staff VT and PTSS, which will improve treatment quality and ultimately MMT retention. The objective of this study is to test the adoption, feasibility, and impact of MPACT on methadone treatment delivery and patient outcomes. There are 6 specific aims for the MPACT study over the 6-year project period. The specific aims are listed here and will be described in the following subsections.

Phase 1, Years 1-2: MPACT Intervention Development and Pilot Testing

Phase 1 aims (1) to develop MPACT through multilevel, iterative planning with methadone clinic staff and people with recent methadone treatment experience; (2) to determine MPACT implementation feasibility, acceptability, and preliminary effect on methadone treatment practice change and clinic culture; and (3) to determine the preliminary effect of MPACT on methadone treatment retention and patient PTSS.

Phase 2, Years 3-6: Hybrid, Cluster Randomized Controlled Trial

Phase 2 aims (4) to quantify the effects of MPACT on methadone treatment practice change and clinic culture, (5) to determine the efficacy of MPACT on methadone treatment retention and patient and staff PTSS outcomes, and (6) to evaluate the effect of patient and staff trauma on primary outcomes and staff MPACT implementation.

Methods

Ethical Considerations

The MPACT study protocol and related documents were reviewed and approved by the University of Arizona Human Subjects Protection Program (pilot: #STUDY00003631 and trial: #STUDY00005677), the single institutional review board overseeing all sites participating in the study: University of Arizona, Indiana University, Western Michigan University, and Columbia University. All participants will engage in a web-based informed consent process prior to study enrollment. The consent will be downloaded and retained by the study as documentation. Patient participants will consent to both survey participation and the release of specified elements of their clinic medical record for the purpose of the study. Confidentiality of staff and patient participants in the enrolled MPACT clinics will be preserved by making every effort to prevent the clinic leadership and staff from knowing which patients are enrolled as study participants and keeping clinic leadership and patients from knowing which staff are enrolled as study participants. Unique identifiers will be created at the time of enrollment and used throughout the study period. All study personnel (staff and investigators) have been trained in human participant protection through the completion of Social Behavioral Research and Biomedical Research modules with the Collaborative Institutional Training Initiative program and the completion of conflict of interest training and have annually declared conflicts of interest for review by the University of Arizona Human Subjects Protection Program. All reported data will be aggregated and deidentified. All information will be stored in a secure and encrypted drive and accessible only by the principal investigator (BEM) and the study coordinator (SY). The study was registered under ClinicalTrials.gov (NCT06513728 for the phase 1 pilot and NCT06556602 for the phase 2 trial). Participants will be offered financial remuneration totaling US $100 for the completion of all 5 surveys on time and during the pilot study period and US $160 for the completion of surveys on time and during the trial study period.

Phase 1, Years 1-2: MPACT Intervention Development and Pilot Testing

Overview

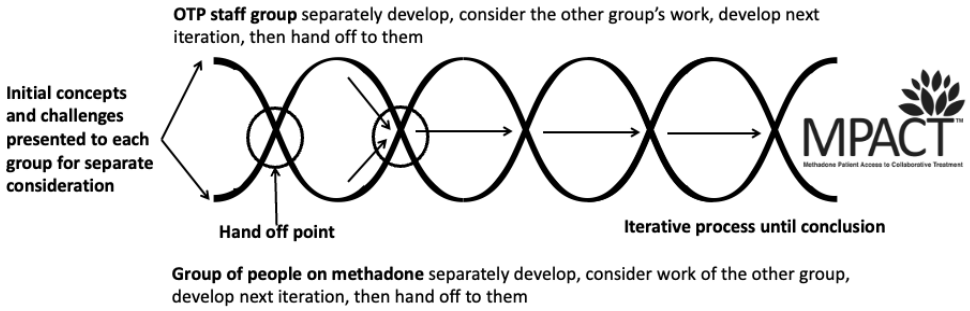
- Aim 1: Develop MPACT through multilevel, iterative planning with methadone clinic staff and people with recent methadone treatment experience.

MPACT is an experimental intervention comprised of 4 evidence-based components adapted by a group of people who have been in methadone treatment within the past 5 years in Arizona, a group of OTP staff in all clinic roles (front desk, peer support staff, case management, counseling, clinical supervision, medical, and administrative) from 3 Arizona OTPs (2 urban and 1 rural), and a group of subject matter experts focused on clinical supervision, human resources, and employee education.

The adaptation of MPACT components was accomplished through an iterative codevelopment process involving OTP staff and methadone community (patient) groups. The creation of a trauma-informed codevelopment space was crucial to facilitate safer and more open discussions. To accomplish this, we established a parallel, intervention refinement process using a helical structure developed by this team and based on our prior research with structural indicators for community-based participatory action research [33]. As shown in Figure 2, the "hand off" of work drives an iterative (helical) thinking process. This structure provides distinct spaces for thoughtful dialogue within and between each group.

The outcome of the codevelopment process was a robust multimodal intervention (MPACT) comprised of the following 4 elements.

Figure 2. Trauma-informed, collaborative development structure to refine MPACT components. MPACT: Methadone Patient Access to Collaborative Treatment; OTP: opioid treatment program.



Accredited Psychoeducational Training

A jointly accredited, self-paced, 3-module psychoeducational training focused on (1) the definition and application of low-barrier, patient-centered, trauma-informed methadone treatment; (2) public and clinic policy (federal and state); and (3) clinic staff opportunities to increase patient-centered, trauma-informed methadone treatment. The training seeks to empower staff to initiate any positive change at the individual and staff group levels. Joint accreditation offers continuing medical education for physicians and nurses as well as continuing education credits for social workers, psychologists, peer support specialists, case managers, and administrators. Training completion is incentivized by the award of 3 free continuing education credits according to professional discipline. While training is voluntary, to receive the continuing education credits, staff of MPACT-enrolled clinics must complete the training within 2 weeks of the MPACT launch within the clinic. New staff can complete the training as they are hired during the MPACT intervention period. This modular training approach was adapted from a prior successful project focused on increasing pharmacy syringe sales to people who use drugs [34].

Staff Wellness Education and Assessment

All staff in MPACT-enrolled clinics will receive training about trauma exposure and reactions, trauma-informed methadone treatment, availability and modalities of trauma treatment, and VT through curated presentation materials. These materials will be accessible to all staff through an MPACT web portal and through training or communications as determined by the enrolled clinics. The training materials include video and visual content designed for easy integration into clinic employee training, onboarding, or as refresher training. As part of the training, staff will be introduced to an anonymous web-based "wellness" screener, which includes an 8-item posttraumatic stress disorder symptoms screener (Posttraumatic Stress Disorder Checklist [PCL-5]) [35,36] and an 8-item Vicarious Trauma Scale [37]. Individual screening outcomes (results) trigger a curated and immediately presented message regarding self-care, referral to the VA PTSD Coach [38,39] (a downloadable, free application) and referral to the employee assistance program offered as a behavioral health benefit to employees where indicated. Employees will have access to wellness training throughout the MPACT intervention period and can use the self-screener repeatedly if desired. The screener will also be "advertised" in staff-only areas with a curated poster on stress, including a link or QR for easy access.

Trauma-Informed Clinic Self-Assessment

A trauma-informed clinic self-assessment (TICA) will be conducted quarterly during the study period. TICA assessment outcomes are generated by data from aggregated responses to a 16-item anonymous survey of staff measuring staff development, available resources, support, safe physical environments, trauma-informed policies, and patient-centered practices specific to methadone clinics. Items were selected and modified by the study team using an organizational trauma-informed practice tool as a reference instrument [40]. Summarized results are discussed with clinic leadership who will decide how and when to share them with clinic staff.

Reflective Supervision Consultation

Reflective supervision is an evidence-based professional development intervention focusing on the relationship and process of collaborative case consultation and reflection for clinicians providing psychosocial support [41,42]. Reflective supervision provides strategic guidance to increase self-reflectiveness and self-awareness and encourages participants to independently process clinical encounters and solve challenges. These skills have been shown to improve patient care [43,44]. To our knowledge, there are no existing reflective supervision consultation models tailored to OTP staff. Therefore, we adapted the standard reflective supervision practices to apply and be accessible to all OTP staff who have intensive and consultative interactions with patients. These staff roles include case managers, counselors, and peer support. Reflective supervision will begin in month 1 of the intervention period and will continue on a biweekly basis throughout the

intervention period for each MPACT-enrolled clinic. Sessions are facilitated by a trained reflective supervisor who will also be trained by the MPACT study clinician.

- Aim 2: Determine MPACT implementation feasibility, acceptability, and preliminary effect on methadone treatment practice change and clinic culture.
- Aim 3: Determine the preliminary effect of MPACT on methadone treatment retention and patient PTSS.

A single-arm 5.5-month pilot study of MPACT will address aims 2 and 3 and involves 2 Arizona-based OTPs (1 rural and 1 urban), 100 patients, and 22 staff (25 patients and 6 staff of the rural clinic and 75 patients and 16 staff of the urban clinic). Data collection will be accomplished through a web-based survey of staff and patient participants monthly during the pilot study period, which began in October 2024 and ended in March 2025. The 4 elements of MPACT intervention were delivered during the 4-month period following study recruitment. Eligibility criteria for study inclusion included being 18 years of age or older, being a staff member or a patient at 1 of the 2 pilot clinics, being willing to participate in monthly surveys during the pilot study period, and (for patients) agreeing to share selected components of their medical charts with the study team.

Measures

The primary study outcome is increased patient methadone treatment retention. This outcome is measured in three ways: (1) time to first treatment interruption, calculated as the number of days to first missed dose from day 0 (MPACT enrollment); (2) evidence of being active in treatment, a binary (yes or no) if receiving dose at points in time on day 0, 30, 60, 90, and 120; and (3) continuous days in treatment during the study period, calculated as time (days) to discharge. Data measuring this outcome are gathered by patient surveys and chart reviews.

Secondary study outcomes include reductions in VT and PTSS among enrolled clinic staff and PTSS among enrolled patients. Data measuring secondary outcomes are gathered by a survey of staff and patients enrolled in the study. For staff and patients, PTSS are measured using the 8-item posttraumatic stress disorder symptoms screener otherwise known as the PCL-5 [35]. Staff VT is measured by the Vicarious Trauma Scale [37], burnout is measured by a 3-item scale [45], and compassion satisfaction and compassion fatigue are measured by the shortened, 9-item Professional Quality of Life Scale for staff [46].

The degree to which methadone treatment is patient-centered is also a secondary outcome measured through staff surveys (assessing whether they believe they are providing it) and patient surveys (assessing whether they feel they are experiencing it). Patient-centered care competency is measured by a 19-item scale [47] including the following subscales: respecting patient perspectives, promoting patient involvement in the care process, providing patient support, and advocating for patients. Patient-centered care, as defined by the study team, is measured using a 5-item instrument that reflects the concepts of patient-centered care introduced during the accredited training modules. This scale is administered to staff, with an adapted version used for patients.

Other individual-level variables of interest for the staff participants include (1) personal characteristics—demographics, personal substance use disorder and treatment experience, and trauma exposure history (measured by the Life Events Checklist-5) [48]; (2) work characteristics—training, education, and licensure related to their clinic role; (3) empowerment using a 5-item empowerment scale [49]; (4) stigma—toward people with OUD with a 9-item scale [50], self-stigma with a 9-item scale [51], and fear of enacted stigma through a 9-item scale [52]; (5) beliefs—about trauma-informed care measured by the attitudes toward trauma-informed care [53] and about abstinence measured by the Abstinence Orientation Scale [54]; (6) comfort with targeted practices related to the most recent federal changes to methadone treatment delivery measured by items adapted from prior studies measuring comfort with practices [34,55,56]; and (7) fidelity to MPACT—the degree to which the clinic implements the MPACT intervention.

Other individual-level variables of interest for the patient participants include (1) personal characteristics—demographics, housing, trauma history (Life Events Checklist-5), and trauma symptoms (PCL-5); (2) methadone treatment—time in treatment and dose sufficiency; (3) empowerment—as measured by a 15-item scale [57] and through an adapted 16-item Kim Alliance Scale [58]; and (4) fidelity to MPACT—the degree to which the clinic implements the MPACT intervention.

As this is a hybrid (implementation and effectiveness) pilot and trial, we are specifically focused on reach, implementation, adoption, and (in the trial) maintenance using the RE-AIM (Reach, Effectiveness, Adoption, Implementation, and Maintenance) framework [59]. Measures collected for the pilot will also be collected for the trial.

Data Collection

Primary and secondary study outcomes will be measured by surveys and patient chart reviews. Surveys will be administered monthly for the pilot study: assessment 1 (baseline at enrollment) and assessment 2-5 in 30-day sequences through the study period, with a contact reminder at day 27 and a completion forgiveness period of 5 days (day 35). Table 1 displays the sequencing of measures across the 5 pilot surveys.

Table 1. Sequencing of Methadone Patient Access to Collaborative Treatment (MPACT) primary and secondary measures (assessment 1-5).

Construct	Assessment 1 (enrollment)		Assessment 2	Assessment 3	Assessment 4	Assessment 5 (study conclusion)
	Staff items, n	Patient items, n				
Personal characteristics						
Demographics	5	6	—[a]	—	—	—
Personal SUD[b] experience	10	—	—	—	—	—
Methadone treatment						
Time in MMT[c] and clinic, reasons for choosing methadone as treatment	—	13	—	—	—	—
Methadone interruption	—	2	✓	✓	✓	✓
Dose, sufficiency, OD[d]	—	13	✓	✓	✓	✓
Trauma history and symptoms						
Trauma history (LEC[e])	17	17	—	—	—	—
Vicarious Trauma Scale	8	—		✓		✓
PCL-5[f] (trauma symptoms)	8	8	✓[g]	✓	✓[g]	✓
Burnout, compassion fatigue						
Burnout scale	9	—	✓	✓	✓	✓
ProQoL[h] (compassion fatigue, Compass Sat, burnout)	9	—	✓	✓	✓	✓
Work characteristics						
Years working (SUD and this clinic) and role	5	—	—	—	—	—
Training and education for role	2	—	—	—	—	—
Baseline exposure to MPACT-related practices						
Reflect Sup (some staff)	1	—	✓	✓	✓	✓
Self-care	9	—	—	✓	—	✓
MPACT-specific practices	9	—	✓	✓	✓	✓
Empowerment						
Staff empowerment scale	5	—	—	✓	—	✓
Patient empowerment (Bann scale)	—	15	✓	✓	✓	✓
Beliefs						
Abstinence Orientation Scale	11	—	—	✓	—	✓
Comfort with MMT innovations	10	—	—	✓	—	✓
ARTIC[i]	10	—	—	✓	—	✓
Person-centered climate (PCQ-S[j])	5	—	—	✓	—	✓
Stigma						
Stigma toward people with OUD[k]	8	—	—	✓	—	✓
Self-stigma	9	—	—	✓	—	✓
Fear of enacted stigma	9	—	—	✓	—	✓
Patient-centered care practices						
PCC[l]	19	—	—	✓	—	✓
Team-derived PCC scale	6	6	✓	✓	✓	✓

Construct	Assessment 1 (enrollment)		Assessment 2	Assessment 3	Assessment 4	Assessment 5 (study conclusion)
	Staff items, n	Patient items, n				
Kim Alliance Scale	—	16	✓	✓	✓	✓
Implementation						
MPACT feasibility, accept and fit; likelihood of continuing practices	5	—	—	—	—	✓

[a]Not applicable.
[b]SUD: substance use disorder.
[c]MMT: methadone maintenance treatment.
[d]OD: opioid overdose.
[e]LEC: Life Events Checklist.
[f]PCL-5: Posttraumatic Stress Disorder Checklist.
[g]Patients only.
[h]ProQoL: Professional Quality of Life Scale.
[i]ARTIC: attitudes toward trauma-informed care.
[j]PCQ-S: Patient-Centered Climate Scale for staff.
[k]OUD: opioid use disorder.
[l]PCC: person-centered competence.

For the 20-month trial, there will be 8 surveys from baseline assessment at enrollment through the remaining 7 assessments conducted every 77 days. Survey responses will be collected using the Qualtrics platform, accessible directly by participants.

For all enrolled patients, a review of their methadone clinic medical chart will include the duration of their treatment at the clinic, from treatment initiation to discharge or study end, whichever occurs first. This review will take place at the conclusion of the study period in accordance with the data sharing agreement (DSA) established between the clinic organization and the University of Arizona. A feasibility test with a sample of 50 charts with deidentified data was conducted in June 2024 and confirmed timely data transfer, data completeness, and utility for outcome measurement for the pilot clinics. Our national survey of OTP clinic directors found that 22.2% of clinics allowed DSAs with researchers, but the vast majority (77.3%) indicated that such agreements were not allowed or that they were not aware of the clinic organization's position on them [60]. For the purposes of the trial, then, only clinics allowing DSAs will be eligible for study enrollment. The following medical chart segments will be requested for each patient participant: (1) the digest of the patient history of starting and leaving treatment at that clinic (dates), (2) case notes, (3) discharge summary, (4) treatment plans, (5) milligram dosing, and (6) take-home medication status over time. Case notes include qualitative data on patient stability, challenges reported by the patient (eg, housing, transportation, safety, and dosing sufficiency), and instances of missed doses. For the trial, the data will be transferred using unique identifiers that will correspond with the study unique identifiers. No personally identifying information (name and street address) will be transferred.

Study Recruitment

Recruitment is stepwise for both the pilot and the trial. For the national trial, clinics will first be recruited through email from a national list of methadone clinics responding to a prior survey by this team during 2024 [60]. A second strategy will involve an email to the state opioid treatment authority with a request to forward study information and the recruitment flyer to methadone clinic directors in their state. State opioid treatment authorities are the single opioid regulator in each state. Clinics that allow study recruitment among staff and patients, establish a DSA for the transfer of patient participant methadone treatment chart data at the conclusion of the 20-month trial, and identify a clinic "champion" to assist with study enrollment and study contact will be eligible for randomization as described below.

Following clinic enrollment, each clinic champion will post recruitment flyers in staff-only areas (for staff participants) and in patient-only areas (for patient participants). Recruitment flyers for staff lead to a study portal (web-based) presenting information about the study and requesting agreement to participate. If agreement is made, staff participants will immediately complete the enrollment survey (baseline assessment 1). The same process will occur for patients. Payment for timely completion of each survey is US $20 for patients and staff. This cost was determined by a group of staff and patients who completed the work associated with aim 1.

Patient and staff confidentiality will be maintained by centralizing the enrollment process. Recruitment flyers will be displayed in staff-only and patient-only areas with a QR code or URL leading to information for potential participants to learn more about the study and to voluntarily enroll. This process ensures the anonymity of study participants within the clinic, meaning that patients and staff participants will not be known to the study clinic. Further, at the time of enrollment, a unique identifier will be established by the participant and will be used

henceforth. At no time will the clinic leadership or clinic champion know the identity of the study participants. The only exception to this is at the conclusion of the study when patient chart data transfer will occur, and at that time, only 1 person handling data transfer will have the name and dates of birth of the participants whose charts will be transferred for study purposes.

Fidelity Tracking and Application of RE-AIM

MPACT fidelity tracking will assess the degree to which clinics assigned to the intervention arm implement MPACT components. This will be evaluated by a fidelity tracking instrument and video conversations with the clinic champions—biweekly during the pilot study and monthly during the trial period. A fidelity tracker will first be populated with data from study databases, including accredited training completion, TICA survey participation (number and ratio of staff completing surveys), number of anonymous wellness self-screenings, and reflective supervision participation (number of staff by role per biweekly session). During fidelity conversations, the clinic champion will indicate the number of wellness trainings offered to staff (current or new staff) in the past 2 weeks, whether posters for the wellness screener were shared in the staff-only areas, and whether there were other issues raised by staff about MPACT participation that may require troubleshooting.

MPACT feasibility will be measured through fidelity tracking (what the clinic does and does not implement and the feedback about issues related to that) and through items measured in the staff survey. The RE-AIM framework will guide the assessment of reach, adoption, implementation, effectiveness, and maintenance. Reach is focused on staff and patient participants in the MPACT study. Measures of reach include the number and proportion of clinics participating in the study (number participating/number in recruitment sample) and the number and proportion of staff and patients participating by the study clinic. Adoption is focused on the participation in MPACT intervention overall and by the MPACT component. This is measured by reported staff participation through the surveys and through completion data gathered through the intervention components. Examples include accredited training completion or progress toward completion, reflective supervision participant reports, and wellness assessment completion reported through study surveys and through wellness screening data output (duplicated unless noted by the participant by selecting “I have taken this assessment before,” and if selected, the participant can select the number of times the assessment has been completed prior). Implementation is measured through the fidelity check meetings with champions and reported MPACT activity (such as posting flyers about particular intervention components). Effectiveness is measured by primary and secondary outcomes related to the aims of this study. Maintenance will not be measured in the pilot study (4-month period) but will be measured through a survey conducted 6 months after the conclusion of the trial period.

Phase 2, Years 3-6: Hybrid, Cluster Randomized Controlled Trial

Overview

- Aim 4: Quantify the effects of MPACT on methadone treatment practice change and clinic culture.
- Aim 5: Determine the efficacy of MPACT on methadone treatment retention and patient and staff PTSS outcomes.
- Aim 6: Evaluate the effect of patient and staff trauma on primary outcomes and staff MPACT implementation.

Findings from the pilot study will determine the preliminary effect size to confirm power analyses and final sampling for a hybrid type 1, 20-month cluster randomized controlled trial among 30 clinics, 600 patients (20 per clinic), and 480 staff (18 per clinic). This hybrid type 1 trial will focus primarily on MPACT’s effect outcomes while examining the association of MPACT implementation fidelity and acceptability and identifying the multilevel factors influencing implementation.

For the trial, the clinic is the unit of randomization. The intervention condition will be the MPACT intervention, and the control condition will involve accredited training about methadone that does not overlap aspects of the MPACT intervention. As shown in Table 2, we will allow a 20-month study period to accommodate staggered trial initiation through month 12 of year 2. Given the 20-month trial period, we will allow for new staff members to enroll through the end of the 7th month of their site’s trial period.

Table 2. Cluster randomized controlled trial of Methadone Patient Access to Collaborative Treatment.

	Year 1		Year 2		Year 3		Year 4	
	Half 1	Half 2	Half 1	Half 2	Half 1	Half 2	Half 1	Half 2
Intervention arm clinics (n=15)	Start-up	Intervention	Intervention	Intervention	Intervention	Intervention	Intervention	Closeout
Control arm clinics (n=15)	Start-up	Usual care	Usual care	Usual care	Usual care	Usual care	Usual care	Closeout
Key processes	Randomization process finalized	Trial allows for staggered starts based on recruitment	Trial allows for staggered starts based on recruitment	Trial allows for staggered starts based on recruitment	Trial follow-up	Trial follow-up	Trial follow-up	Trial outcome analyses and dissemination

Clinic Stratification Factors

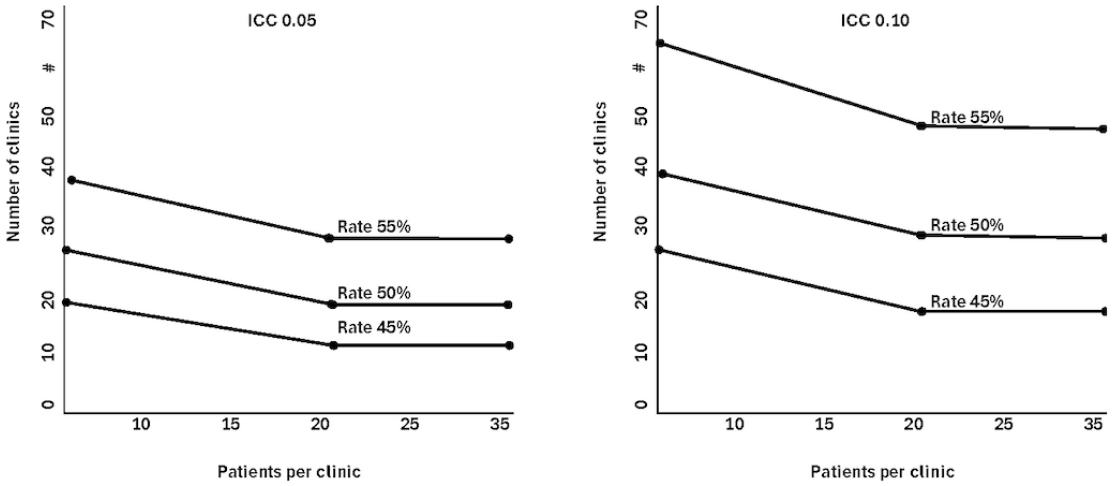
By the time of trial planning finalization, we anticipate that the state regulatory environment in each trial location will be a likely outer setting impact. Given the importance of state policy for regulating OTPs and methadone treatment, we will measure state regulatory favorability toward OTPs using a 2-level coding structure used in prior studies by this team [60]. We will code state laws based on the Pew state regulatory review [8] as "expanding methadone access" or "not expanding or limiting access." Randomization to trial condition will be stratified based on outcomes of this state regulatory coding.

Statistical Analysis

Our primary outcome is patient time to first treatment interruption (confirmed in the pilot). Secondary outcomes include treatment retention (yes or no) at selected time points (1, 3, 6, and 12 months) and time to treatment discontinuation. To accommodate the clustering induced by nesting patients within clinics, we will use a mixed effects Cox proportional hazards model (shared frailty model) [61,62] to accommodate differential survival probability among clusters. The mixed model will include a random intercept for the clinic and a fixed treatment effect for MPACT or control assignment. We will also include patient-level covariates for age, sex, and time in MMT.

Our initial sample size calculation uses asymptotic normal results for log hazard ratio as well as sample size inflation factors (eg, Donner) [62] for cluster randomized trials. In designing the future R33 trial, we will make use of specific sample size methods for cluster randomized trials with time-to-event outcomes [63,64]. The relative frequency of first treatment interruption [65] is estimated as 66% at 12 months of MMT until we have confirmation from the pilot. We evaluate the number of clinics and number of patients, assuming that MPACT intervention reduces this frequency to 45% (n=240), 50% (n=300), and 55% (n=330). The power curves based on independent observations (no cluster effect) are shown in Figure 3. The graph shows that the recruitment of 30 clinics, with 20 patients per clinic, provides greater than 80% power to detect a difference in treatment interruption rates of 66% (control) and 55% (MPACT) with α=.05. Consistent with the cluster randomization trial design, we also consider the average number of patients per clinic as 10, 20, and 40 and different degrees of intraclinic clustering using intraclass correlation coefficients of 0.05 and 0.10.

Figure 3. Number of clinics and patients for 80% power (vs 66% treatment interruption rate), MPACT trial. ICC: intraclass correlation coefficient; MPACT: Methadone Patient Access to Collaborative Treatment.



Results

The pilot study is funded by the National Institute on Drug Abuse (award R61DA059889, funded September 2023), and the field trial will be funded under the associated R33 mechanism in September 2025. The pilot study was completed on March 17, 2025. We are currently analyzing the pilot study findings. The randomized controlled trial will begin in December 2025.

Discussion

The MPACT study will provide a foundation for an evidence-based, staff-level intervention aimed at improving patient retention in MMT. We anticipate a decrease in reported levels of VT and PTSS among staff and an increase in methadone treatment retention among patients. The pilot outcomes are focused primarily on implementation with a preliminary indication of impact or effectiveness. The preliminary outcomes from the pilot will inform the final sampling to properly power the study. The trial outcomes are focused both on the implementation and effectiveness of the MPACT intervention. Future studies should examine the individual components of MPACT to determine their differential contributions to the primary outcome of patient MMT retention and to secondary outcomes of staff and patient reduction in stress symptoms.

Acknowledgments

The authors are grateful to the group of people with methadone treatment experience and the OTP staff group who collaboratively advised the development of Methadone Patient Access to Collaborative Treatment. The authors also thank the Drug Policy Research and Advocacy Board for their support and direction to improve the health of people who use drugs in Arizona. Research reported in this publication was supported by the National Institute on Drug Abuse of the National Institutes of Health (award R61DA059889). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Data Availability

The datasets generated and analyzed during this study will be made available in the HEAL data ecosystem through the Inter-University Consortium for Political and Social Research within 1 year of the pilot and of the trial conclusion, or at the time of first publication from the pilot (or trial), whichever occurs first.

Authors' Contributions

BEM led the study conceptualization, data curation, funding acquisition, investigation, and methodology and provided project administration and supervision of study staff and investigators. BEM also led the visualization and original writing and editing of the manuscript. AD supervised data curation and conducted formal analysis. AD also advised the methodology and conducted data validation. AD participated in the editing of the manuscript. RAC advised study conceptualization, data curation, funding acquisition, investigation, and methodology. RAC also participated in the editing of the manuscript. LBLK assisted study conceptualization, funding acquisition, investigation, and methodology and participated in the editing of the manuscript. BRB and ANM assisted study conceptualization, funding acquisition, and methodology and participated in the editing of the manuscript. GAC assisted study conceptualization, funding acquisition, investigation, and methodology and participated in the editing of the manuscript. DF, JR, ED, JE, MFJ, MJ, BL, HML, MDP, and KT assisted study methodology and participated in the editing of the manuscript. SY assisted data curation and investigation, managed software, and participated in the editing of the manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer review report from ZDA1 SKP-E (O2) - National Institute on Drug Abuse Special Emphasis Panel HEAL Initiative: Translating Research to Practice to end the Overdose Crisis (National Institutes of Health, USA).
[PDF File (Adobe PDF File), 89 KB - resprot_v14i1e69829_app1.pdf]

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Abbreviations

DSA: data sharing agreement
MMT: methadone maintenance treatment
MPACT: Methadone Patient Access to Collaborative Treatment
OTP: opioid treatment program
OUD: opioid use disorder
PCL-5: Posttraumatic Stress Disorder Checklist
PTSS: posttraumatic stress symptoms
RE-AIM: Reach, Effectiveness, Adoption, Implementation, and Maintenance
TICA: trauma-informed clinic self-assessment
VT: vicarious trauma

Edited by A Schwartz; submitted 09.12.24; this is a non–peer-reviewed article;accepted 18.03.25; published 15.04.25.

Please cite as:
Meyerson BE, Davis A, Crosby RA, Linde-Krieger LB, Brady BR, Carter GA, Mahoney AN, Frank D, Rothers J, Coffee Z, Deuble E, Ebert J, Jablonsky MF, Juarez M, Lee B, Lorenz HM, Pava MD, Tinsely K, Yousaf S
Methadone Patient Access to Collaborative Treatment: Protocol for a Pilot and a Randomized Controlled Trial to Establish Feasibility of Adoption and Impact on Methadone Treatment Delivery and Patient Outcomes
JMIR Res Protoc 2025;14:e69829
URL: https://www.researchprotocols.org/2025/1/e69829
doi:10.2196/69829
PMID:40105313

Protocol

Calibration and Validation of Machine Learning Models for Physical Behavior Characterization: Protocol and Methods for the Free-Living Physical Activity in Youth (FLPAY) Study

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Abstract

Background: Wearable activity monitors are increasingly used to characterize physical behavior. The development and validation of these characterization methods require criterion-labeled data typically collected in a laboratory or simulated free-living environment, which does not generally translate well to free-living due to limited behavior engagement in development that is not representative of free living.

Objective: The Free-Living Physical Activity in Youth (FLPAY) study was designed in 2 parts to establish a criterion dataset for novel method development for identifying periods of transition between activities in youth.

Methods: The FLPAY study used criterion measures of behavior (direct observation) and energy expenditure (indirect calorimetry) to label data from research-grade accelerometer-based devices for the purpose of developing and cross-validating models to identify transitions, classify activity type, and estimate energy expenditure in youth aged 6-18 years. The first part of this study was a simulated free-living protocol in the laboratory, comprising short (roughly 60-90 s) and long (roughly 4-5 min) bouts of 16 activities that were completed in various orders over the span of 2 visits. The second part of this study involved an independent sample of participants who agreed to be measured twice (2 hours each time) in free-living environments such as the home and community.

Results: The FLPAY study was funded from 2016 to 2020. A no-cost extension was granted for 2021. A few secondary outcomes have been published, but extensive analysis of primary data is ongoing.

Conclusions: The 2-part design of the FLPAY study emphasized the collection of naturalistic behaviors and periods of transition between activities in both structured and unstructured environments. This filled an important gap, considering the traditional focus on scripted activity routines in structured laboratory environments. This protocol paper details the FLPAY procedures and participants, along with details about criterion datasets, which will be useful in future studies analyzing the wealth of device-based data in diverse ways.

International Registered Report Identifier (IRRID): RR1-10.2196/65968

(JMIR Res Protoc 2025;14:e65968) doi:10.2196/65968

KEYWORDS

physical behavior assessment; youth activity; wearable devices; activity monitoring; digital health; physical behavior characterization; criterion dataset

Introduction

Device-based assessment of physical behavior has become common in health research [1-6]. Despite significant advancements in this field, a major challenge remains: the translation and generalization of device outputs, which are crucial for accurate interpretation and use [1,7]. This challenge arises partly from the methodological approaches used, as well as from the way data are collected to calibrate and validate these methods. Traditional static regression models for physical behavior assessment, such as those used in the 2003-2006 National Health and Nutrition Examination Survey [8], rely on population-, attachment site-, and device-specific cut points or regression equations to estimate energy expenditure (EE) and physical activity intensity [9]. However, these models tend to perform poorly when applied to the dynamic and complex nature of real-world behavior, as well as when tested on out-of-sample datasets [10,11]. For example, legacy models such as the Freedson equation for children [12] have been shown to underestimate moderate-to-vigorous physical activity by up to 51% during free-living conditions [11], highlighting a key limitation in the field. This discrepancy arises because these models were developed using structured laboratory data, which fail to capture the sporadic and irregular movement patterns typical of free-living environments. Furthermore, traditional methods often segment accelerometer data into fixed time intervals (eg, 1-min epochs), assuming that each data point is independent and represents a continuous bout of activity—an assumption that is rarely valid in real-world settings [13-15].

Advancements in sensor technology, including the use of wrist-worn accelerometer-based devices and the integration of additional sensor types (ie, gyroscopes and magnetometers), have improved the potential ability to capture a broader range of movement behaviors with different characteristics, such as the discrimination of sedentary behavior [16-18]. These innovations offer promising solutions for improving physical behavior assessment, particularly in youth populations. However, challenges remain in using raw data from these devices to accurately predict EE and categorize activity types [1,19,20]. The use of machine learning algorithms has been an interesting development in this space, showing potential for improving activity classification and EE estimation [21-24]. However, as with traditional methods, these machine learning algorithms have been primarily trained on structured laboratory activities, leading to poor performance when applied in free-living conditions and to new datasets [21,25]. The key issue lies in the segmentation of activity bouts and the identification of transitions between activities, which are much more subtle and irregular in free-living environments compared to the abrupt transitions typical of laboratory-based protocols [26-28].

The Free-Living Physical Activity in Youth (FLPAY) study was an effort to address these gaps by collecting transition-rich data in free-living conditions for calibration and validation of device-based models of physical behavior. The purpose of this paper is to describe the methods and data associated with the FLPAY study, thereby encouraging procedural replication in future studies and providing a comprehensive background for future analyses of data from this study. By addressing the complexities of free-living data, particularly the segmentation of activity bouts and transitions, this study aims to improve the accuracy, precision, and applicability of device-based physical behavior assessments and contribute to the development of more effective methods for characterizing physical behavior in youth.

Methods

Study Design

The FLPAY study was a 2-part investigation to develop and validate sensor-based methods for detecting transitions between activities as a precursor to predicting EE. The first part of this study took place in a simulated free-living laboratory environment conducive to method development (calibration), while the second took place in unstructured free-living environments conducive to method validation. Both studies were for youth participants aged 6-18 years who were recruited through word of mouth and flyers. The overall study design was conceived to address common limitations of prior method development studies, which have focused on the collection of steady-state laboratory data and structured ambulatory activities, rather than allowing naturalistic transitions and data collection in free-living.

Below, we present protocol and data summaries for each component of this present study in separate subsections. Portions of the information have been reported previously [26,29-31]. This present study was not a clinical trial. Due to the overlap in the methods for each part of this study (eg, similar equipment), the following sections are focused primarily on unique elements of each part, while recurring elements are presented in Multimedia Appendix 1.

Ethical Considerations

Both parts of this study were approved by the University of Tennessee Knoxville Institutional Review Board (UTK IRB-15-02487-FB). For all participants, written informed consent was obtained from a parent. Participants also provided written informed assent. Both parts of this study involved video recording on an opt-in basis, and thus, there were separate consent and assent signatures for general enrollment and video recording. However, for both parts of this study, the consent and assent documents did not include language for public data sharing, and thus, only deidentified data will become available from the FLPAY study. For screening, parents filled in a health history questionnaire, with participants being excluded if they had medical conditions or musculoskeletal injuries that prevented engagement in physical activities. Additional exclusion criteria included conditions or medications affecting metabolism. Participants were compensated for their participation in this study. Details on compensation are included within the subsections for each study component.

Part 1: Laboratory-Based Component

Participants—Laboratory-Based Component

A total of 100 participants were recruited. Approximately even distributions were recruited across sex and age groups (6-9, 10-12, 13-15, and 16-18 years). Participant characteristics are shown in Table 1.

Table 1. Physical characteristics of participants from the laboratory study.

	Full sample (N=100)	Male (n=48)	Female (n=52)
Age (years)			
Mean (SD)	12.1 (3.53)	12.3 (3.32)	11.9 (3.74)
Median (IQR)	12.1 (9.3-15.2)	12.4 (9.9-15)	11.7 (9-15.2)
Age group (years), n (%)			
6-9	33 (33)	13 (27.1)	20 (38.5)
10-12	25 (25)	15 (31.3)	10 (19.2)
13-15	23 (23)	12 (25)	11 (21.2)
16-18	19 (19)	8 (16.7)	11 (21.2)
Height (cm)			
Mean (SD)	150 (19.2)	152 (20.5)	148 (17.9)
Median (IQR)	151 (134-166)	156 (140-167)	150 (133-162)
Sitting height (cm)			
Mean (SD)	74.9 (9.5)	75.4 (9.7)	74.3 (9.5)
Median (IQR)	74.5 (66.5-83.1)	74.5 (68.6-84)	74.4 (65.9-82.6)
Leg length (cm)			
Mean (SD)	75 (11.4)	77 (11.8)	73.2 (10.8)
Median (IQR)	76 (66-82.8)	77.5 (69.6-85.8)	74.3 (63.8-80)
Weight (kg)			
Mean (SD)	44.7 (18.7)	46.5 (20.3)	43 (17.2)
Median (IQR)	40.5 (29.6-55.7)	41 (34.1-56.3)	38.3 (29.3-55.7)
Fat mass (kg)			
Mean (SD)	10.4 (7.5)	9.2 (6.8)	11.4 (7.9)
Median (IQR)	7.5 (5.7-12.1)	7 (5.6-10)	9.5 (6.5-13.7)
Body fat (%)			
Mean (SD)	21.9 (6.4)	18.7 (4.8)	24.9 (6.3)
Median (IQR)	20.8 (17.5-24.5)	17.5 (15.6-19.7)	23.7 (21.1-27.5)
Fat-free mass (kg)			
Mean (SD)	34.3 (12.9)	37.2 (14.6)	31.6 (10.6)
Median (IQR)	32.7 (23.3-42.8)	33.8 (27.3-48.1)	30.3 (22-41.6)
BMI (kg/m^2)			
Mean (SD)	19 (4.4)	19.1 (4.4)	19 (4.5)
Median (IQR)	18 (16.2-20.5)	18 (16.3-19.9)	17.9 (16.2-20.6)
BMI percentile (%)			
Mean (SD)	51.6 (27.4)	50.9 (26.8)	52.3 (28.2)
Median (IQR)	49.4 (33.6-73.3)	48.8 (34.2-72.2)	49.6 (33.6-74.6)
BMI classification			
Underweight	5 (5)	2 (4.2)	3 (5.8)
Healthy weight	80 (80)	40 (83.3)	40 (76.9)
Overweight	9 (9)	2 (4.2)	7 (13.5)
Obese	3 (3)	3 (6.3)	0 (0)
Severe obese	3 (3)	1 (2.1)	2 (3.8)
Race or ethnicity			

	Full sample (N=100)	Male (n=48)	Female (n=52)
Hispanic White	4 (4)	1 (2.1)	3 (5.8)
Non-Hispanic African American	9 (9)	3 (6.3)	6 (11.5)
Non-Hispanic White	87 (87)	44 (91.7)	43 (82.7)
Handedness			
Right	94 (94)	45 (93.8)	49 (94.2)
Left	6 (6)	3 (6.3)	3 (5.8)

Laboratory-Based Component Procedures

All research visits were conducted in the Applied Physiology Laboratory and the surrounding area at the University of Tennessee Knoxville. The protocol entailed 2 visits on separate days, each lasting approximately 2-2.5 hours. The main feature of the protocol was the completion of 16 activities (Table S3 in Multimedia Appendix 1) that were divided across the 2 visits. A key goal of this study's design was to simulate realistic transitions between activities. Therefore, each activity was performed twice, with 1 instance lasting approximately 60-90 s and the other lasting approximately 4-5 min. Within those ranges, participants self-selected when they transitioned to the next activity unless guidance was needed from the research team (eg, if the upper limit of 90 s or 5 min was reached or if the walking circuit reached a specific stopping point to facilitate speed calculations). They also self-selected the order of the 8 activities they were prescribed each day, except that the same activity could not be performed twice in a row, and the activities were grouped by location (ie, in an upstairs laboratory or a separate recreation area) to minimize total transition time. The order of short and long bouts for each activity was randomized.

Throughout each research visit, participants wore a portable indirect calorimeter and a variety of activity monitors. Participant behavior and posture were coded by direct observation, using a focal sampling approach that allowed continuous logging of behaviors, transitions, and posture. Video recording was also performed for most participants. The video recordings served as a backup in case the live coded observation records needed to be reviewed and revised for any reason (eg, adjusting timestamps if an error was noted during the live coding process).

Laboratory-Based Component Detailed Timeline

For the first visit, participants were asked to refrain from eating or drinking (except water) for 2 hours before the visit and to wear lightweight athletic clothing and closed-toed shoes. After completing the enrollment and consent processes, they removed their shoes and socks and had anthropometric measurements taken. Standing and sitting height (cm) were measured using a wall-mounted stadiometer. Body mass (kg) and body fat (%) were measured using a Tanita BC-418 bioelectrical impedance analyzer (Tanita Co. of America, Inc).

Following the anthropometric measurements, participants were fitted with this study's equipment and completed a 30-minute assessment of resting metabolic rate (RMR). The remainder of the visit involved completing the 8 activities assigned for that day. Participants received a US $30 gift card at the end of the visit.

For the second visit, participants were given the same previsit instructions. Upon returning to the laboratory, they were fitted with the same study equipment as visit 1 before performing the remaining 8 activities, such that all participants completed the full set of 16 activities under normal circumstances (ie, assuming there is no withdrawal, refusal, or space unavailability due to scheduling). Participants received a US $45 gift card at the end of the visit.

Laboratory-Based Component Equipment

All participants wore 5 ActiGraph GT9X devices (GT9X; ActiGraph LLC), which were the primary activity monitors of interest for this study. One was placed on the right hip, 1 on each wrist, and 1 on each ankle. The hip-worn device was worn on an elastic belt and positioned over the right iliac crest along the anterior axillary line and secured using a manufacturer-specific belt clip. The wrist-worn devices were worn in manufacturer-specific watch bands that the devices clipped into. The watch bands were positioned proximal to the styloid processes with the devices oriented where the LCD could be read naturally by the participant, as a standard watch face would be. The ankle-worn devices were clipped into manufacturer-specific clips worn on slip-through Velcro bands. The clips were positioned so that the devices were on the lateral aspect of the ankle proximal to the lateral malleolus. Additional detail is given in Section S1.1 in Multimedia Appendix 1.

Secondary activity monitors, both research- and consumer-grade, were also worn in various locations on the body as detailed in Sections S1.2 and S1.3 in Multimedia Appendix 1.

Criterion Measures

Participants were observed using the Noldus Observer XT and Pocket Observer software platforms (Noldus Information Technology), which served as a criterion measure of behavior and posture. Participants also wore a Cosmed K4b^2 (COSMED s.r.l.), which was the criterion measure of EE. General details of these tools can be found in Sections S1.4 and S1.5 in Multimedia Appendix 1. Specific details applicable to part 1 of this study are discussed below.

The Observer XT desktop platform (version 12.5) was used to create a 2-class focal sampling coding scheme, which was then exported for use in the Noldus Pocket Observer application (version 3.2). The latter application was run on Samsung Galaxy Tab 4 tablets (Samsung) and used for real-time coding of participant behavior and posture. Several activity monitoring

studies have taken a similar approach to direct observation using Noldus products [22,28,32-34].

The coding scheme included a 19-item list of activity behaviors (ie, for the 16 activities listed in Table S3 [Multimedia Appendix 1], plus labels for the start time of the observation period, transitions between activities, and unknown activities) and a 6-item list of postures (lying, reclining, sitting, standing, stepping, or unknown). The label for unknown activities was used whenever an unlisted activity occurred, such as a water break or bathroom break, and was accompanied with a posture label of unknown.

Whenever a new activity was initiated, users tapped the corresponding label in Pocket Observer, which issued a timestamp for the new activity and then prompted the user to indicate the participant's posture. This created a continuous and timestamped record of activities and postures. After finishing the protocol, live-coded observations were imported back into the Noldus Observer XT software program for conversion to Excel format. The resulting files were then processed in R (R Foundation).

Section S1.5 in Multimedia Appendix 1 describes the procedures that were used when syncing data from the various sources.

Processing of Criterion Data for Laboratory-Based Component

While the activity monitor data were collected for flexible use (eg, to be processed and tested in different ways across future studies), the criterion data from direct observation and indirect calorimetry were designed for consistent usage across future studies. Therefore, we describe the processing and aggregation of criterion data in the sections that follow, while monitor data processing is left for future studies to describe according to the unique needs of the study.

Direct Observation Data

Each participant was observed by a single trained observer in real time during each study visit. The observation files were inspected for comments and anomalies that indicated errors (eg, the user entered a comment indicating a button was pressed at the wrong time or that the activity duration was outside the expected range). Corrections were made by a senior reviewer cross-referencing the video recordings and adjusting labels or timing accordingly. For participants without video recordings, observations were used as they were created from the live coded direct observation (n=3). Each row of the observation files indicated a start time and duration for the corresponding activity and posture, and by definition, there were no gaps between activities. Thus, every second of the data collection period could be mapped to a specific activity and posture label that was active at that time, allowing a second-by-second record to be constructed from the information in the observation files.

Portable Indirect Calorimeter Data

EE was calculated based on oxygen consumption (VO_2) and RMR, both measured by the K4b^2. The values were expressed in youth metabolic equivalents (MET_y), where

As described in the Sections S2.1 to S2.3 in Multimedia Appendix 1, calculations for RMR and continuous VO_2 were the same for parts 1 and 2 of the FLPAY study. Below, we provide additional detail about calculating steady state EE as this was unique to part 1 of this study.

Steady state periods were defined for the longer activity bouts. All bouts longer than 3 minutes, 40 seconds were included in the analysis. The steady state period was defined as the last 60 seconds of each activity, after discarding the final 10 seconds. For each of these periods, the corresponding K4b^2 data were extracted in breath-by-breath format. An average VO_2 was then calculated using manufacturer-specified procedures (Section S2.1 in Multimedia Appendix 1). This value was divided by RMR to obtain MET_y for the steady state period. Posture was determined by cross-referencing the direct observation data from the steady state period.

Activity intensity was derived from EE (MET_y) and posture, using the following accepted definitions [35]: for sedentary behavior, ≤1.50 MET_y and seated, lying, or reclining posture; for light physical activity, 1.51-2.99 MET_y regardless of posture (or ≤1.50 MET_y if posture was upright); and for moderate-to-vigorous physical activity, ≥3.00 MET_y regardless of posture. For each activity and age group (ie, those aged ≤12 versus >12 years), data were cleaned by removing values <0.2 MET_y, or >2 SD above or below the mean.

Part 2: Unstructured Free-Living Study

Unstructured Free-Living Study Participants

A total of 84 participants were recruited to this study, of whom one was excluded (final N=83). Participant characteristics are shown in Table 2.

Table 2. Physical characteristics of participants from the free-living study.

	Full sample (N=83)	Male (n=39)	Female (n=44)
Age (years)			
Mean (SD)	11.2 (3.4)	11.1 (3)	11.3 (3.7)
Median (IQR)	10.6 (8.5-13)	10.5 (8.9-12.7)	11.2 (8.4-13.6)
Age group (year), n (%)			
6-9	35 (42.2)	17 (43.6)	18 (40.9)
10-12	26 (31.3)	13 (33.3)	13 (29.5)
13-15	14 (16.9)	6 (15.4)	8 (18.2)
16-18	8 (9.6)	3 (7.7)	5 (11.4)
Height (cm)			
Mean (SD)	146 (19.4)	145 (16.1)	147 (22.2)
Median (IQR)	144 (132-162)	143 (135-159)	145 (130-164)
Sitting height (cm)			
Mean (SD)	73.5 (9.2)	73.3 (8.4)	73.7 (10)
Median (IQR)	73 (67-80)	73 (67-79.5)	73 (66-80.3)
Leg length (cm)			
Mean (SD)	72.5 (10.9)	72 (8.3)	72.9 (12.8)
Median (IQR)	71 (66-81)	70.5 (67.3-78.9)	71.8 (63.4-84.9)
Weight (kg)			
Mean (SD)	42 (18.6)	39.9 (13.9)	43.9 (22)
Median (IQR)	36.1 (28.4-53.9)	36.1 (30.7-50)	37.6 (26.5-55.2)
Fat mass (kg)			
Mean (SD)	8.9 (7.8)	9.7 (6.6)	8.2 (8.8)
Median (IQR)	6.2 (3.9-11.8)	8.6 (4.3-13.4)	4.8 (3.7-7.5)
Body fat (%)			
Mean (SD)	19.3 (9.3)	21.9 (9.1)	17.1 (9)
Median (IQR)	17.9 (13.6-24)	22.2 (15.4-27.1)	15.3 (12.6-18.3)
Fat-free mass (kg)			
Mean (SD)	33.1 (13.5)	30.2 (8.2)	35.7 (16.5)
Median (IQR)	30.2 (23.3-39.7)	27.6 (23.7-37.5)	31.7 (21.9-42.8)
BMI (kg/m^2)			
Mean (SD)	18.7 (4.3)	18.3 (3.5)	19.1 (4.9)
Median (IQR)	17.7 (15.8-19.7)	17.8 (15.9-19.6)	17.6 (15.7-20)
BMI percentile (%)			
Mean (SD)	53.3 (26.2)	51.5 (24)	55 (28.2)
Median (IQR)	52.8 (33.4-72.4)	47.6 (33.7-72.3)	54.5 (33.9-72.5)
BMI classification, n (%)			
Underweight	3 (3.6)	1 (2.6)	2 (4.5)
Healthy weight	67 (80.7)	34 (87.2)	33 (75)
Overweight	6 (7.2)	2 (5.1)	4 (9.1)
Obese	4 (4.8)	1 (2.6)	3 (6.8)
Severe obese	3 (3.6)	1 (2.6)	2 (4.5)
Race or ethnicity, n (%)			

	Full sample (N=83)	Male (n=39)	Female (n=44)
Hispanic Hawaiian or Pacific Islander	1 (1.2)	0 (0)	1 (2.3)
Hispanic White	2 (2.4)	2 (5.1)	0 (0)
Latino White	1 (1.2)	0 (0)	1 (2.3)
Non-Hispanic African American	2 (2.4)	0 (0)	2 (4.5)
Non-Hispanic Asian	6 (7.2)	1 (2.6)	5 (11.4)
Non-Hispanic Native American or Alaskan	1 (1.2)	0 (0)	1 (2.3)
Non-Hispanic White	70 (84.3)	36 (92.3)	34 (77.3)
Handedness, n (%)			
Left	3 (3.6)	0 (0)	3 (6.8)
Right	80 (96.4)	39 (100)	41 (93.2)

Unstructured Free-Living Study Procedures

The overall goal of this part of this study was to collect free-living data with diverse activities and transitions between them. Therefore, research visits were conducted in varied settings, such as in the community, participants' homes, local parks, and approved facilities of community partners. Data were collected across 2 separate days, with the goal to have one in the participant's home and the other somewhere else.

The first study visit was generally conducted in the participant's home environment and began with the informed consent and assent process and participant screening. Once enrolled, participants had anthropometric measurements taken, including standing and sitting height (cm) using a portable stadiometer and body mass (kg) and body fat percentage measured using a Tanita BF-350 bioelectrical impedance analyzer. Anthropometric measurements were taken with shoes and socks removed. Following the completion of the anthropometric measurements, a 30-min RMR assessment was conducted using a Cosmed K4b^2 or K5 (used in breath-by-breath mode to align with the K4b^2) portable indirect calorimeter before participants engaged in activities of their choice for up to 2 hours. In some cases, the RMR assessment was conducted on a separate visit (for a total of 3). Participants were compensated US $25 for the RMR assessment and US $25 for the free-living data collection period.

For the second study visit, an alternative environment was sought for each participant. When this was not possible, participants were asked to engage in different activities than what they chose during their initial visit, which helped to mimic different environments and promote engagement in a wide range of activity behaviors. Similar to the first visit, the participants engaged in behaviors of their choice for up to 2 hours. An additional US $25 of compensation was given for completing the second study visit.

Throughout this study's visits, participants were given free rein to select activities, so long as they had parental permission, did not put the equipment at risk (eg, from water damage), and did not risk harming themselves or others.

All participants wore the same research-grade devices as described in the equipment portion of part 1 including the primary devices of interest (ActiGraph GT9X on the hip, both wrists, and both ankles; see also Section S1.1 in Multimedia Appendix 1) and the secondary research- and consumer-grade monitors (see Sections S1.2 and S1.3 in Multimedia Appendix 1, respectively). Participants wore a Cosmed K4b^2 or K5 portable indirect calorimeter, both of which collected breath-by-breath data as a criterion measure of EE (see Section S1.5 in Multimedia Appendix 1 for more detail). During the consent process, participants were able to opt-in to be video recorded throughout each research visit, and only 3 participants did not do so. Live coding was performed for those who did not opt into the video recordings. For the others, the video recordings were later used for direct observation to obtain a record of the behaviors and postures they engaged in, along with relevant contextual factors (eg, indoors versus outdoors and alone versus with others). These video-based observations were performed using the Noldus Observer XT software program for Windows desktop computers.

Unstructured Free-Living Study Equipment

Most equipment matched what was used for part 1 of the FLPAY study, with the addition of the Cosmed K5 alongside the K*4b^2*. The main difference in part 2 was the coding scheme used for direct observation and the reliance on video recordings for direct observation rather than live-coded observations. For participants who did not opt into video recording, real-time observations were performed using similar procedures to those described in part 1 above, except that a new coding scheme was used (Table S2 in Multimedia Appendix 1). Otherwise, the video recordings were coded using the Noldus Observer XT Direct Observation software program (version 12.5) for Windows desktop machines.

The coding scheme for part 2 included a longer list of potential activities and postures, as discussed below. It also included prompts about the activity context (eg, indoor or outdoor and alone or with others). Otherwise, the general structure of the coding scheme matched with part 1, such that every second of the data collection period could be mapped to a single entry in the observation record.

Table S4 in Multimedia Appendix 1 lists the main activities that were included in the coding scheme. As before, extra labels were included for coding the start of the observation period, transition behaviors, and unknown activities (ie, activities not previously defined), and events where the participant was off-camera (ie, in a private space, bathroom, etc). After the primary activity behavior was coded, posture was coded as lying, sitting, standing, standing or stepping, squatting or kneeling, reclining, mixed posture, or unknown (used only when the activity behavior was "off camera"). Section S1.5 in Multimedia Appendix 1 describes the procedures that were used when syncing data from the various sources.

Unstructured Free-Living Study Processing of Criterion Data

The data processing procedures for part 2 broadly mirrored what has already been discussed in part 1 resulting in a second-by-second dataset with information about EE, behavior, posture, and context. The direct observation procedures differed from part 1 due to the open-ended nature of this study and the reliance on video recordings. Specifically, at least 2 trained reviewers coded each video, and a third senior reviewer then compared their observations side-by-side. Additional detail is available in S1.4.3 in Multimedia Appendix 1.

Results

The FLPAY study was funded in June 2016, and recruitment and data collection for part 1 began in January 2017. Funding ended in March 2019, and the project and data collection concluded in March 2020. Some preliminary and auxiliary findings have been reported previously [26,29-31], whereas the protocol described herein will serve as the authoritative guide for ongoing research with the finalized dataset. Part 1 of this study enrolled 100 individuals, and part 2 enrolled 84 individuals. Data loss is described in Section S3 in Multimedia Appendix 1. The overall sample characteristics are shown in Table 1 and Table 2, whereas sample sizes for individual analyses may differ depending on overlap with additional missing data for different activity monitors. Table 3 provides an overview of prior completed analyses and current and ongoing analyses.

Table 3. Summary of research activities related to the FLPAY[a] study.

Component	Notes
Completed analyses	• Please see references [26,29-31].
Ongoing analyses	
ActiGraph, GENEActiv, and Axivity	• Please see references [36-38]. • Ongoing analyses include the development and testing of models to predict energy expenditure [36,37] and classify activity type [38]. • Additionally, we are preparing the dataset such that it can be used for out-of-sample validation of models developed by other research groups.
activPAL	• Please see reference [39].

[a]FLPAY: Free-Living Physical Activity in Youth.

Discussion

Contributions

The design of the 2-part FLPAY study emphasized naturalistic behaviors and periods of transition between activities. This filled an important gap in prior development studies focused on physical behavior characterization. In this paper, we summarized the FLPAY procedures and participants, along with details about criterion datasets that will be useful in future studies that look at various aspects of the data from the activity monitors. Future studies can proceed with novel method development and testing for a variety of research-grade and consumer-grade wearable devices. These data may be especially useful for ongoing work to refine methods involving transition detection for data segmentation [27,30].

It is worth noting that the main device from this study (ActiGraph GT9X) has been replaced by a newer model (ActiGraph LEAP). Although the manufacturer remains committed to backward compatibility, testing will be necessary to compare outputs from the GT9X and LEAP. Such comparisons should include not only direct factors such as agreement of the accelerometer and gyroscope outputs but also indirect factors such as battery life, memory consumption, and participant acceptability. Unpublished data from our laboratory showed that the GT9X battery life was <36 hours when collecting data from both the accelerometer and gyroscope. The LEAP includes a different gyroscope sensor that may be longer-lived, and it also includes additional sensors for richer monitoring (eg, barometer and microphone). These factors may affect usability in lengthy protocols (eg, >1 week) and vary from study to study depending on what sensor configuration is selected. It will also be important to consider the volume of data collected by LEAP, as our unpublished data showed that the GT9X was able to generate >1 GB of data before depleting its battery. As future studies begin to draw on the wearable data from the FLPAY study (especially, but not exclusively, the ActiGraph GT9X data), the implications of these decisions will be important to consider.

Strengths and Limitations

The FLPAY study had notable strengths, including its collection of data from both laboratory and free-living contexts, with realistic transition periods and behavioral patterns. Another

strength was the inclusion of criterion measures for EE, behavior, and posture. These will substantially benefit future work toward the development and validation of novel methodological approaches for the variety of research-grade devices that were used in this study.

Despite its strengths, the FLPAY study also had limitations. A key limitation was the limited diversity of the samples along the lines of racial and ethnic background. While the recruitment strategy was designed to mirror the census makeup in the surrounding area, results may not be fully generalizable for youth who come from underrepresented backgrounds. The open-ended nature of the free-living component could also be viewed as both a strength and a limitation, as the heterogeneity of the data may create a high level of variability that is difficult to address or interpret in future analyses. Lastly, we emphasized detailing the criterion data measurements of RMR, EE, and direct observation in the FLAY study as these will be foundational for a wealth of secondary research that is possible when paired with the monitor data collected in this study.

Acknowledgments

The authors would like to thank the participants from both parts of this study. We also gratefully acknowledge the contributions of Andrew Kaplan, MS, Minttu Hukka, MS, Andrew Blythe, PA-C, Brice Walkowski, BS, B Jesse Clendenin, DO, Josephine Jennings, PA-C, Marisa Varrone Mengel, BS, Polina Krassovskaia, PhD, and Brianne Clure Taylor, PA-C. Wei Ding, PhD, and Eamonn Keough, PhD, were collaborators.

This study was supported by the National Institutes of Health (grant R01HD083431). The funder was not involved in designing this study or analyzing the data. No financial support was received from any of the activity monitor manufacturers, importers, or retailers.

Data Availability

Deidentified data from the FLPAY study may be available upon reasonable request from the corresponding author. Video data cannot be deidentified and cannot be shared under any circumstances.

Conflicts of Interest

PRH has received funding from ActiGraph LLC. This study predates said funding, representing no conflict of interest. The authors have no conflicts of interest to report.

Multimedia Appendix 1
Additional digital content.
[DOCX File , 63 KB - resprot_v14i1e65968_app1.docx]

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Abbreviations

EE: energy expenditure
FLPAY: Free-Living Physical Activity in Youth
METy: youth metabolic equivalent
RMR: resting metabolic rate
VO2: oxygen consumption

Edited by A Schwartz; submitted 03.09.24; this is a non–peer-reviewed article;accepted 20.03.25; published 16.04.25.

Please cite as:
LaMunion SR, Hibbing PR, Crouter SE
Calibration and Validation of Machine Learning Models for Physical Behavior Characterization: Protocol and Methods for the Free-Living Physical Activity in Youth (FLPAY) Study
JMIR Res Protoc 2025;14:e65968
URL: https://www.researchprotocols.org/2025/1/e65968
doi:10.2196/65968
PMID:

Protocol

Interactive Computer-Adaptive Chronic Kidney Disease (I-C-CKD) Education for Hospitalized African American Patients: Protocol for a Randomized Controlled Trial

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Abstract

Background: End-stage kidney disease (ESKD) or kidney failure is a condition where the kidneys lose the ability to function. African American individuals are 4 times as likely to develop ESKD compared to White American individuals. In addition, African American patients are less likely to have an optimal dialysis start and to choose renal replacement therapy modalities that align with their goals and values. Our prior work shows that culturally tailored, in-person education improves patient outcomes. This is the foundation for our innovative intervention using an African American virtual patient educator as an option for hospitalized patients with chronic kidney disease (CKD).

Objective: The Interactive Computer-Adaptive Chronic Kidney Disease (I-C-CKD) study will determine whether the computerized adaptive education and usual hospital care impact the health literacy of African American patients with kidney disease. It will also assess how patients' lifestyle and commitment to health goals are impacted by the method of health literacy education.

Methods: We will screen, recruit, and enroll hospitalized patients who self-identify as African American and have advanced CKD based on their estimated glomerular filtration rate. Eligible patients who verbally consented will be randomly assigned into either the computerized adaptive education intervention group or the control group (usual hospital care). Patients in the intervention group will receive a culturally tailored, adaptive education module. To analyze pretest, posttest, and follow-up survey results on patient CKD knowledge, ESKD treatment options, and health goals, we will use a paired, 2-tailed *t* test with a Bonferroni adjustment for multiple comparisons.

Results: Recruitment for the I-C-CKD study began on May 2, 2023. We are currently recruiting and have enrolled 96 patients who completed both pretest and posttest surveys as of December 2024. This includes 50 patients in the control group and 46 patients in the intervention group. Data analysis has not occurred.

Conclusions: African American individuals often receive less patient education about self-care and treatment options for CKD. We hope this study provides a solution to increase hospitalized African American patients' knowledge of CKD and motivation for CKD self-care through computerized adaptive education, reduce disparities, and improve patient outcomes.

Trial Registration: ClinicalTrials.gov NCT06364358; https://clinicaltrials.gov/study/NCT06364358

International Registered Report Identifier (IRRID): DERR1-10.2196/66846

(JMIR Res Protoc 2025;14:e66846) doi:10.2196/66846

KEYWORDS

chronic kidney disease; computerized adaptive education; end-stage kidney disease; end-stage renal disease; glomerular filtration rate; kidney failure; usual hospital care; inpatient

Introduction

Background

End-stage kidney disease (ESKD) or kidney failure is a condition where the kidneys lose the ability to function. African American individuals are 4 times as likely to have ESKD compared to White American individuals [1]. African American patients are more likely to have comorbidities such as diabetes, obesity, high blood pressure (hypertension), and heart failure, which all increase the risk of developing kidney disease [1].

Hemodialysis can help patients with ESKD feel better and live longer. However, dialysis is not a cure for ESKD, and patients on hemodialysis have high morbidity and mortality rates [1]. Patients on hemodialysis can also experience side effects such as low blood pressure (hypotension), muscle cramps, sleep problems, anemia, bone disease, high blood pressure (hypertension), and access-site complications [2]. In-center hemodialysis (IHD) with thrice weekly sessions in a dialysis unit is the most common treatment for ESKD. Patients who use IHD experience greater inconvenience, worse waste clearance, and more issues with transportation in comparison to other ESKD options. Alternatives to IHD include home hemodialysis, peritoneal dialysis, and kidney transplantation. These methods are associated reduced morbidity and mortality, or improved quality of life, compared to IHD [3].

There are racial disparities in the use of these renal replacement therapy (RRT) modalities. African American patients are less likely to be informed about better RRT options. African American patients are 47% less likely to use peritoneal dialysis and 3.5 times less likely to have a kidney transplant [4]. Often, African American patients are less likely to receive information from their provider about their CKD stage, treatment options, and self-care to prevent and treat CKD [3]. The hospital can be an important intervention site because hospitalization rate rises sharply in the 3 months before dialysis initiation. In addition, even patients who are not connected to primary or specialty care can present to the hospital.

Our previous work to was to develop and test a hospital-based CKD intervention, PREP RRT (Patient Referral and Education Program Prior to Renal Replacement Therapy). To develop the intervention, we interviewed African American patients about CKD knowledge and barriers to RRT preparation [4,5]. The intervention in that study includes an in-person African American health educator and written materials [2]. Our results showed an increase in knowledge in the intervention group compared to control group. We also found that culturally tailored interventions improved patient outcomes [6]. Drawing from insights gained in our prior work, our research team developed and implemented the Interactive Computer-Adaptive Chronic Kidney Disease (I-C-CKD) education as a patient education intervention to inform hospitalized African American patients with advanced CKD about their CKD and RRT options. This computer-based education is predicted be more accessible for hospitalized patients through videos that are culturally tailored with a virtual African American narrator, as in-person educators have some limitations.

Primary Hypothesis

Our primary hypothesis is that the computerized adaptive education will be more effective than usual hospital care in improving knowledge about CKD, CKD self-care, and RRT options (primary outcome).

Secondary Hypothesis

Our secondary hypothesis is that the computerized adaptive education will increase patients' intent to participate in CKD self-care compared to usual hospital care. We also believe that the computerized adaptive education will increase patients' action and commitment to CKD health-seeking behavior, access planning prior to dialysis initiation, initiate home dialysis modalities, and/or have a transplant evaluation after discharge and beyond 30-day follow-up.

Methods

Trial Design

The I-C-CKD study is a hospital-based, randomized controlled trial of a computerized patient education intervention compared to usual hospital care. After obtaining verbal consent (Multimedia Appendix 1), each patient will be randomly assigned into two groups: usual hospital care (control group) and the computerized adaptive education (intervention group), which is assisted by a research assistant (RA).

The usual hospital care control group will feature a baseline General Health Knowledge and Intent survey. Participants in the usual hospital care control group will receive the pretest survey and education materials but will not receive specific knowledge about CKD or their CKD condition. Participants in the control group will receive printed patient education materials informing them of the importance of a general healthy lifestyle, including diet, physical activity, and medication adherence. The printed materials for the usual hospital care control group are meant for patients with cardiovascular conditions and do not have any information about CKD. Participants who receive the control condition will also be able to speak with the patient educator if they want to.

The computerized adaptive education intervention group will receive the advanced CKD education module with information on the risk factors, stages, treatment options, and lifestyle of patients with CKD (see Figures 1 and 2). The RAs will assist with the program but not offer any information or knowledge about CKD. Following the patient's review of the advanced CKD education module, the RAs will administer the posttest General Health Knowledge and Intent survey.

Figure 1. Screenshot of the computerized adaptive education intervention featuring a personal story.

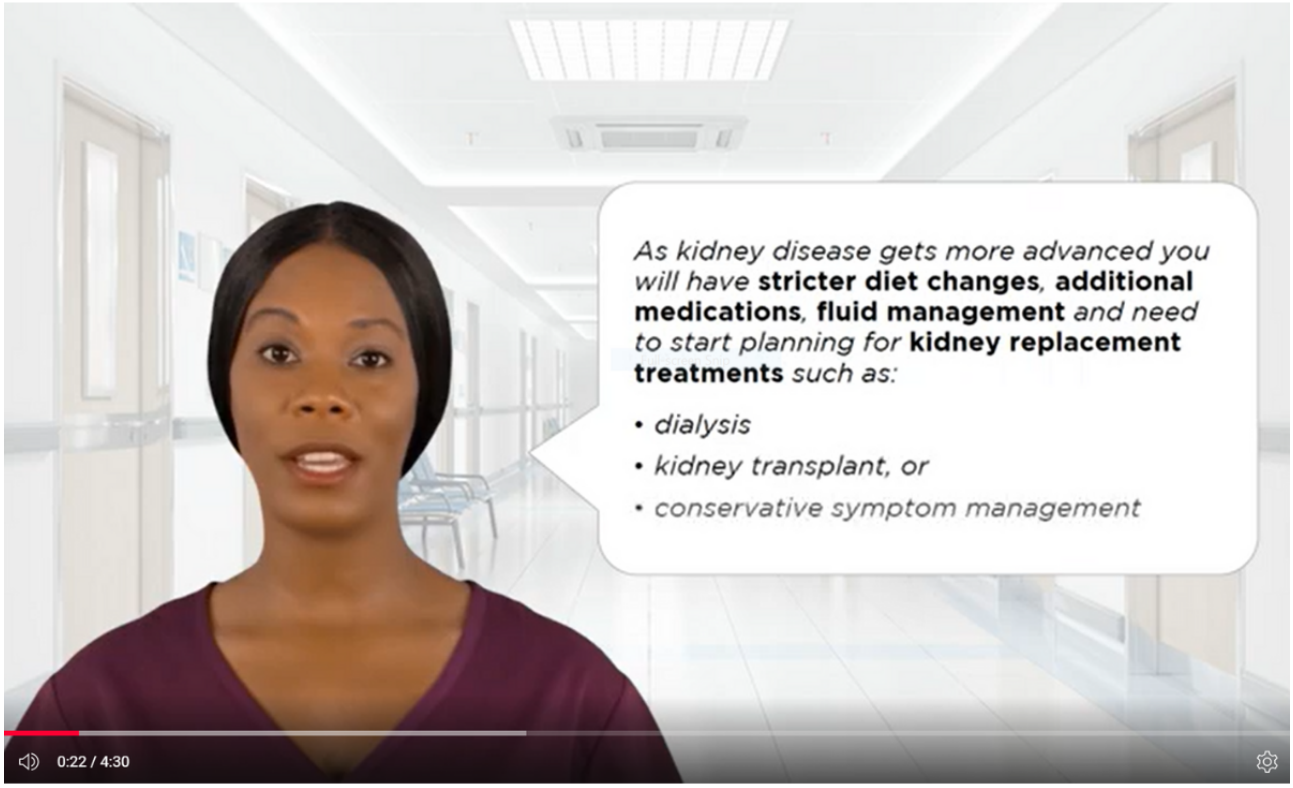
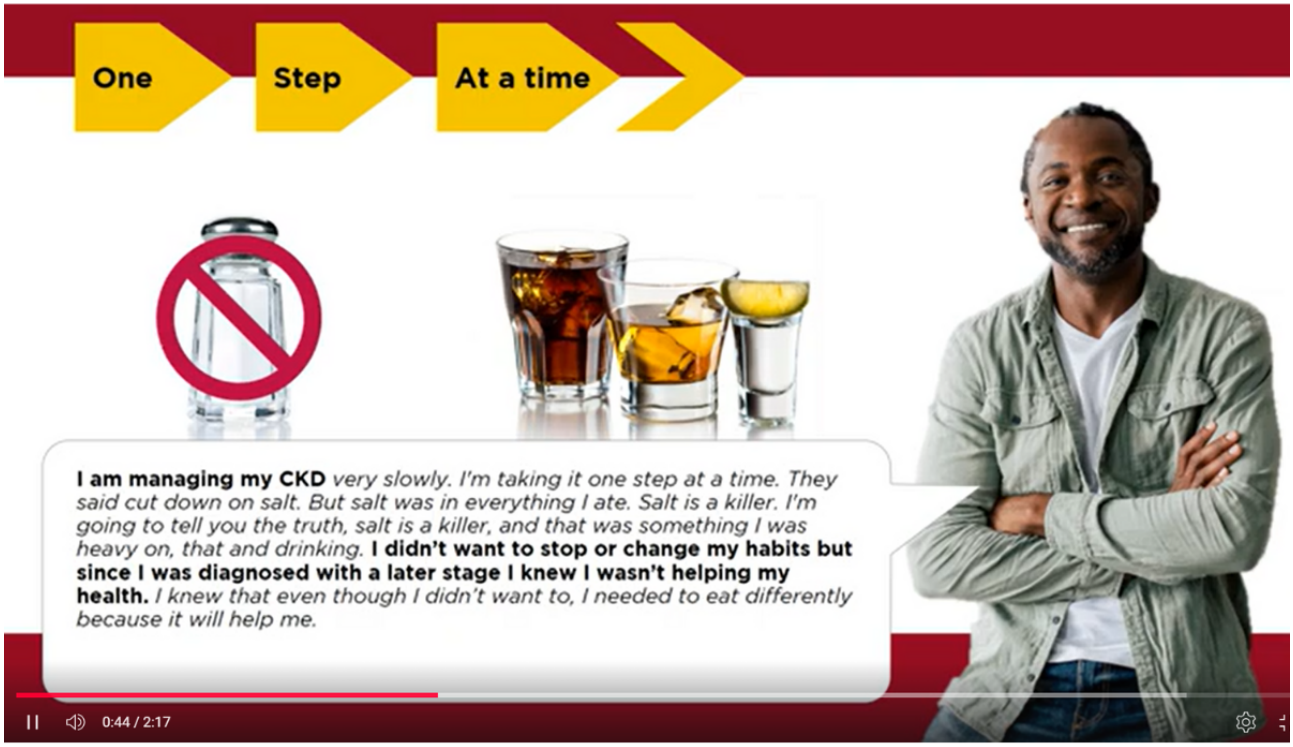


Figure 2. Screenshot of the computerized adaptive education intervention regarding treatment options. CKD: chronic kidney disease.



Both the usual hospital care control group and the computerized adaptive education intervention group will complete the "What's Next" form, to assess the patient's commitment to specific self-care activities. Patients will select their top-3 health goals, rate how confident they are about each goal, and identify how important each goal is to them. Patients will also report on their health resources. All the forms will be sent to the patient educator, a trained nephrology social worker.

Each patient will be contacted 30 days after discharge to ask about their commitment to health goals, barriers to self-care, and treatment plans.

The SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) checklist is provided in Multimedia Appendix 2.

Participants and Eligibility

The study will take place at the University of Chicago Medical Center (UCMC). We will approach hospitalized, English-speaking, African American patients at UCMC, aged 18-70 years, who meet the criteria for advanced CKD (Stage 3b or greater) with an estimated glomerular filtration rate (eGFR) <45 mL/min/1.73 m^2; they must not be on dialysis yet or have a history of kidney transplant. In order to be eligible, patients must have an eGFR <45 mL/min/1.73 m^2 during the current hospitalization in addition to prior hospitalizations and/or outpatient visits. We will have access to prior UCMC inpatient and outpatient laboratory values. We will also have access to some inpatient and outpatient laboratory values from other medical centers through Epic Care Everywhere. The exclusion criteria include patients who are hospitalized in the intensive care unit, meet the Montreal Cognitive Assessment criterion for cognitive impairment, or require a proxy for study consent. We will enroll 170 participants and randomly assign 85 to the computerized adaptive education and 85 to usual hospital care.

Recruitment

This study will be a substudy of the Hospitalist Project, an ongoing clinical study that examines a variety of outcomes of patients hospitalized in our general internal medicine services, and includes the analysis of administrative data, inpatient interviews, and 30-day follow-up by phone [7]. Hospitalist Project staff will obtain basic demographic information and medical history. Per the Hospitalist Project protocol, staff will also obtain permission to contact patients after discharge and to access their medical records (ie, at UCMC, from other medical systems, and through Medicare linkage). All inpatients recruited to the Hospitalist Project will be screened daily by the RA to identify patient eligibility for the study.

We will approach all Hospitalist Project–enrolled patients who meet study criteria and obtain informed verbal consent.

Randomization

Participants will be randomly assigned using a computerized spreadsheet, assigning each participant a random number. Participants who are assigned an odd number will be assigned to the intervention group. Participants who are assigned an even number will be assigned to the control group. The RA will begin by identifying an eligible participant who consented to the Hospitalist Project. Then, they will use the randomization spreadsheet to determine if the participant will be part of the intervention group or the control group. They will then approach the patient with the appropriate form and study packet.

The RA will complete the randomization, assignment, and enrollment process.

Blinding

Trial participants will be blinded after group assignment. Participants will view the survey as a Google Form and will not be informed whether they are part of the intervention or control group. They will also receive a study packet, which will not identify if they are part of the intervention or control group. The research team will not be blinded.

Intervention Group

The RA will meet each participant and conduct the pretest survey in the participant's private hospital room. The computerized adaptive education intervention group will receive an advanced CKD education module with information about CKD risk factors, stages, treatment options, and lifestyle modifications. The RA will assist in advancing program modules but not offer any information or knowledge about CKD. The avatar will be an African American woman who will present statistics about African American individuals and CKD. The interactive component will allow participants to personalize the information received based on prior CKD knowledge, diabetes status, and the level of motivation. The interactive CKD video can be completed in 30-45 minutes. Following the patient's completion of the advanced CKD education module, the RA will then readminister the General Health Knowledge and Intent survey.

The computerized adaptive education intervention group (and the usual health care control group) will complete the "What's Next" form, to assess the patient's commitment to specific self-care activities. Patients will select 3 health goals from a list of 10 options, rate their level of confidence in the ability to make change, and identify an action plan to accomplish each goal. Moreover, patients will be asked to report their needs from the medical care team and for community assistance, and they will be provided a resource list. The study will also ask if patients would like a primary care doctor and/or a nephrologist. This information will be relayed to the primary inpatient team. All the forms will be sent to the patient educator, a trained nephrology social worker.

We will encourage participants to complete the voluntary study in one visit. At 30 days after discharge, both groups will complete a follow-up call with the project RA. Participants will be queried about progress on goals set on the health commitment form, knowledge, and health intent.

Control Group

The RA will meet each patient and conduct the pretest survey in the participant's private hospital room. The usual hospital care control group will receive the General Health Knowledge and Intent pretest survey and printed education materials without explicit CKD information or knowledge about their CKD condition. The distributed education materials were intended for patients with cardiovascular conditions and focus on the importance of a general healthy lifestyle, including diet, physical activity, and medication adherence, and does not include CKD specific information. Following the patient's completion of the general health education video module, the RA will then readminister the General Health Knowledge and Intent survey.

The usual hospital care control group (and the computerized adaptive education intervention group) will complete the "What's Next" form, to assess the patient's commitment to 3 participant-selected self-care activities. Participants also will

be contacted 30 days after discharge to complete the follow-up survey.

Outcomes

Primary Outcome

The primary outcome of this study is the changes in patient knowledge, attitudes, and behavior about CKD and RRT. To evaluate CKD and CKD self-care knowledge, we will use a modified Kidney Knowledge Survey; the CKD Self-Management Knowledge Toolkit, which is a validated instrument [8,9]; and an investigator-developed ESKD knowledge survey. We will measure the change from the baseline observed via the pretest, posttest, and follow-up surveys. The pretest and posttest surveys comprise 20 mixed format multiple-choice and Likert-scale questions (ranging from strongly agree to strongly disagree; from no knowledge to a great deal of knowledge; and from extremely unlikely to extremely likely) to examine the patient's basic understanding of their health, general CKD knowledge, and health management.

Secondary Outcomes

The secondary outcomes are patient motivation and intent. We will administer the CKD Self-Efficacy Scale [10], the Patient Activation Measure [11], and the Kidney Failure Treatment Preferences [12] before the intervention, immediately after the intervention, and at 30 days after discharge. We will administer the General Health Knowledge and Intent survey, an investigator-developed instrument, to assess RRT preferences and commitment to CKD self-care activities, including intent to seek a nephrologist, noncatheter dialysis access initiation, and completion of a transplant evaluation. Each patient will be contacted 30 days after discharge to discuss their commitment to each selected health goals, barriers, and treatment plan.

Data Collection and Management

We will retrieve baseline survey information from the Hospitalist Project, which includes patient demographics and comorbidities. The initial trial data will be collected, stored, and saved in Google Forms with linked Google Sheets for the pretest and posttest surveys on the computer. The RA will photograph and save participants' written packet responses digitally. The RA will deidentify the packet responses and save them according to their initials, study visit date, and enrollment number. We will ensure participant responses remain confidential. Information about the patient's medical status, enrollment, and participation will be maintained through a password-encrypted file.

The RA will use password-encrypted laptops to conduct the study. The participant's responses on the study packet will be photographed, deidentified, and saved in a password-encrypted digital folder. The analysis file will not be attached to protected health information to protect patient privacy. We will conduct analysis in a locked office with a password-protected computer. All transcripts and surveys will be deidentified.

Statistical Methods

The planned total sample size is 170 (85 per group), which accounts for participant dropout due to unexpected discharges, changes in clinical status, or study disenrollment. The primary outcome will be measured by the change in baseline observed via the pretest, posttest, and follow-up surveys. Using a 2-sample, 2-tailed *t* test, a total of 154 (77 per group) participants is required to obtain >90% power to detect at least a 10% difference with the most conservative SD of 21% with a 1-sided type-1 error of 5%.

Our team will use the paired, 2-tailed *t* test with a Bonferroni adjustment for multiple comparisons with the usual hospital care and computerized adaptive education groups. We will use one-way ANOVA and chi-square tests to examine the significance between the usual hospital care and computerized adaptive education groups. This will determine whether there is a statistically significant difference between the two groups. We will also determine if the difference between observed and expected data is because of chance or a relationship between the usual health care and computerized adaptive education groups.

Data analysis will take place in an UCMC office. We will continue to monitor patient medical records after the study to determine whether they may be later included or excluded from the study.

Data Tracking

Data will be tracked in Google Sheets, linked to each survey. This will also help identify participant's responses with the date, time, and enrollment number. Study packet responses will be saved in a password-protected box. Retrospective review will also be done to ensure each enrollment number matches the correct medical record number. Our research team will have access to the final trial dataset, and we will keep the data for 5 years after the study is completed.

Ethical Considerations

We obtained institutional review board (IRB) approval for this protocol (IRB 23-0385), and the parent study (the Hospitalist Project) is also IRB approved (IBR 16-1131). Written, informed consent to participate in the Hospitalist Project will be obtained from all participants. Participants will also verbally consent and be enrolled in the I-C-CKD study.

Patients will be informed that the study is completely voluntary and may withdraw at any time. Discontinuation will also occur if patients are in acute distress or experience declining health conditions during hospitalization. For example, if the patient is transferred to intensive care unit, is intubated, or has an altered mental status and can no longer participate, then we will withdraw them from the study. Patients will also be able to meet with patient educator who is a licensed clinical social worker if they are interested in additional information, are under distress, or want posttrial care.

Patients will receive US $25 gift cards upon completion of the pretest and posttest surveys and US $10 for partially completed surveys. All participants will be compensated. This study is minimal risk, as an education intervention is the only experimental procedure involved. Additionally, reports will be made to the IRB in the case of an adverse event, along with any

protocol modifications to the investigators, IRB, trial participants, journals, and regulators.

Results

Recruitment for the I-C-CKD study began May 2, 2023. We are currently recruiting and have enrolled 96 patients who completed both pretest and posttest surveys as of December 2024. This includes 50 patients in the control group and 46 patients in the intervention group. Data analysis has not occurred. We will communicate trial results to trial participants, health care professionals, and the public via a journal publication.

Discussion

We believe our study will result in the computerized adaptive education intervention group experiencing a greater improvement in CKD knowledge, CKD health-seeking behavior, and self-care in comparison to the control group. The goal of this study is to increase hospitalized African American patients' knowledge of CKD and motivation for CKD self-care. We have created and will assess a culturally tailored, computerized adaptive education intervention that expands on the information gathered from in-person interventions. Computerized adaptive education can evaluate patients' concerns and provide personalized education. Customized patient education information is more likely to be recalled and significantly influence a patient's motivation and behavior modification.

African American patients diagnosed with CKD experience inequities in the quality of health education, self-care, and medical treatment for ESKD [13]. Patient education can encourage African American patients with advanced-stage CKD to make informed decisions and take control of self-care and health decisions to delay progression to ESKD. Providing CKD education during hospitalization can address gaps in care to help patients initiate preventative care, plan for future RRT, and build a treatment team that aligns with their health and lifestyle preferences.

This intervention focuses on hospitalized African American patients who represent more than 80% of the general medicine population at our medical center. The intervention is culturally tailored to African American patients. The hospital also serves patients who are not followed by routine medical providers and have trouble accessing outpatient care due to limited transportation, limited or no insurance, mobility issues, and socioeconomic constraints [14]. Hospitalized patients may be more open and responsive to CKD education efforts when they are focused on their health during a hospital stay. The intervention can also link these patients to outpatient care. We will also ask if patients would like a primary care doctor and/or a nephrologist. This information will be relayed to the primary inpatient team.

Limitations of this study include the single-hospital study design, which reduces the generalizability of the results. In addition, we are testing the intervention only among hospitalized African American patients who are generally admitted with urgent or acute health concerns, which may reduce their ability to fully participate or complete this study. An additional barrier for inpatient kidney education to be disseminated on a large scale is that the results may differ among a different group or in a different health care setting.

In conclusion, African American individuals often receive less patient education about self-care and medical treatments for CKD. We hope our study provides one way to reduce this disparity. However, to improve CKD outcomes, African American patients—and all patients with CKD—require frequent, understandable education about CKD across all sites of care.

Acknowledgments

The authors appreciate the faculty and staff of the Hospitalist Project, particularly Ms Neha Khadka, who made this study possible. The study was funded by the National Institutes of Health's National Institute of Diabetes and Digestive and Kidney (R21DK121262). The project is sponsored by the University of Chicago Medical Center's General Internal Medicine department. This research did not receive any specific grant from funding agencies in the commercial or not-for-profit sectors.

Data Availability

The datasets generated or analyzed during this study are not publicly available as data analysis has not occurred at this time but are available from the corresponding author on reasonable request.

Authors' Contributions

MS is the primary investigator. All authors read and approved the final manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Institutional review board–approved consent form.
[PDF File (Adobe PDF File), 81 KB - resprot_v14i1e66846_app1.pdf]

Multimedia Appendix 2
SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) checklist.
[PDF File (Adobe PDF File), 122 KB - resprot_v14i1e66846_app2.pdf]

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Abbreviations

CKD: chronic kidney disease
eGFR: estimated glomerular filtration rate
ESKD: end-stage kidney disease
I-C-CKD: Interactive Computer-Adaptive Chronic Kidney Disease
IHD: in-center hemodialysis
IRB: institutional review board
PREP RRT: Patient Referral and Education Program Prior to Renal Replacement Therapy
RA: research assistant
RRT: renal replacement therapy
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials

UCMC: University of Chicago Medical Center

Edited by A Schwartz; submitted 26.09.24; this is a non–peer-reviewed article;accepted 07.03.25; published 17.04.25.

Please cite as:
King A, Omoniyi T, Zasadzinski L, Gaspard C, Gorman D, Saunders M
Interactive Computer-Adaptive Chronic Kidney Disease (I-C-CKD) Education for Hospitalized African American Patients: Protocol for a Randomized Controlled Trial
JMIR Res Protoc 2025;14:e66846
URL: https://www.researchprotocols.org/2025/1/e66846
doi:10.2196/66846
PMID:

Protocol

Evaluating the Impacts of Community-Campus Engagement on Population Health in Ottawa and Thunder Bay, Canada: Protocol for a Mixed Methods Contribution Analysis

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Abstract

Background: Municipalities play a crucial role in population health due to their community connections and influence on health determinants. Community-campus engagement (CCE), that is, collaboration between academic institutions and communities, is a promising approach to addressing community health priorities. However, evidence of CCE's impact on population health remains limited. Measuring the impacts of CCE is inherently complex due to factors such as diverse stakeholders, context-specific variables, and dynamic interactions within a community.

Objective: This study aims to develop robust evidence on the impacts of CCE on population health outcomes in Ottawa and Thunder Bay, Ontario, Canada, focusing on 5 shared health priorities: housing, discrimination, poverty, violence, and mental health.

Methods: We will use a proven CCE model called CityStudio, which has been implemented in both cities. We will use Mayne's mixed methods contribution analysis in three stages: (1) formulating a theory of change that outlines the expected contributions of CCE to population health outcomes; (2) gathering qualitative and quantitative data in line with the established Theory of Change; the data will be collected from various sources, including case studies of existing CityStudio projects, a web-based CCE stakeholder survey, a literature review, and population and community health data; and (3) reviewing the gathered evidence to determine the extent of CCE impacts on population health.

Results: Ethical approval for this project was granted in May 2023. We have since initiated stage 1 by reviewing the literature to inform the development of the theory of change. We expect to complete this study by May 2026.

Conclusions: This study will address two critical gaps about how improving health outcomes depends on CCE: (1) how academic institutions can best engage with their communities to improve population health outcomes, and (2) how municipalities can engage with academic institutions to address their community health priorities. Conducting our work in differing contexts will allow us to consider a broader range of other influences on outcomes, thus making our work applicable to various settings and outcomes.

International Registered Report Identifier (IRRID): PRR1-10.2196/58546

(JMIR Res Protoc 2025;14:e58546) doi:10.2196/58546

KEYWORDS

community-campus engagement; population health; contribution analysis; mixed methods; health determinants; community health; CityStudio; theory of change; impact evaluation

Introduction

Background

Achieving improved population health outcomes requires a comprehensive, multisectoral approach beyond healthcare [1-3]. With their robust community ties and influence over various health determinants, municipalities are well-positioned to drive progress [1-3]. In Canada, local governments and community partners often identify their communities' priority health needs through established safety plans or social policy frameworks [3]. These needs are expressed in Ontario, the country's most populous province, through provincially mandated Community Safety and Well-Being Plans (CSWBPs) [4]. Updated every 4 years, these plans serve as strategic roadmaps, guiding municipalities' efforts to improve population health outcomes [4,5].

Collaborations between municipalities and their local academic institutions have the potential to contribute positively to the health of the local community [6-9]. Through collaborative efforts, community-campus engagement (CCE) fosters mutually beneficial relationships between local stakeholders (eg, community organizations, city representatives, and residents) and academic institutions (eg, universities and research centers) [6-8]. Municipalities can contribute their deep understanding of local needs and priorities to such engagement, while academic institutions provide research expertise and resources [6,8,10]. This collaborative framework facilitates shared decision-making, efficient resource allocation, and the development of tailored strategies to directly address specific health concerns within the community, ultimately leading to improved health outcomes [6,10].

CCE can take various forms, such as community-based research and service learning [6,10]. Community-based research involves collaboration between faculty members, students, and local communities to address critical issues [6,10]. On the other hand, service-learning integrates classroom learning with community service, equipping students with the skills to tackle real-world challenges while also improving their communities [6,10]. Each form can potentially contribute to the community's health in different ways. For instance, community-based research can identify emerging health disparities in specific neighborhoods, while service-learning programs can equip future health care professionals with the skills to address these issues.

While CCE shows promise in supporting municipalities' health agenda goals, there remains significant uncertainty about the specific mechanisms and pathways through which it influences population health outcomes, underscoring the need for further research to understand its impact at the municipal level [11]. Existing literature in this area is mainly reflective [12,13] or qualitative [14,15], primarily focusing on health outcomes resulting from individual partnerships [16-19] and the perspectives of faculty and students involved in CCE [10,14,20,21]. Although these studies provide valuable insights, they offer only a partial understanding of CCE's broader impact on population health because they do not fully investigate the pathways, conditions, and contextual factors that influence outcomes.

Some studies have reported positive health outcomes, such as reduced substance misuse [16] and increased physical activity [17]. However, these studies often fail to clearly outline the change processes that explain these positive outcomes, focusing mainly on end results. This emphasis on outcomes, with insufficient attention to the processes, limits our understanding of how specific actions, stakeholder interactions, and contextual factors contribute to health improvements. Consequently, the complexity of the mechanisms driving these changes remains underexplored, making it difficult to pinpoint the pathways through which CCE initiatives achieve their impact. This knowledge gap highlights the need for more robust research to evaluate the impact of CCE on population health at the municipal level that specifically focuses on the contexts and mechanisms that result in change.

Contribution Analysis: a Promising Approach for Evaluating the CCE Impacts

As with community engagement in general, the complexity of measuring CCE impacts on population health makes experimental approaches to measuring CCE impacts neither practical nor feasible, as many factors cannot be controlled for [22], such as the involvement of diverse stakeholders with diverging interests (eg, local governments, faculty and students, community groups) [15,23,24], the evolving dynamics of operations [25], and the influence of external factors like governmental policies and local socioeconomic conditions [15,26,27]. Experimental approaches may thus overlook the underlying causes of an intervention's success or failure, providing limited insights into the causal mechanisms at play [28,29].

Contribution analysis is a theory-based impact evaluation approach that is particularly suited to contexts of high uncertainty, where the goal is not to prove causation definitively but to reduce uncertainty by establishing a plausible association between interventions and outcomes [28-32]. This emphasis on reducing uncertainty makes CA particularly suitable for evaluating the CCE impact on population health [11].

An integral component of contribution analysis is the theory of change, which outlines the causal mechanisms in a results chain running from inputs to impact and illustrates how the intervention being examined is expected to bring about change [31]. However, the theory of change goes beyond a standard results chain or logic model by elucidating assumptions, risks, unintended effects, and other vital factors underpinning the relationships [30,31].

Narrative statements, known as contribution claims, are generated once the theory of change has been developed [32]. These claims are presented as hypotheses, proposing how the intervention's activities and outputs contribute to the observed outcomes while considering influencing factors and context [30]. The theory of change and contribution claims are refined and validated iteratively using qualitative and quantitative data and stakeholder participation [22,32]. This process alternates between theory development and empirical testing, resulting in a robust, evidence-based theory of change [30]. The ensuing theory is the foundation for the contribution story, which offers a detailed account of the intervention's impact and the stakeholders' perspectives [33].

Contribution analysis may be carried out at 3 levels: minimalist, direct influence, and indirect influence, each tailored to the complexity of the intervention and the depth of the assessment [22]. Minimalist contribution analysis is ideal for interventions with clear, measurable outcomes. It formulates a theory of change, confirms output delivery, and validates contribution claims using existing data and evidence [22,32]. Direct influence contribution analysis is suitable for complex interventions with diverse outcomes, as it builds on minimalist analysis by using empirical data to confirm the intervention's contribution to the impact [22]. Indirect influence contribution analysis, suitable for complex interventions with uncertain, emergent outcomes, builds on direct influence analysis by further testing contribution claims against alternative explanations, offering a more comprehensive understanding of what caused an observed impact [31,32].

Objective

This research project uses contribution analysis to rigorously assess and reduce uncertainty about whether, how, and to what extent CCE has contributed to improving population health in Ottawa and Thunder Bay, Ontario, Canada. The study will focus on 5 specific shared population health priorities for both municipalities: housing, discrimination, poverty, violence, and mental health. Our specific objectives are as follows.

- Identify and outline the key mechanisms and processes through which CCE is anticipated to impact population health outcomes in Ottawa and Thunder Bay.
- Assess the extent to which CCE has contributed to the targeted population health outcomes, evaluating their impact against the mapped mechanisms and processes.

Methods

Study Setting

Our study will be conducted in Thunder Bay and Ottawa, 2 Ontario municipalities with medical schools and health education institutions. These cities have developed CSWBPs by reviewing local data comprehensively and holding community consultation sessions to identify their population's unique needs and characteristics [34,35]. Despite differences between the Ottawa and Thunder Bay CSWBPs, both cities have identified 5 similar priorities related to population health, as outlined in Table 1.

Table 1. Shared priorities in the Thunder Bay and Ottawa Community Safety and Well-Being Plans.

Priority areas	Description
Housing	Ensuring all residents have access to safe, affordable, and suitable housing.
Discrimination	Addressing systemic issues perpetuating discrimination, marginalization, and racism within the community.
Poverty	Achieving financial security and reducing poverty for community members.
Violence	Preventing and reducing gender-based violence and violence against women in the community.
Mental health	Promoting positive mental health and well-being for all community members.

To help address these priorities, both municipalities have adopted CityStudio, a transferable, nonprofit, project-oriented, evidence-based model of CCE [36,37]. This model aims to innovate how cities are co-created to become healthier communities and assist community stakeholders in improving their neighborhoods [38]. The model is demand-driven, leveraging expertise and resources from educational institutions to meet the priority needs identified by the city. The CityStudio project cycle encompasses 5 stages, from initial collaboration for project development and confirmation through work on a real site to final project design for scalability [36].

The cities of Ottawa and Thunder Bay have formally launched CityStudio and initiated and completed various projects. To date, 63 projects have been carried out involving community groups, city staff, and faculty and students from 6 academic institutions in these regions. CityStudio Ottawa and CityStudio Thunder Bay are engaged in this research study, providing full access to a list of stakeholders involved in their projects and data on an inventory of CCE projects.

Study Design

We will apply Mayne's contribution analysis within a convergent parallel mixed methods design to assess the contribution of CCE to population health in Ottawa and Thunder Bay [39]. A convergent parallel design allows for the simultaneous collection and independent analysis of both qualitative and quantitative data, with results from each strand analyzed for congruence and integration during the interpretation phase [40]. Mayne's approach is particularly suited for complex interventions such as CCE and has been effectively used in assessing the impacts of interventions and policies in fields such as international development [41] and public administration [42]. However, our recent scoping review suggests that this approach is infrequently applied in health-related interventions [43]. Therefore, our research aims to both generate rigorous

evidence of CCE's impact on health and provide valuable insights for using contribution analysis in health research and evaluation.

The following preliminary evaluative questions will direct our analysis. These questions will be refined further upon the completion of stage 1.

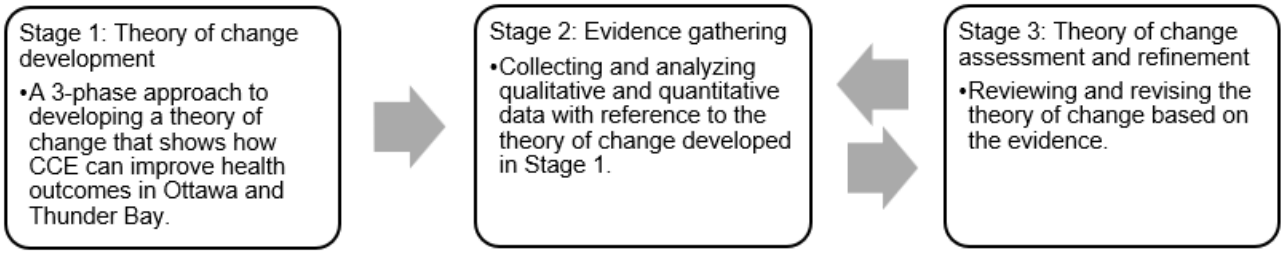
- What are the specific mechanisms and pathways by which CCE influences population health outcomes in Ottawa and Thunder Bay?
- To what extent does CCE contribute to changes in population health outcomes relative to other factors in both cities?

We will specifically use the cause-to-effect strategy, which begins with CCE and works forward to understand how it contributes to health outcomes. The cause-to-effect strategy focuses on identifying "causal packages"—combinations of CCE activities and other contributing factors that collectively explain the observed changes [44]. We will adopt a streamlined version of Mayne's 6-step approach to contribution analysis, condensing it into the 3 crucial stages described by Delahais [30]. The 3 stages are as follows.

- Stage 1—theory of change development: This stage involves using a 3-phase approach to developing a robust theory of change that accurately represents the potential pathways and external factors describing how CCE is expected to contribute to improved population health outcomes in Ottawa and Thunder Bay. This stage is expected to last 7 months.
- Stage 2—evidence gathering: Both qualitative and quantitative methods are used to generate evidence in line with the established theory of change. The collected evidence forms the basis for empirical examination. This stage is expected to last 11 months.
- Stage 3—theory of change assessment and refinement: This stage involves reviewing the gathered evidence to determine the extent of CCE impacts on population health. Any identified limitations lead to a return to stage 2 for additional data collection until satisfactory evidence is gathered. This stage is expected to last 5 months.

Figure 1 provides a visual overview of the research process, illustrating the dynamic relationship between data collection (stage 2) and theory testing (stage 3) [30].

Figure 1. Overview of the research process. CCE: community-campus engagement.



This study adheres to the Good Reporting of A Mixed Methods Study (GRAMMS) guidelines [45] to ensure comprehensive and transparent reporting of the mixed methods design, including the justification for the approach, the integration of qualitative and quantitative data, and the insights gained from their convergence (Multimedia Appendix 1).

Stage 1: Theory of Change Development

Overview

Stage 1 will use a 3-phase approach to construct a credible theory of change. Each phase corresponds to one of the approaches proposed by Funnell and Rogers [46] for purposeful theory development: (1) deductive, (2) articulation of mental models, and (3) inductive, which will be implemented sequentially in the theory of change development process, with the potential for iteration to accommodate evolving requirements. An overview of each phase and corresponding methods is presented in Table 2. While our approach follows a structured sequence, we acknowledge that the evolving nature of developing a theory of change requires flexibility, allowing for iteration as needed. Each step of the theory of change development will be carefully documented to maintain transparency in this iterative process. This includes tracking the initial assumptions, the evolution of claims based on stakeholder input and empirical evidence, and the methodological adjustments made throughout the process. The documentation will highlight how and why specific claims were refined, discarded, or validated, ensuring that the process remains transparent and aligned with best practices in contribution analysis.

Table 2. Overview of the study's 3-phase approach to developing the theory of change.

Phases	Description	Proposed methods
Phase 1: Deductive	Draft an initial theory of change based on existing theories and knowledge.	Conduct a narrative literature review on the health impacts of CCE[a], focusing on the 5 shared Ottawa and Thunder Bay priorities.
Phase 2: Mental model articulation	Express the implicit assumptions or mental models of stakeholders.	Hold stakeholder workshops to provide feedback on the drafted theory of change and identify context-specific factors influencing outcomes.
Phase 3: Inductive	Validate and refine the theory of change using practical insights and external expertise.	Conduct semistructured interviews with experts in CCE and program evaluation for validation and refinement.

[a]CCE: community-campus engagement.

Phase 1: Deductive

Phase 1 uses Funnell and Rogers' deductive approach [46] to formulate an initial theory of change based on existing theories and knowledge, ensuring a solid theoretical foundation. To accomplish this, we will conduct a narrative literature review chosen for its flexibility and capacity to identify critical theories, concepts, and findings related to CCE and its impact on population health concerning the five identified areas of population health [47]. The results of this review will lay the groundwork for the development of the theory of change, as detailed in the subsequent sections.

Narrative Literature Review Procedures

In collaboration with a librarian, we will design and execute a comprehensive search strategy that encompasses relevant health databases and sources. The selected literature will be imported into Covidence (Veritas Health Innovation Ltd), a web-based literature review tool, for screening by independent reviewers [48]. At least 3 research team members will review various sources, including academic papers, reports, and policy documents, to inform the initial development of the theory of change. Screening criteria will include relevance to the 5 key population health priorities and use for the theory of change.

Team members will create an annotated bibliography for each paper using a standardized template based on Bennett's hierarchy [49], a framework that categorizes program outcomes (inputs, activities, outputs, and impacts) [50]. The template will be divided into three sections: (1) CCE implementation, focusing on inputs, activities, participation, and reactions; (2) knowledge and practice change, focusing on knowledge, awareness, skills, attitude, and practice change; (3) results and impact, focusing on final health impacts or changes for individuals, communities, systems, or organizations. Team members will hold weekly meetings to share insights from the literature and discuss potential pathways.

Development of the Initial Theory of Change

Following the literature review, team members will convene to create the initial theory of change using Vogel's team-based approach, which is specifically designed to develop theories of change for research projects. This approach includes guiding questions on 5 key areas: context analysis, long-term change, sequence of events, assumptions, and diagram and narrative summary [51]. To document decisions and track modifications, the team will use Theory of Change Online 3.0 (ActKnowledge), a web-based software designed explicitly for the collaborative theory of change building [52]. This initial theory of change will remain adaptable, allowing for iterative revisions based on feedback and new data. Once the initial draft of the theory of change is completed and agreed upon, the team will proceed to the mental model articulation phase.

Phase 2: Mental Model Articulation

In phase 2 of the theory of change development, we will use Funnell and Rogers's mental model articulation approach [46]. This approach will help us integrate stakeholder insights, ensuring they are context-specific, comprehensive, and account for relevant influencing factors. To achieve this, we will conduct participatory workshops with stakeholders involved in CCE through CityStudio Ottawa and Thunder Bay [53,54].

Recruitment of Stakeholders

We will use a purposeful sampling strategy to invite stakeholders based on specific criteria such as their location (Ottawa and Thunder Bay), experience with CCE, stakeholder roles (academics, community partners, and city staff), and knowledge related to the 5 shared population health priorities. This approach will ensure a diverse representation of stakeholders, balancing their professional backgrounds, geography, and CCE experience. [55].

Our initial outreach will target CityStudio Ottawa and CityStudio Thunder Bay stakeholders who expressed interest in our workshops during 2 information sessions held in May 2023, which aimed to gather feedback on the proposed protocol and identify potential workshop participants. The participants will include academics, community partners, and city representatives involved in CCE who expressed interest and shared their contact details through a web-based survey during their participation in the information session.

We will engage CityStudio coordinators in Ottawa and Thunder Bay if additional participants are needed. They will circulate an invitation email to their contact lists, which include a broader network of individuals involved in CCE. The email will provide information about the project, the purpose of the workshops, and the importance of their participation. All participants will be asked to sign a consent form before their involvement.

Stakeholder Workshops Procedures

We plan to conduct 2 separate workshops conducted via Zoom. The first workshop will assemble 10-12 stakeholders from Ottawa, and the second will gather a similar group from Thunder

Bay. Each workshop, lasting 3 hours, will be divided into 2 parts.

- Introduction and overview: We will provide essential details about contribution analysis and the theory of change. We will then present an overview of our draft theory of change and explain the process used to develop it.
- Feedback and identification of context-specific factors: We will use Kranias' participatory facilitation techniques [56] to collect feedback on the plausibility of our initial theory of change and, for each city, identify the roles of other influencing factors and alternative explanations that could affect the theory of change's impact pathways. To identify specific contextual factors with participants, we will use the classification of Pawson et al [57], which divides these factors into 4 categories: individual, interpersonal, institutional, and infrastructure. This classification has proven helpful for identifying contextual factors in a workshop setting in previous applications of contribution analysis [50,58]. This classification and stakeholder input will be revisited iteratively as needed, ensuring the theory of change remains aligned with emerging contextual insights.

At least 2 research team members will facilitate each workshop, following a facilitation guide based on Vogel's approach [50]. With participant consent, workshops will be recorded for review purposes. Workshop participants will receive CAD $100 compensation (approximately US $71 at the exchange rate at the time of the study: CAD $1=US $0.71) for their time and contribution and a summary of the key outcomes and changes made to the theory of change for validation.

Phase 3: Inductive

Phase 3 involves assessing the theory of change's coherence, logic, and theoretical foundations and identifying potential gaps or areas for enhancement. Following Funnell and Rogers [46], we will conduct semistructured interviews with experts. This method is particularly effective for gathering in-depth, expert-based insights, which will be instrumental in refining our theory of change and ensuring its robustness and relevance.

Recruitment of Experts

We will use a snowball sampling strategy to identify 5-6 experts in population health, CCE, and theory-based evaluation. Our research partners will provide us with a list of potential interviewees. These individuals will receive an invitation via email, including a detailed description of the study and their expected participation. Before participating, they must sign a consent form and declare no conflict of interest. Each expert will be compensated CAD $150 (US $105.87) for their time.

Data Collection and Analysis

We will send a documentation package to the experts for review 3 weeks before the interview. This package will include the drafted theory of change and its narrative, the development process used, and an assessment grid based on Mayne's validated criteria for an in-depth theory of change analysis [31]. The assessment grid will contain questions to assess the overall logic and structure of the theory of change, the clarity of its expected outcomes, the validity of its assumptions, and the independence of assumptions for each causal link [31]. A research team member will contact the experts to ensure they understand the documentation and answer any questions.

The semistructured interviews will combine structured questions from the assessment grid with open-ended questions for comprehensive feedback [53]. To avoid potential bias, the interviews will be conducted by research team members who were not involved in the theory of change development process. During the interview, we will collect their comments and suggestions. All interviews will be recorded for accuracy.

Formulation of Contribution Claims

Upon completion of the interviews, we will collate and discuss the differences and similarities between the reviewers' assessments and the feedback received. Based on their suggestions, we will adjust the theory of change and formulate initial contribution claims. As mentioned, these claims are narrative statements derived from the theory of change that articulates the anticipated pathways through which CCE is expected to improve population health outcomes in the specific contexts of Ottawa and Thunder Bay [30]. The initial theory of change and contribution claims developed during this phase are considered provisional. As new evidence is gathered and stakeholder insights are integrated, these claims will be iteratively refined. This flexibility is essential to capturing the complex and context-specific pathways through which CCE impacts population health. We will proceed to the second stage of the study once we reach a consensus that the theory of change and the generated contribution claims are sufficiently articulated, credible, plausible, and logical.

Stage 2: Evidence Gathering

Overview

In this stage, we will use a mixed methods approach to gather substantial evidence that will be used to examine the theory of change and the associated contribution claims developed in stage 1 [30]. The evidence-gathering process is designed to be adaptive. If emerging data suggest new pathways or causal mechanisms, earlier stages may be revisited, and claims adjusted accordingly. This iterative approach ensures that the contribution claims remain aligned with the evolving evidence base. We will create a data collection plan to identify specific indicators, data sources, and methods for examining each contribution claim and its assumptions. The plan will identify at least three evidence sources for each claim, using Delahais' triangulation approach [30] for validation, to allow examination from multiple perspectives.

Data Collection

We will collect qualitative and quantitative data from various sources: (1) case studies, (2) a web-based stakeholder survey, (3) pathway-specific literature review, and (4) population and community health data. Flexibility in data collection will be maintained by revisiting or expanding data sources as necessary, based on initial analyses or gaps identified during triangulation. Table 3 provides an overview of the data sources and their respective aims.

Table 3. Overview of data collection and sources for stage 2.

Data collection	Aim	Data sources
Case studies	Examine the impact of existing CCE[a] projects with high potential for positive health outcomes in Ottawa and Thunder Bay on the 5 population health outcome areas.	Interviews and document reviews from appropriately 30 CityStudio projects.
CCE Health Impact Survey	Identify the perceived health impacts of CCE projects not selected for case studies.	A web-based survey for stakeholders involved in or impacted by CCE projects through CityStudio Ottawa and CityStudio Thunder Bay.
Pathway-specific literature review	Assess the evidence for CCE's impact on population health outcomes.	Peer-reviewed research and evaluation literature related to health outcomes in CCE.
Population and community health data	Identify trends in disparities to understand CCE's impact on health outcomes.	Data from Community Safety and Well-Being Plans of Ottawa and Thunder Bay and other health indicators.

[a]CCE: community-campus engagement.

Case Studies

Aim

Case studies involve a detailed examination of a selection of CCE projects with the most significant potential to positively influence Ottawa and Thunder Bay health outcomes. They can provide evidence on the theory of change and have often been used in contribution analysis to understand the factors contributing to intervention success or failure in different contexts [46,50].

Case Selection

We will collaborate with CityStudio Ottawa and Thunder Bay coordinators to identify and rank approximately 15 CCE projects from each city with the most promise for positively impacting at least one of the shared population health priorities. We aim to have at least 1 case study for the 5 health priorities. We will create a checklist based on a review of existing tools and measurement instruments to evaluate projects on successful engagement, possible health impact, and data reliability and accessibility. The final selection of projects will be determined through group consensus using the checklist. The rationale for each selection will be documented in a report for transparency and accountability. The case study pool may be expanded or adjusted accordingly if new CCE projects emerge during data collection that shows high potential for positive outcomes.

Data Collection Tools for Case Studies

As suggested by Yin [59], we will use 2 sources to enhance the rigor of case studies: semistructured interviews and organizational documents.

Semistructured Interviews

We will conduct semistructured 1-hour interviews with key stakeholders in each selected case using an interview guide based on the components of our theory of change. Each interview will focus on uncovering the initiative's perceived impacts, foundational mechanisms, and broader outcomes. We will record each interview and take notes during the interviews. Participants will be asked to sign a consent form before the interview and receive CAD $25 (US $17.64) compensation for their contribution. The interviews will be transcribed, with copies uploaded to a secure database in PDF format.

Project Document Review

Our study team will review documents related to selected CityStudio projects, such as project descriptions, monitoring and evaluation reports, output reports, progress reports, and annual reports. We will obtain project documentation from our research collaborators, CityStudio Ottawa and CityStudio Thunder Bay. This review will help us identify expected activities, outputs, and outcomes and provide insights into the strategies used, challenges encountered, and the overall progress and impact of the projects. The total number of documents we will review will depend on the number of projects and their complexity. However, we aim to review as many relevant documents as possible to understand the projects comprehensively. All project documentation will be securely stored for future reference and analysis.

CCE Health Impact Survey

Aim

The CCE Health Impact Survey is designed to collect insights from diverse stakeholders involved in or impacted by CCE projects in Ottawa and Thunder Bay. The survey aims to understand potential health outcomes related to housing, discrimination, poverty, violence, and mental health.

Sampling Strategy

We plan to gather data from individuals who have actively participated in or been affected by projects from CityStudio Ottawa or CityStudio Thunder Bay. Individuals must not be case study participants to be eligible for the survey. They must also belong to one of the following stakeholder groups: students, faculty or researchers, city representatives, or community members. If survey participation is lower than expected or new stakeholder groups are identified, the sampling strategy may be adjusted to ensure comprehensive data collection.

Potential participants will be selected for our survey through convenience sampling. The CityStudio coordinators from Ottawa and Thunder Bay will email these individuals, outlining the project's objective and emphasizing the importance of their participation. Before participating in the survey, individuals must complete a consent form.

The recruitment for the survey will conclude once we have received a sufficient number of completed surveys to ensure

robust statistical analysis. The exact number will be determined using the Cochran formula [60], which accounts for a 95% CI and a 5% margin of error. Additionally, we will aim to ensure a diverse and representative sample by including participation from each stakeholder group and maintaining balanced representation from both cities.

Measures

The survey will consist of 3 sections. The first section will collect details about the respondents' involvement in the CCE project, such as their role, duration of participation, and affiliation with the organization. The second section will delve into the specifics of the CCE project, including its objectives, the strategies used for its implementation, the deliverables, and the stakeholders involved. The final section will focus on the perceived health impacts of the CCE project. Respondents will be asked to share their observations and experiences and to report any noticeable changes they have observed in 5 key areas: housing, discrimination, poverty, violence, and mental health.

Before launching the survey, we will conduct a pretest with potential participants from all targeted groups to ensure its clarity and relevance. The survey will include Likert scales and open-ended questions, and we anticipate it will take approximately 15 minutes to complete. Participants will receive a CAD $25 (US $17.64) compensation upon completion.

Pathway-Specific Literature Review

Aim

We will synthesize peer-reviewed literature to evaluate the significance and evidence level for each pathway in the theory of change. This will help us understand how these pathways influence the impact of CCE on population health outcomes. Our process will include an analysis of studies that have investigated similar pathways. We will scrutinize their methodologies, findings, and conclusions and assess the overall robustness and limitations of the existing literature. The literature review process will be iterative, allowing for additional rounds of review if new gaps or needs are identified during data collection or analysis. The review procedure for pathway-specific literature will adhere to the guidelines for the narrative literature review outlined in stage 1.

Population and Community Health Data

Aim

We will collect health data to evaluate the impact of CCE on health outcomes in Ottawa and Thunder Bay. This will include information on health behaviors, outcomes, access to health care services, and social determinants of health. By examining population characteristics, health measures, and factors influencing health outcomes, we aim to understand how CCE affects immediate and downstream health outcomes. We will also draw on indicators, results, and performance measures developed and tracked by the municipal CSWBP teams. Domains of eligible indicators include (1) socioeconomic environment (income, social support, education, and employment); (2) physical environment (green space, air quality, housing, and transportation); (3) healthy child development (birth weight, immunization, and early development indicators); (4) health behaviors (smoking, substance use, diet, and physical activity); (5) individual capacity and coping skills; (6) biology and genetic endowment; (7) health services; and (8) sociodemographic environment (culture, race or ethnicity, and sex or gender).

Data Analysis Approach

Our data analysis approach involves qualitative and quantitative analysis, followed by aggregation.

Qualitative Data Analysis

At least 2 research team members will perform a thematic analysis of project documents and semistructured interviews. We will adhere to the 6-step thematic analysis coding framework proposed by Braun and Clarke [61], which includes (1) familiarization of data, (2) generation of codes, (3) combining codes into themes, (4) reviewing themes, (5) determining the significance of themes, and (6) reporting of findings [57]. The thematic analysis will be conducted iteratively, allowing for additional rounds of coding and theme development if new insights or patterns emerge. For example, if initial analysis reveals unexpected causal pathways or unanticipated factors, further in-depth analysis will be conducted to explore these themes. We will focus on identifying linguistic indicators of change or cause-effect relationships in interviews using Nour et al's argumentative discourse analysis [62]. This process entails a detailed examination of specific linguistic markers such as "it is obvious/clear that" and "compared to." These markers serve as indicators of patterns or relationships in the data. We will use NVivo software (Lumivero) [63] for data organization and analysis.

Quantitative Data Analysis

We will collect quantitative data from CityStudio projects, the CCE Health Impact Survey, and existing, deidentified publicly available population and community health indicators. We will use descriptive and appropriate inferential statistical analysis using statistical software (STATA version 14.2, StataCorp LLC) [64] to describe and analyze patterns, relationships, and impacts pertinent to the contribution pathway.

Aggregation of Evidence

We will use Delahais and Toulemonde's Evidence Analysis Database [32] to combine, examine, and summarize the evidence gathered for our theory of change and the contribution claims and related assumptions or risks associated with it. Triangulation will be conducted iteratively, allowing for the inclusion of new evidence sources or reexamination of previously collected data if discrepancies are identified during the analysis. The database will be structured as a digital spreadsheet, with each row corresponding to a piece of evidence linked to a specific contribution claim from our theory of change. For each piece of evidence, we will record the following details: label (an identifier for the evidence), statement (a brief description of the evidence), data source (case studies, CCE Health Impact Survey, pathway-specific literature review, and population and community health data), type of evidence (primary or secondary), interpretation (confirming or refuting the claim), strength of evidence (rating of the evidence's strength and

justification), and comments (additional notes or observations about the evidence or implications based on the city).

Stage 3: Theory of Change Assessment and Refinement

Overview

In this stage, our objective is to assess and refine the contribution claims formulated from our theory of change based on the evidence gathered and analyzed in the preceding stage. To ensure a rigorous assessment, we will adopt Downe's approach [65] of using an independent review panel, consisting of experts recruited in the inductive phase of the theory of change development (stage 1). If those experts are unavailable, we will use a snowballing strategy to find other relevant experts.

Review Panel Procedures

We will send a review package to the experts 3 weeks before the panel meeting. This package will include the draft theory of change and its narrative, the development process used, and an assessment grid for the contribution claims. The number of claims will be determined based on the theory of change. The assessment grid will contain questions to assess the plausibility and strengths of these claims, along with the overall logic and structure of the theory of change. A research team member will contact the experts to ensure they understand the documentation and answer any questions they may have. Workshop participants will be asked to sign a consent form and will receive compensation of CAD $200 (US $141.15) for their time.

The panel meeting will last 4 hours and will be facilitated by 2 research team members who were not involved in data collection and analysis. It will be divided into 2 parts.

- Introduction and question-and-answer: Panel members will receive presentations from the research team on the methods and contribution claims, followed by a question-and-answer session where they can ask for clarifications or additional information about the presented materials.
- Assessment: Panel members will be invited to share their feedback on the contribution claims and rate them by consensus according to their plausibility and rigor on a scale from 1=very weak to 4=very strong. They will use the aggregated data in Delahais and Toulemonde's Evidence Analysis Database [32] to verify the coherence of the contribution claims by contrasting both qualitative and quantitative data collected on them. Contribution claims with low scores will be used to prompt panel members for additional information sources. This feedback leads to another round of targeted data collection using data sources described in phase 2, ensuring our findings are reliable, accurate, and context specific.

Refinement and Reporting

After the panel meeting, the research team will compile a detailed report that includes the theory of change, the supporting evidence, and the panel's ratings and feedback. By documenting the evidence and the narrative of how it substantiates the theory of change, along with the expert panel's evaluations, this report aims to present a comprehensive and credible account of the contribution story. The report will also highlight the iterative nature of the process, documenting how contribution claims were progressively refined, validated, or adjusted based on new evidence. This transparency in the evolution of claims is crucial for demonstrating the credibility and robustness of the evaluation findings.

Ethical Considerations

This study adheres to the ethical guidelines and principles relevant to human research. It has been granted ethical approval by the Bruyère Research Ethics Board (M16-23-009) on May 4, 2023. Ethical approval for our site in Thunder Bay is currently pending, and as such, no data will be collected at the site until we receive the necessary approval. This research is supported by the Canadian Institutes of Health Research (PJT-180529). All participants will provide written informed consent after being fully informed of the study's purpose, procedures, potential risks, and their right to withdraw at any time without consequence. Identifiable information will not be disclosed in study publications or presentations. Our approach to compensation is described in the Method section.

Results

Our study is in the second stage, focusing on evidence gathering. We anticipate study results will be available by the end of May 2026. The findings will provide insights into the impact of CCE initiatives on population health in Ottawa and Thunder Bay, contributing to the broader understanding of these complex relationships.

Discussion

Expected Findings

CCE is increasingly recognized for its potential to address local health needs. However, a more rigorous and precise understanding of its impact on population health is needed. This research uses a 3-stage, convergent parallel mixed method design combined with contribution analysis to provide robust evidence on how CCE has improved population health in Ottawa and Thunder Bay, 2 distinct settings in Ontario, Canada. The study will provide evidence for CCE's impact on 5 shared population health priorities for both municipalities: housing, discrimination, poverty, violence, and mental health. By focusing on reducing uncertainty and disentangling the complex interactions among contributing factors, our study will provide a clearer and more nuanced understanding of how and under what conditions CCE contributes to these health outcomes. This approach goes beyond simply assessing whether CCE has an impact and delves into the mechanisms, contexts, and pathways through which these contributions occur.

While Mayne's approach has been effectively used in assessing the impacts of interventions and policies in fields such as international development [32] and public administration [39], its application in health research is less explored. Our study aims to generate rigorous evidence of CCE's impact on health and provide valuable insights for applying contribution analysis in health research and evaluation. Our protocol ensures robust findings using 3 triangulation types: data triangulation using a mixed methods approach, analyst triangulation by involving various members of the research team and stakeholders in all 3

stages of the study, and external validation for an objective evaluation of our theory of change and contribution story. This ensures reliable and context-specific results.

The implications of these findings are substantial. Policy makers will be equipped with evidence-based insights that can be used to refine community engagement strategies and optimize resource allocation for improved population health outcomes. Health education institutions can leverage these insights to strengthen their community engagement endeavors, enrich curricula, and demonstrate their commitment to social accountability. Furthermore, communities will gain invaluable evidence for a scalable CCE model that can be applied across diverse settings.

While this study focuses on CCE initiatives in Ottawa and Thunder Bay, the findings are intended to be transferable to other contexts. By identifying common configurations, mechanisms, and contextual factors that contribute to health outcomes, this study offers insights that can be adapted and tested in different settings. For instance, understanding the conditions under which CCE initiatives are most effective can inform similar efforts in municipalities with comparable socioeconomic conditions or health challenges. The transferability of findings will be discussed in detail, emphasizing the specific aspects of the intervention that may be generalizable across contexts.

Limitations

The precision of our analyses may be constrained by the challenge of obtaining high-quality data for CCE projects. Contribution analysis is relatively novel, adding complexity to our study. Stakeholder participation in participatory research presents challenges such as ensuring effective communication, equitable authorship access, and fair compensation mechanisms. The potential for participant bias exists, which could affect data objectivity but will be mitigated by maintaining neutrality during data collection and analysis and providing clear study guidelines to participants. Another limitation is the dependence on perceived outcomes and correlational relationships, which will be addressed through triangulation methods involving multiple data sources to cross-verify findings and provide a comprehensive understanding of impacts.

Conclusions

This protocol outlines a novel approach to assessing the impact of CCE on Ottawa and Thunder Bay population health. The study aims to provide robust evidence on how CCE contributes to population health improvements by using a convergent parallel mixed methods design and contribution analysis. The study's findings are expected to fill critical knowledge gaps regarding the specific pathways, configurations, and contextual factors that influence CCEs. These insights will be valuable for policy makers, health education institutions, and communities seeking to optimize their engagement strategies. Despite the limitations, such as geographical scope and potential participant bias, the iterative, flexible, and rigorous design enhances the reliability and applicability of the findings. The research team anticipates that the findings will validate and refine the contribution claims derived from the theory of change and guide future research and interventions in community engagement and health. This study represents a significant step forward in understanding and harnessing the potential of CCE in improving population health.

Acknowledgments

Funding from the Canadian Institutes of Health Research (PJT- 180529) is supporting this work.

Authors' Contributions

All authors contributed to drafting and revising the manuscript and approved the final version for publication. Each author is accountable for the content and will address any inquiries about its accuracy and integrity.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Good Reporting of a Mixed Methods Study (GRAMMS) checklist.
[DOCX File , 17 KB - resprot_v14i1e58546_app1.docx]

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Abbreviations

CCE: community-campus engagement
CSWBP: Community Safety and Well-Being Plans
GRAMMS: Good Reporting of A Mixed Methods Study

Edited by T Leung; submitted 25.03.24; peer-reviewed by T Delahais, D Podder; comments to author 08.07.24; revised version received 25.09.24; accepted 30.10.24; published 17.01.25.

Please cite as:
Buetti D, Larche C, Fitzgerald M, Bourgeois I, Cameron E, Carr K, Aubry T, Persaud S, Kendall CE
Evaluating the Impacts of Community-Campus Engagement on Population Health in Ottawa and Thunder Bay, Canada: Protocol for a Mixed Methods Contribution Analysis
JMIR Res Protoc 2025;14:e58546
URL: https://www.researchprotocols.org/2025/1/e58546
doi:10.2196/58546
PMID:

Protocol

Decentralized Management of Home Care Services for Seniors: Protocol for a Participatory Action Research

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Abstract

Background: The centralization of decision-making power in the public health care system has a negative impact on the practice of professionals and the quality of home care services (HCS) for seniors. To improve HCS, decentralized management could be a particularly promising approach. To be effective, strategies designed to incorporate this management approach require attention to 3 elements: autonomy of local stakeholders, individual and organizational capacities, and accountability for actions and decisions. Not many studies have focused on strategies for integrating decentralized and collaborative management at the local level in HCS.

Objective: The overall aim of this study is to coconstruct HCS management strategies and explore decentralized practices in the day-to-day work of low-level managers and professionals. The specific objectives, in collaboration with local HCS stakeholders, are to (1) identify concrete and achievable strategies for decentralized management, and (2) describe factors (facilitators and obstacles) that could potentially influence their integration.

Methods: This participatory action research involves a cyclical process. Before initiating the cycles, a preliminary stage consists of forming a steering committee composed of managers (n=3), professionals (n=3), seniors (n=3), informal caregivers (n=3), and the research team (n=3). This committee will facilitate multistakeholder consultation to coconstruct local management strategies based on a real-life problem identified by the committee. The steering committee will also guide the research process. The first cycle will consist of establishing an initial plan of decentralized management strategies. During the observation phase, meetings of 4 homogeneous focus groups, including managers, professionals, seniors, and informal caregivers, will be held. During the reflection phase, a thematic analysis will be carried out, and data will be interpreted and validated by the steering committee. Then, in the action phase, results will be presented to managers and professionals so that they can coconstruct a plan of decentralized management strategies to prioritize. The second cycle will explore the factors involved. The observation, reflection, and action phases will be repeated. Ultimately, the results of the 2 cycles will be integrated in a model coconstructed by the steering committee.

Results: Data collection is in progress; the partnership officially began on February 1, 2024, and the plan is to continue data collection through 2025. The steering committee will validate the data to ensure that they are accurate and that the results reflect the reality of local stakeholders.

Conclusions: By identifying decentralized and collaborative management strategies at the local level as well as factors to facilitate their integration in HCS, this approach can be used for other decentralized management projects in different areas of the health care system. This study will give decision makers insight into strategies aimed at improving the management of their institution, which will enhance seniors' well-being and the quality of their health care services.

International Registered Report Identifier (IRRID): DERR1-10.2196/58271

(JMIR Res Protoc 2025;14:e58271) doi:10.2196/58271

KEYWORDS

health system; decentralization; management; home care services; seniors; collaboration

Introduction

Background

Over the past 4 decades, health care systems in most countries have been reshaped by reforms based on new public management (NPM) [1]. NPM aims to improve the effectiveness, efficiency, and quality of services by focusing on results-based management and cost control [2]. Inspired by NPM [3,4], the last 2 health and social service reforms in the Canadian province of Québec made a shift toward the centralization of management practices [5,6]. With the aim of improving health system performance, the 2003 [7] and 2015 reforms [8,9] gradually concentrated decision-making power, responsibilities, and control, and moved them from lower management to the senior management level of the health system [3,6]. The trend toward centralized management seems to be continuing with the new 2024 reform [10-12], which will concentrate decision-making power in the hands of a new agency called *Santé Québec* [13]. Such centralization of decision-making power necessarily relies on management by results, accountability, and partial privatization of services [9,14]. Consequently, departmental priorities focus on effectiveness and efficiency [14]. The changes resulting from centralized management can have an impact on the conditions of practice of local stakeholders [14], including low-level managers, professionals, seniors, and informal caregivers. These changes also influence the quality of home care services (HCS) for seniors [14], a sector where demand is increasing as the population ages [15,16]. Centralization reduces the latitude of managers and professionals [5], which in turn is associated with a reduction in how meaningful they find their work [14,17]. Their ability to offer services that are accessible and adapted to the needs of the population diminishes [18-20]. Professionals and seniors agree that the continuity and quality of HCS must be improved [18].

To address the present challenges faced by HCS, decentralization could be a particularly promising approach [5,21]. Decentralization implies the delegation of decision-making, power, and responsibilities [21]. The decentralization process involves reconfiguring relations among the national, regional, and local levels to work toward collaborative vertical and horizontal management [22]. A decentralization process involves decentralized management strategies, which are management practices that promote the delegation of decision-making, power, and responsibilities from a higher to a lower level [23]. To be effective, local decentralized management involves three elements: (1) delegating authority to lower-level managers and professionals, (2) strengthening their individual and organizational capacities, and (3) sharing accountability for decisions to be made [23]. Decentralization has the potential to improve the performance of the health system [21,24], the efficient allocation of material and human resources, and responsiveness to the needs of seniors [22].

Moving toward decentralized management is particularly relevant when we consider the main effects of the current centralized management on the health system in Québec. First, administrative reforms and a centralized management approach can reduce the autonomy of professionals [4,14], whose decisions must be approved by senior management, which delays the taking of concrete action in the field [5,19]. The centralization of decision-making power and formalized communication mechanisms limit direct relationships between different local stakeholders [19]. Second, the standardization of practices and use of statistics have increased the focus on performance optimization (eg, cost-effectiveness) [19]. On the one hand, the management and organizational techniques put in place to optimize the work of professionals (eg, standardized clinical tools) [14] require them to invest a great deal of time in their daily tasks [15,19], which decreases the time they devote to direct care for seniors [14,19]. On the other hand, this standardization leads to a tightening of HCS allocation criteria, which impacts the accessibility of services [19]. Some seniors are being denied services, although they were eligible before the 2015 reform [19]. Third, there is a wide gap between the expectations of professionals and managers [15]. Professionals are mainly concerned with improving the quality of care and services for seniors [15]. Managers are more focused on the performance of HCS. For example, HCS must contribute to reducing hospitalization times and increasing the number of seniors who received services [15]. Fourth, services are developed in silos, without any overall coordination [25,26]. This leads to the duplication of services, blurred roles for each HCS provider, a lack of coordination, and competition between service providers [27]. As a result, overly centralized management has negative effects on the practice of professionals and the quality of services for seniors.

Now that the Québec government has made decentralization a priority [28-30], documenting decentralized management in its HCS becomes relevant. Some studies have examined the integration of decentralization in a health care system but generally only from the viewpoint of evaluating this in a specific context. However, each health system has its own management context and structure [31]. Thus, in today's hypercentralized system, bringing decision-making closer to Québec managers, professionals, seniors, and informal caregivers requires finding a way to integrate decentralized management strategies at the local level of HCS. This study aims to answer the following question: To integrate decentralized management in HCS effectively, what potential strategies should be used and what factors should be considered? The overall aim of this study is to coconstruct HCS decentralized management strategies in the day-to-day work of low-level managers and professionals. The specific objectives, in collaboration with local HCS stakeholders, are to (1) identify concrete and achievable strategies for decentralized management, and (2) describe factors (facilitators and obstacles) that could potentially influence their integration.

Theoretical Model

According to the theoretical model of Ohrling and colleagues [24], decentralization is a dynamic process that evolves over time and in which three elements interact: (1) delegation of authority to local stakeholders, (2) strengthening of individual and organizational capacities, and (3) accountability for actions and decisions. *Authority* refers to the different degrees of decision-making power and autonomy delegated to lower levels

of managers and professionals [24]. To achieve a balanced distribution of authority at different levels of management, managers need to identify tasks and decisions that can be delegated. To ensure that the selection of priorities is in line with the needs of seniors, managers must have a certain amount of latitude in their decision-making [32]. Thus, strategies that support effective decentralized management involve low-level managers having sufficient authority to select those priorities, identify tasks and decisions that can be delegated, and allocate resources [24]. *Capacities* involve the possibility of strengthening individual and organizational abilities to assume delegated decision-making power and responsibilities [24]. The individual ability of managers and professionals to take the initiative is based on their personal aptitudes [33]. As for organizational capabilities, certain norms and culture help encourage the initiatives of managers and professionals [24]. Finally, managers and professionals need to be *accountable* for their decisions and their impacts on HCS [24]. This element involves specifying how responsibilities will be integrated and distributed between managers at all levels and professionals [24]. Also, to facilitate the delegation of authority and sharing of responsibility, managers and professionals should coordinate services, ensure quality, and meet institutional standards [24]. To be effective, strategies must include a sufficient degree of delegation, combined with the capacity on the part of local stakeholders and institutions to make choices in line with optimized performance and to be accountable for these choices aligned with local needs and priorities [34].

Literature Review

This study addresses the question: What potential strategies should be used and what factors should be considered to effectively integrate decentralized management into HCS? Based on the 3 elements of the model of effective decentralization (authority, capacity, and accountability) [24], the literature review presents these strategies and factors.

Decentralizing Management: Strategies to Be Explored at the Local Level

The main strategy of *authority* involves establishing clear policies that contain guidelines regarding the changes to be made to the degree of autonomy and decision-making power at each management level (provincial, regional, and local) [35-37]. When local stakeholders are involved in developing them, these policies are closer to local needs and improve the quality of services [38]. However, these policies often have gray areas that make them difficult to integrate at the local level [37], such as poor communication between provincial, regional, and local levels regarding policy applications [35,39]. Furthermore, it is important to consider the financial dimension of HCS with respect to managers' decision-making power over budget allocation [23]. This strategy involves increasing local control and autonomy over budget management, including the choice of how to allocate funds [40,41]. This control enables choices to be made in line with local needs, which leads to more responsive services [41].

Capacity strategies comprise ways to increase managers' individual capabilities. For example, training programs should focus on managerial leadership skills, health management organization, and organizational changes to come with decentralized management strategies [33,35]. To increase organization capacity and sustain local control and autonomy with respect to budget management requires a system for allocating financial resources [37]. Under such a system, the provincial level retains the power to divide tax revenues equitably between various local institutions [40,42].

Accountability calls for a variety of strategies that are easier to integrate at the local level and have more lasting positive effects [40]. The most promising of these strategies is, first, the creation of clinical networks or committees that give local stakeholders a voice with HCS senior management [38,43]. Second, one of the most common strategies is to reorganize responsibilities between the central government and the local institutions to increase the latters' autonomy [24,36,37,41,44,45]. Third, the reorganization of human resources management responsibilities includes increasing the decision-making power of local organizations in recruiting and training professionals [36,37,46]. A fourth strategy is to have provincial and regional levels use a bottom-up approach to plan health priorities that involve local managers and communities in identifying initiatives and projects for strategic planning of HCS [47,48]. A fifth strategy involves local managers using clear report cards that include objectives, concrete strategies, and performance indicators for decentralization-related changes in the institution [24].

Factors Influencing the Integration of Decentralized Management Strategies

Factors facilitating (n=8) the integration of decentralized management strategies are presented first, followed by factors representing obstacles (n=7). Regarding *authority*, 2 facilitators encourage the delegation of decision-making power to lower-level managers and professionals [24]. The willingness of managers at different levels to delegate certain tasks and responsibilities encourages their participation in the integration of decentralized management strategies [32]. Coaching senior managers through monthly meetings can help build a relationship of trust between the provincial and local levels [49]. Senior management's commitment helps motivate lower-level managers to take on accountability [39]. Two facilitators can help strengthen organizational *capacities*, leading to enhanced integration of decentralized management strategies [24]. First, the institution must have the material, human, and financial resources needed to put the strategies into practice [35,46,48,50]. For example, quality equipment (such as a high-performance IT system) [39], the right infrastructure, a qualified workforce, and budget planning facilitate the integration of changes linked to decentralization [35]. Creating a culture of mutual trust within the institution encourages managers and professionals to take the initiative and make decisions [33]. In terms of individual capacities, 2 facilitators reflect the personal skills of managers at different levels and professionals [33]. The first concerns coping strategies for managers and professionals, which are methods they can put in place to help them reorganize their work routines [51]. These methods enable them to spend more time on their new tasks and responsibilities, for instance, by reducing the number of meetings they need to attend [41,51]. Senior managers can help by limiting the amount of bureaucracy they have to deal with [33,52]. The second facilitator is the

leadership skills of managers at different levels. These skills can facilitate the integration of decentralization to define new relationships with provincial and regional levels, plan resource allocation, build a new shared vision, and lead change [43,53]. Two facilitators are associated with *accountability*. Clarity of roles and responsibilities between provincial and local levels regarding resource allocation and accountability for action enables proactive integration of decentralized management strategies [33,47]. Collaboration between provincial and local levels facilitates the integration of a budget that respects local needs, strategic direction, and government priorities [46].

Several factors stand in the way of integrating decentralized management strategies. Regarding *authority*, 2 factors make it more difficult for the provincial level to delegate to lower levels [24]. Difficulties communicating between the provincial level and local institutions regarding the execution of a policy or reform can lead to confusion [37,41,51]. As a result, a gap may be created between policy and its implementation [39]. Good communication means that information about the new policy to be implemented is clear, accurate, and transmitted to the right individuals [39]. Moreover, when the provincial level decides to retain a high degree of control over local institutions, it is more difficult to integrate decentralized management strategies [41,47]. Local managers then lack autonomy [41] and decision-making power [36], which makes it difficult to lead change. As for organizational *capacity*, lack of resources and funds can limit the changes to be integrated [46,49,51,52]. Concerning individual capacity, limited managerial skills [49,54], and lack of preparation [48,51] can affect managers' ability to make decisions in their new role and demotivate them [48]. In addition, 2 obstacles are associated with *accountability* for coordinating quality services aligned with local needs [24]. A lack of clarity in roles and responsibilities is a source of confusion when new responsibilities linked to decentralized management strategies are added [37,38]. Managers and professionals then find it difficult to assume their new responsibilities, for which they may be accountable. The second obstacle concerns budget allocation based on the central government's political motivations. This factor can create a gap between government funding and actual budgetary needs at the local level [46].

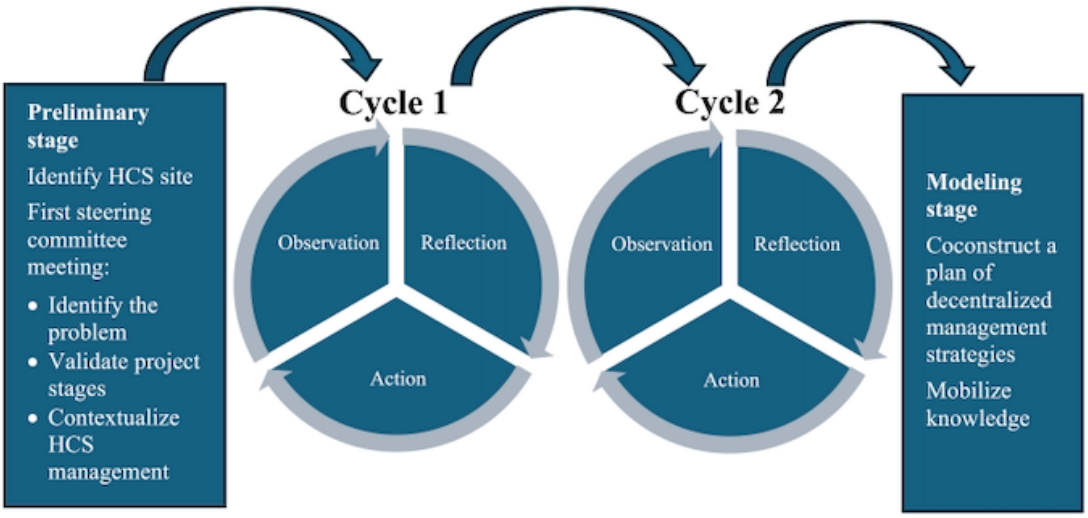
The studies discussed in the aforementioned literature review are useful as they focus on decentralized management strategies and factors likely to influence their integration. However, some of them were carried out in countries where the political, organizational, and legal structures of the health care system differ from those in Canada and Québec [24,29,55]. Furthermore, some studies did not involve the participation of all local stakeholders in developing decentralized management strategies. As a result, none of them fully captures the complexity of the dynamic and evolving process of decentralization and the factors that can influence it in the Québec context.

Methods

Design

To meet our objectives, a participatory action research (PAR) design was chosen [56]. The PAR design gives HCS stakeholders the power and the tools to explore and coconstruct management strategies adapted to their context and to solve a specific problem that they have identified [56]. The study will start with a preliminary stage, followed by 2 cycles, each composed of 3 phases (observation, reflection, and action), and end with a modeling stage (Figure 1 [57]). The preliminary stage consists of selecting the research site and forming a steering committee. The first cycle will establish a plan of decentralized management strategies (objective 1). The second cycle will consolidate the decentralized management strategy plan and anticipate its integration in HCS by describing factors that could potentially influence the integration of these strategies (objective 2). Finally, the modeling stage will combine the results of the 2 cycles and consolidate the decentralized management strategy plan. A cyclical reflective process is necessary for PAR to ensure constant 2-way feedback between theory and practice [58,59].

Figure 1. Cyclical process of participatory action research based on the participatory action research model developed by Roy and Prévost [57]. HCS: home care services.



Study Components (Preliminary Stage)

To define the problem and initiate the PAR process, a steering committee will be set up, composed of 3 managers, 3 professionals, 3 seniors, and 3 informal caregivers identified at the site as well as 3 members of the research team (VS, JQ, and AC). Each type of stakeholder will be equally represented to encourage constructive exchanges and ensure that all steering committee participants feel free to express themselves [56]. The committee will enable a concerted stakeholder approach to the study, aimed at coconstructing [56] decentralized management strategies based on a real-life problem identified by the committee. Before starting the PAR cycles, an initial meeting of the steering committee will be held to discuss everyone's role and involvement [56]. In addition, this meeting will provide an opportunity to contextualize current HCS management and identify a target problem to be addressed in this study. Committee members will be invited to comment on the proposed research process [56]. Members of the research team on the steering committee will play a facilitating role and support the other members in the effective search for solutions [56].

Cycle 1: Identify Decentralized Management Strategies (Objective 1)

Observation Phase: Data Collection

A convenience sample of 24 participants will be recruited to form 4 focus groups of 6 participants each (managers, professionals, seniors, and informal caregivers) to collect data [60]. Each group will be homogeneous to encourage participants to express themselves freely [61]. The qualitative research literature recommends having 6-8 participants in each focus group to ensure interesting exchanges and the opportunity for each participant to answer questions and share their point of view and experience [60]. These focus groups will be used to gather views on decentralized management strategies and the factors influencing their integration as identified in the literature, according to their different status (manager, professional, senior, or informal caregiver) [62]. A member of the steering committee will be present during the discussions to assist the research team. Focus group meetings will last 90 minutes [62]. The aim will be to identify decentralization strategies to solve the target problem. Focus group interviews will be recorded and conducted with the help of a guide [60]. In addition, the student researcher (VS) will document her reflections and the different stages of the study in a research journal [63].

Reflection Phase: Data Analysis

First, an initial list of potential codes will be drawn up from the literature review on decentralized management strategies (objective 1), for example, establishing clear policies [64]. Second, initial deductive codes will be generated by identifying the units of meaning linked to a list of codes based on the literature review. The emergent initial codes will be generated by identifying the units of meaning in the data relating to decentralized management strategies that are not included in the list of codes (objective 1). Third, to search for themes, codes will be selected to create potential themes. Relevant coded data extracts will be collected for the created themes [64]. To ensure that the themes and subthemes are meaning-based interpretative stories [65], each will have a definition based on the extracted codes. Fourth, the themes will be examined in relation to the coded data extracts and the data as a whole [64]. Themes and subthemes will be organized in a chart to think creatively and reflexively the data and facilitate communication with steering committee members [56,65]. Fifth, the themes, subthemes, and overall chart will be revised and defined [61]. Sixth, relevant and illustrative data extracts will be selected to represent the themes [64]. The 6 steps of the Braun and Clarke's [65] analysis will be carried out by the student researcher (VS) and validated by 2 members of the research team (AC and JQ). Seventh, a meeting will be held with steering committee members to validate and enrich these analyses. The validation will enable us to make sure that the themes that have been created represent the perspective of field stakeholders [65]. The chart resulting from the data analysis will be presented to the steering committee and will help members reflect on the solutions and decentralized management strategies to be integrated.

Action Phase: Identify and Coconstruct Decentralized Management Strategies

During this phase, the results of the reflection phase will be shared with all HCS stakeholders involved in the strategies identified (ie, professionals on the HCS team). These stakeholders will be identified by the steering committee. A meeting will be held with these stakeholders led by the student researcher (VS) and a member of the steering committee. First, the student researcher will present the decentralized management strategies. Then she will invite the stakeholders to prioritize the strategies according to 3 criteria: strategy's relevance to the problem identified, strategy's feasibility in terms of accessibility of the necessary resources, and strategy's acceptability to all stakeholders (managers, professionals, seniors, and informal caregivers) [66]. Finally, a plan of decentralized management strategies will be drawn up with the stakeholders [56,67]. This will identify the decentralized management strategies to be prioritized, the associated tasks, the resources needed, and the time required [56].

Cycle 2: Identify Factors Influencing the Integration of Decentralized Management Strategies (Objective 2)

Observation Phase: Data Collection

With the same 24 participants, meetings of 4 homogeneous focus groups of 6 participants each (managers, professionals, seniors, and informal caregivers), lasting 90 minutes [62], will be conducted. In the second cycle, the focus groups will be used to anticipate and coconstruct factors that could potentially influence the integration of decentralized management strategies in HCS.

Reflection Phase: Data Analysis

A thematic analysis using Braun and Clarke's 6 steps [64] will be conducted to interpret the data collected and will be carried out in the same way as in the first cycle. Both deductive and inductive approaches will be used to define an initial list of potential factor codes based on the literature and to allow new themes to emerge [64]. The analysis will generate a chart of factors linked to the decentralized management strategies

identified in the first cycle. A steering committee meeting will then be held to present the chart and validate the factors involved in integrating decentralized management strategies [56].

Action Phase: Describe the Factors Influencing Integration of the Strategies

In the second cycle, the action phase will consist of a meeting with the same stakeholders as in the first cycle. This meeting will provide an opportunity to share the factors (facilitators and obstacles) identified and to reflect on those most likely to influence the integration of the decentralized management strategies identified in the first cycle. This discussion will lead stakeholders to consolidate the plan of decentralized management strategies and anticipate their integration [56,67]. Thus, at the end of the 2 cycles, the data collected should enable empirical saturation to be reached, with further collection no longer providing sufficiently new or different information to justify another PAR cycle [68].

Modeling Stage

The PAR process will end with a fourth meeting of the steering committee. At this meeting, the results (decentralized management strategy plan and factor figures) will be integrated into a model coconstructed by the steering committee [56,67]. Based on this model, the decentralized management strategy plan will be converted into recommendations regarding which strategies to prioritize to resolve the management issues identified.

Recruitment and Sampling

The participants will be main HCS stakeholders: managers, professionals, seniors, and informal caregivers. They will be recruited with the help of steering committee members, who will explain the research project to them and verify their interest in participating. Convenience sampling will then be used to target a total of 6 managers, 6 professionals, 6 seniors, and 6 informal caregivers (n=24) [64]. Participants will be recruited according to the following inclusion criteria: (1) they must have received services or worked in HCS for a continuous period of at least 6 months; (2) they must have an interest in HCS management; (3) they must be able to express themselves in French; and (4) they must be able to consent to participate in the study. They will participate in the observation phase in both cycles.

Ethical Considerations

This study was approved by the research ethics board of the integrated university health and social services center (#2024-5221/Carrier). All participants will be required to provide free and informed written consent for each cycle. Participants will be able to withdraw from the study at any time without any repercussions. They will also be informed of the confidential nature of the data collected and the procedures followed to ensure confidentiality and anonymity. The data collected will be secured (on a password-protected computer or in a locked fireproof filing cabinet at the Research Centre on Aging) and only the research team will have access to them. Members of the steering committee will fill out a collaboration protocol, based on the one developed by Fortier et al [69]. As a PAR, the impact of change on participants must be considered. The study, which is conducted in partnership with the participants [61], who are treated with respect throughout the research process, cannot be used to evaluate their work [61]. Seniors and informal caregivers will receive financial compensation of CAD $25 (US $17.67) for their transportation to a point of service offering HCS.

Results

The study started in February 2024 and will be carried out according to an optimal schedule over a 1½ period (Table 1). In the preliminary stage, we obtained ethical approval and developed the interview guides. We also developed a research partnership with an HCS site. Initially, one meeting of the steering committee was planned. However, 2 additional meetings were necessary to contextualize the management and organization of the HCS site. The first cycle began in July, with the first focus group in July 2024. We had recruited 12 managers and 7 home care workers. We are currently at the stage of conducting focus groups with seniors and caregivers. Each cycle will last approximately 4 months. To ensure knowledge mobilization, the research team will prepare scientific papers and make presentations. Members of the steering committee will be invited to participate. This study received financial support (June 2023) from a major Canadian funding body, the Social Sciences and Humanities Research Council of Canada (#430-2023-00783/Carrier).

Table 1. Tasks and timeline for each cycle of the participatory action research.

Task	Time
Preliminary stage	
Ethics approval	December 2023[a]
Development of interview guides	December 2023[a]
Development of research partnership	February 2024[a]
First meeting of steering committee	March 2024[a]
Second and third meetings to contextualized HCS[b]	June-July 2024[a]
First cycle	
Focus group	July-October 2024[a]
Thematic analyses	November-December 2024[a]
Fourth (initially second) meeting of steering committee	December 2024[a]
Meeting with local stakeholders	January 2025
Second cycle	
Focus group	January 2025
Thematic analyses	February-March 2025
Fifth (initially third) meeting of steering committee	March 2024
Meeting with local stakeholders	April 2025
Modeling stage	
Sixth (initially fourth) meeting of steering committee	April 2025
Dissemination and mobilization strategies	June-October 2025

[a]Tasks completed at the time of publication of this paper.

[b]HCS: home care services.

Discussion

Strengths and Limitations

This study is designed to explore decentralized management strategies that are concrete and adapted to the realities of local stakeholders as well as to anticipate factors involved in integrating the strategies. The methodological choices are scientifically rigorous and will be validated in each phase of the study by members of the steering committee [68,70]. To encourage greater reflexivity on the part of the student researcher (VS), the focus group interviews will be cocoded with at least 1 member of the research team, and the analyses will be validated by the steering committee. The research team's experience in the health care system is an asset as they are familiar with the management context [61,68,70]. However, decentralized management strategies will be developed in a centralized management context, which could present an obstacle to the integration of some strategies. In addition, given the power relationship between managers and professionals, social desirability is a potential bias. Nonetheless, the views of various local stakeholders will enrich the steering committee's discussions [56]. In addition, the research team members will play a facilitating role and support other members in effectively identifying decentralized management strategies and the factors involved [56]. The research team will pay attention to power issues during discussions to ensure that all members can express themselves freely [56].

Broad Implications

The research project will address a gap in the literature by identifying concrete decentralized management strategies adapted to the local reality of an HCS site and anticipating factors involved in integrating these strategies. The results will advance practical knowledge regarding decentralized management, which can serve as a basis for further studies designed to advance knowledge in this field.

This study will provide recommendations for innovative solutions to a management issue identified by an HCS site. It considers the main stakeholders in HCS in the search for innovative solutions and helps identify decentralized management strategies that meet the needs of the institution. The strategies identified can also be adapted to other environments with similar characteristics [71]. Knowledge of decentralized management will be transferred between participants and members of the steering committee [58]. In addition, this project will increase the self-determination of steering committee members through the PAR process, which will encourage them to get involved in the search for strategies [58]. By involving seniors and informal caregivers in the steering committee and focus groups, this study encourages

community participation in the search for management strategies. As a result, the decentralized management strategies identified will undoubtedly meet seniors' needs [72].

Acknowledgments

Financial support for this study is provided by the Social Sciences and Humanities Research Council (SSHRC; grant 430-2023-00783). AC is a Fonds de recherche du Québec—Santé Junior 1 researcher (#296437).

Conflicts of Interest

None declared.

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Abbreviations

HCS: home care services
NPM: new public management
PAR: participatory action research

Edited by A Schwartz; submitted 15.03.24; peer-reviewed by KL Silva, M Macdonald, MH Yarmohammadian; comments to author 02.10.24; revised version received 14.11.24; accepted 19.11.24; published 17.01.25.

Please cite as:
Savaria V, Queenton J, Carrier A
Decentralized Management of Home Care Services for Seniors: Protocol for a Participatory Action Research
JMIR Res Protoc 2025;14:e58271
URL: https://www.researchprotocols.org/2025/1/e58271
doi:10.2196/58271
PMID:

Protocol

User-Oriented Requirements for Artificial Intelligence–Based Clinical Decision Support Systems in Sepsis: Protocol for a Multimethod Research Project

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Abstract

Background: Artificial intelligence (AI)–based clinical decision support systems (CDSS) have been developed for several diseases. However, despite the potential to improve the quality of care and thereby positively impact patient-relevant outcomes, the majority of AI-based CDSS have not been adopted in standard care. Possible reasons for this include barriers in the implementation and a nonuser-oriented development approach, resulting in reduced user acceptance.

Objective: This research project has 2 objectives. First, problems and corresponding solutions that hinder or support the development and implementation of AI-based CDSS are identified. Second, the research project aims to increase user acceptance by creating a user-oriented requirement profile, using the example of sepsis.

Methods: The research project is based on a multimethod approach combining (1) a scoping review, (2) focus groups with physicians and professional caregivers, and (3) semistructured interviews with relevant stakeholders. The research modules mentioned provide the basis for the development of a (4) survey, including a discrete choice experiment (DCE) with physicians. A minimum of 6667 physicians with expertise in the clinical picture of sepsis are contacted for this purpose. The survey is followed by the development of a requirement profile for AI-based CDSS and the derivation of policy recommendations for action, which are evaluated in a (5) expert roundtable discussion.

Results: The multimethod research project started in November 2022. It provides an overview of the barriers and corresponding solutions related to the development and implementation of AI-based CDSS. Using sepsis as an example, a user-oriented requirement profile for AI-based CDSS is developed. The scoping review has been concluded and the qualitative modules have been subjected to analysis. The start of the survey, including the DCE, was at the end of July 2024.

Conclusions: The results of the research project represent the first attempt to create a comprehensive user-oriented requirement profile for the development of sepsis-specific AI-based CDSS. In addition, general recommendations are derived, in order to reduce barriers in the development and implementation of AI-based CDSS. The findings of this research project have the potential to facilitate the integration of AI-based CDSS into standard care in the long term.

International Registered Report Identifier (IRRID): DERR1-10.2196/62704

(JMIR Res Protoc 2025;14:e62704) doi:10.2196/62704

KEYWORDS

medical informatics; artificial intelligence; machine learning; computational intelligence; clinical decision support systems; CDSS; decision support; sepsis; bloodstream infection

Introduction

The first clinical decision support systems (CDSS) date back to the 1970s. Early systems, such as MYCIN, a program designed to advise on the choice of therapy selection for patients with infections [1], were rule-based expert systems. Nowadays, a wide variety of CDSS exist. These can be categorized as either knowledge-based or non–knowledge-based systems.

Knowledge-based systems operate on logical decision rules (IF <condition> THEN <action>). The system retrieves data and transforms it into an output following distinct rules. Further segmentation can be made into Bayesian networks, causal-probabilistic networks, and rule-based systems: The latter are usually based on medical guidelines [2].

Non–knowledge-based CDSS require a clinical data source and generate recommendations using artificial intelligence (AI) including machine learning or statistical pattern recognition [3,4]. The potential of AI models to sustainably improve patient care is estimated to be enormous for almost all aspects of the clinical decision-making process (prevention, diagnostics, and therapy) [5]. Based on big data analytics, AI-based CDSS offer the ability to pool, link, and combine data, that would be impossible for humans to interpret due to its complexity. In this way, these models can improve medical outcomes by optimizing care [6].

While AI is established in some disciplines, such as radiology (eg, automated image recognition), the transfer of AI-based CDSS into clinical use is lagging behind. Due to the inhomogeneity of different disease patterns, AI-based CDSS are often developed specifically for a target disease or a selected group of disease patterns, such as sepsis [7,8].

Sepsis is a life-threatening organ dysfunction caused by a dysregulated immune response to infection. It is a leading cause of mortality, with 49 million cases and 11 million deaths each year [9]. So far, only symptomatic therapies are available, that attempt to replace the function of the failed organ systems. Treatment of the dysregulated immune response as a cause of sepsis has not been successful in large trials and subsequently has therefore not found its way into clinical practice or sepsis guidelines.

AI-based CDSS could be particularly useful in sepsis care due to the high heterogeneity and complexity of the disease [10]. Non–knowledge-based respectively data-based CDSS are subject to a trade-off between model complexity and interpretability. As sepsis is an extremely complex condition, a majority of machine learning–based CDSS for this disease can be considered “black box” systems. Their treatment recommendations cannot or can only be interpreted by health care providers, with relatively high effort [11,12]. Health care providers may have to rely on these systems without understanding how the algorithms reach their conclusions, due to their black box nature. This lack of transparency can negatively impact the acceptability of such systems [13-15].

In addition to the black box nature of AI-based CDSS, there may be other possible reasons why such systems do not manage the transition into standard care, such as a nonuser-oriented development approach without or at least without sufficient consideration of the needs and preferences of future users [16-18], resulting in reduced user acceptance and implementation barriers (eg, computer literacy of the future users, data availability or legal issues) [4].

These may be possible reasons why there is still no AI-based CDSS for sepsis in Germany that is included in the standard care of the statutory health insurance (SHI) system and is used nationwide. Currently, only a few prototypes in the form of individual solutions are in use or under development (eg, [19,20]).

The reluctance to adopt AI-based CDSS does not appear to stem from the performance of such systems. The sepsis prediction algorithm InSight, developed by AI start-up Dascena, has been demonstrated in several articles to outperform traditional rule-based scores such as the Systemic Inflammatory Response Syndrome, the Sequential Organ Failure Assessment or the quick Sequential Organ Failure Assessment [21,22]. This and other developed algorithms have the potential to improve patient-relevant outcomes. In particular, this encompasses a reduction of sepsis-related mortality, a reduced average length of hospitalization, or an earlier treatment, for example, in the form of the timely administration of antibiotics [21,23,24]. Instead, the reluctance to implement AI-based CDSS can be attributed to a number of factors that are independent of their performance. These include a paucity of evidence, particularly prospective studies [22], a lack of capacity in health care systems to integrate AI into current workflows [25], and ethical concerns, such as the risk of discrimination against certain populations [25-27]. Also in other indications, despite a high frequency of development, only a marginal proportion of such systems successfully transition from the development phase into standard care.

Therefore, the multimethod research project “User-Oriented Requirement Profile for AI-Based Clinical Decision Support Systems Using the Medical Example of Sepsis – KI@work,” seeks to investigate AI-based CDSS in the above-mentioned disease context. In the framework of this research project, it is assumed that there are 2 reasons for the lack of implementation. First, there are administrative and organizational barriers (data availability, data collection, knowledge gaps among potential users) as well as legal and institutional hurdles (implementation of European and national legal requirements, [medical] liability law, competent bodies) within the German health care system that make it difficult to transfer and integrate AI-based CDSS

into the SHI system. Second, to ensure (sustainable) use and acceptance of AI-based CDSS, the system must have a high perceived usefulness according to the Technology Acceptance Model [28]. In addition, future users should be involved in the development phase, as suggested by the Recursive Innovation Management Model [18]. Due to the strongly technology-driven development of AI-based CDSS, this is currently only done in a fragmentary manner, so that the requirements and preferences of users are only insufficiently taken into account within the framework of such systems.

The multimethod research project addresses both aspects, resulting in two equally important research objectives, that are (1) to identify and remove or overcome barriers by developing health policy recommendations for action to facilitate the transfer of AI-based CDSS across all indications in the German health care system in the future and (2) to develop a clinical requirement profile that can be incorporated into the initial development of CDSS or can be considered in the further development of existing systems. This should enable an increase in usability and thus the acceptance of AI-based CDSS. The requirement profile is developed using the example of sepsis and is, therefore, indication-specific.

In order to achieve the objectives, 3 research questions and 3 sub-questions were determined (Textbox 1).

Textbox 1. Research questions of the multimethod research project.

- What insights can be gained from AI-based clinical decision support systems (CDSS) that are already established in health care and which best practices can be derived?
  - What is the data basis of these CDSS (input)?
  - How are the decisions and recommendations of the CDSS presented to the health care providers (output)?
  - How does the interaction between health care providers and CDSS take place (setting)?
- What specific problems exist or are seen in the establishment of AI-based CDSS in patient care, with a particular focus on clinical sepsis care as well as on the German health care system?
- What are the preferences of health care providers regarding the use and design of CDSS in the prevention, diagnosis, and treatment of patients with sepsis?

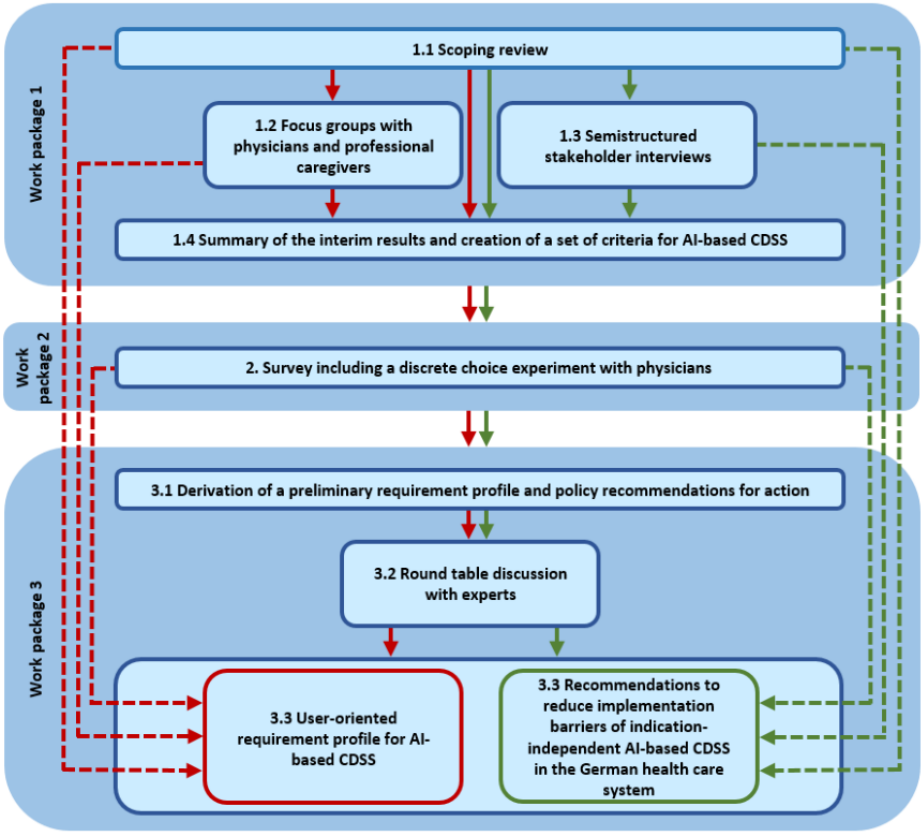
The research project is conducted by the Institute for Health Care Management and Research at the University of Duisburg-Essen. Consortium partners are the Department of Anesthesiology, Intensive Care Medicine and Pain Therapy at the University Hospital Knappschaftskrankenhaus Bochum, the Knappschaft Kliniken GmbH, the Department of Medical Informatics, Biometry and Epidemiology at the Ruhr University Bochum and the German Sepsis Society. The research project is funded by the Innovation Fund of the German Joint National Committee (funding code: 01VSF22050).

Methods

Overview

The research project is conducted over a period of 36 months (cf Multimedia Appendix 1) and uses a multimethod approach. It is separated into 3 work packages. Work package 1 combines a scoping review, focus groups with physicians and professional caregivers, and semistructured interviews with relevant stakeholders of the German health care system. At the end of this work package, the interim results (problems, barriers, and corresponding solutions) of the research project are summarized and a set of criteria for AI-based CDSS is derived. Based on the results of the preceding work package, work package 2 includes the central element of the research project: a survey of physicians, including a discrete choice experiment (DCE). Work package 3 involves the development of a requirement profile for AI-based CDSS and the derivation of health policy recommendations for action, which are discussed in an expert roundtable discussion. The research project concludes with a summary of the results in a white paper (cf Figure 1).

Figure 1. Overview of the multimethod research project. The results of work packages 1 and 2 are indirectly incorporated into module 3.3, as indicated by the dashed lines. AI: artificial intelligence; CDSS: clinical decision support system.



Work Package 1

Work package 1 addresses both research objectives. It serves to identify problems and barriers regarding the transfer of AI-based CDSS into the SHI system (first research objective) and to create a preliminary set of criteria for AI-based CDSS in sepsis care (second research objective). Work package 1 is divided into 4 modules.

Scoping Review (Module 1.1)

The scoping review combines systematic and structured research. The focus of the scoping review lies on research questions 1 and 2, thus addressing both research objectives.

Scoping Review

The actual scoping review examines the currently available evidence on the patient-relevant benefit of AI-based CDSS in the field of sepsis. Furthermore, it aims to identify factors that pose barriers to the transition of CDSS into the health care system and to identify solutions that reduce or overcome these barriers. Methodically it is based on the Joanna Briggs Manual for Evidence Synthesis [29]. Further development of the foundational work of Arksey and O'Malley [30] and Levac et al [31]. The documentation of the scoping review is based on the PRISMA Extension for Scoping Reviews [32]. The search strategy is designed using the PCC (Population, Concept, and Context) framework. The population encompasses individuals with or at risk of sepsis, the concept used is AI and the context are CDSS. Relevant search terms according to the predefined PCC framework are identified and linked with "OR" operators in order to form search blocks. The search blocks are linked with "AND" operators to generate search strings. All search terms are restricted to their occurrence in the abstract, the title, or as a keyword, and in the case of existing index terms (eg MeSH and Emtree), the corresponding terms are added. The databases examined are Medline and Embase as well as ACM Digital Library and IEEE Xplore. This proceeding is to ensure that the interdisciplinary character of the research project can be adequately investigated from both the medical and the informatics perspectives. Following the identification and removal of duplicates, 2 reviewers (GDG and PR) independently screen the titles and abstracts against predefined inclusion and exclusion criteria (cf Textbox 2) to determine whether an article is eligible for full-text screening. Subsequently, the same 2 reviewers conduct a full-text screening of the included articles against the same criteria.

The reviewer PR then uses the program MAXQDA (VERBI Software GmbH) to identify and tag relevant content in the included articles. The final categories are then discussed and systematized in a workshop (NB, GDG, and PR). The results of the workshop are recorded in Microsoft Excel.

In order to add further evidence, the reference lists of the articles identified in the scientific databases are screened. In addition, a structured search is conducted for gray literature (eg, working papers and guidelines) from various governmental and nongovernmental stakeholders, such as associations or public institutions, and their websites.

Textbox 2. Inclusion and exclusion criteria for the scoping review.

Inclusion criteria

- Articles focusing on sepsis and
- involving AI-based clinical decision support systems, that
  - describe patient-related benefits
  - describe problems with development, implementation, or application, or
  - describe approaches to overcome identified problems

Exclusion criteria

- Exclusively technical description of systems.
- Focus on the description of the evaluation of binary classifiers.
- Articles describing AI-based clinical decision support systems for neonates and children or animals.
- Not addressing any of the research questions in more detail.
- Research protocols, conference abstracts, letters to the editor, or expression of opinions.
- Article published before 2008.
- Language other than English or German.

Additional Structured Medical Device Database Search

The additional structured search aims to provide an overview of authorized AI-based CDSS already in use (irrespective of the indication area of sepsis). In order to identify such systems, the European Database on Medical Devices is analyzed. The filters “system,” “software,” and “risk class (IIa, IIb, III)” are used. The structured search examines the data on which the decisions of the systems are based (input), how the results are presented (output), and how the CDSS are integrated into the clinical context (setting). Particular focus is placed on the search for best practice examples and the identification of clinical areas where the use of AI is already established. These examples are used to recognize aspects that increase the likelihood of such systems being implemented.

Focus Groups With Physicians and Professional Caregivers (Module 1.2)

The focus groups with physicians and professional caregivers build on the interim findings of the scoping review (module 1.1). The findings of the focus groups contribute to the preparation of a standardized questionnaire for the survey in work package 2. Relevant aspects of input, output, and setting in the context of AI-based CDSS in the field of sepsis diagnosis and therapy are collected and derived, thus addressing the second research objective.

Five web-based focus groups are held using the conferencing tool integrated in Microsoft Teams. The participants include physicians and professional caregivers familiar with the care and treatment of adult patients with sepsis, as well as those who contribute to the prevention and diagnosis of sepsis. During the process of participant recruitment, attention is paid to ensure the inclusion of a heterogeneous group of hospitals, representing various levels of care (from primary to quaternary care). In addition, a balanced composition of focus groups in terms of gender is prioritized. Furthermore, participants with differing levels of experience are integrated into the individual focus groups. Three focus groups are conducted with physicians and 2 with professional caregivers. The discussions are based on semistructured guidelines. The focus groups are led by a moderator team according to Krueger and Casey [33], recorded and transcribed. They are then subjected to thematic qualitative content analysis based on Kuckartz and Rädiker [34] using the program MAXQDA (VERBI Software GmbH). The aspects of input, output, and setting represent deductive codes and are defined before data analysis. Inductive codes are supplemented during the process of analysis. A final categorization is conducted in a workshop (NB, GDG, and PR). The findings of the workshop are recorded in Microsoft Excel.

Recruitment of participants is supported by the Department of Anesthesiology, Intensive Care Medicine, and Pain Therapy of the University Hospital Knappschaftskrankenhaus Bochum and the Knappschaft Kliniken GmbH. In addition, participants from other hospital providers are also invited in order to represent a broad and provider-independent perspective of physicians and professional caregivers.

Semistructured Stakeholder Interviews (Module 1.3)

Semistructured interviews with stakeholders from different domains of the German health care system are conducted to complement the results of the scoping review (module 1.1) with the perspectives of various stakeholders. The expert interviews are undertaken to identify problems and barriers related to the implementation of AI-based CDSS in standard care (first research objective). Experts in the field of medical device law, representatives of the SHI system, patient representatives, physicians, and professional caregivers, representatives of quality management, data protection, and ethics, and various research institutions as well as private developers are interviewed. Similar to the focus groups, the interviews are recorded, transcribed, and subjected to qualitative content analysis according to Kuckartz and Rädiker [34].

Summary of the Interim Results (Problems, Barriers, and Corresponding Solutions) and Creation of a Set of Criteria for AI-Based CDSS (Module 1.4)

Based on the results of the first work package, a set of criteria for AI-based CDSS in sepsis care is developed in module 1.4 (second research objective), which is based on national and international evidence and qualitative survey methods. Furthermore, the identified problems and barriers as well as corresponding solutions are systematized and summarized (first research objective).

Work Package 2

The central element of work package 2 is a cross-sectional survey to identify perceived problems and barriers to the integration and usage of AI-based CDSS (first research objective) and to ascertain physicians' preferences regarding the design of AI-based CDSS in sepsis care (second research objective). The results of work package 1 serve as a basis for the development of the survey, including the DCE.

The questionnaire is divided into 3 sections. First, sociodemographic data and general attitudes toward AI applications are collected; the second section aims to identify potential barriers to the integration of AI-based CDSS into care; and third, a DCE is conducted to determine preferences for the criteria in the preliminary AI requirement profile. In particular, preferences are sought regarding the preferred information content and the appropriate integration into the care process.

The sociodemographic section comprises personal details, such as age groups or gender of the respondents, in addition to occupational data. This includes, for instance, professional experience in intensive care medicine (in 5 groups from none to >10 years), the medical specialty in which the participants are active as well as an evaluation of the degree of digitalization within the hospital where the respondents work. This procedure ensures the anonymity of the participants. The section concludes with an evaluation of general attitudes toward AI.

The second section of the questionnaire focuses on the potential barriers and problems associated with the integration of AI-based CDSS into standard care. It begins with questions concerning non–AI-based CDSS and then progresses to questions related to the use of AI in health care in general. The section concludes with questions on AI-based CDSS. In this part of the questionnaire, problems are primarily assessed using the Likert scale.

The last section of the questionnaire is intended to ascertain the requirements and preferences of physicians with regard to AI-based CDSS. For this purpose, a DCE is conducted to determine preferences regarding the design of such systems. Participants are presented with 2 fictitious systems and asked to indicate their preference.

The sample size of the survey could not be defined before the development of the questionnaire as it depends on the attributes queried in the DCE in the third section. The attributes are derived from the results of work package 1 and were thus not available at the time of the preparation of the grand proposal. Moreover, no comparable research projects could be identified from which recommendations for the required sample size and estimates of the utility of the items could have been derived [35]. Nevertheless, for orientation, initial sample size planning was done according to the heuristics developed by Johnson and Orme [36]. Therefore, 12 choice decisions, 2 selection sets per task, and a maximum of 3 levels were assumed, for which 125 evaluable questionnaires must be available. Since an additional evaluation according to subgroups such as gender (male, female, or diverse), age, or occupational group is to be conducted, the necessary number increases to 125×8=1000 completed questionnaires. Once the exact number of choice decisions, tasks, and levels is known, a statistical assessment is made to ensure statistical power for the given sample size.

In accordance with Pöge et al [37] gender identity is used as a binary variable, so transgender and cisgender people are evaluated together. Gender-diverse people are not reported separately in order to avoid identifiability due to the expected low number of cases but are included in the overall category of all respondents.

A total of 6667 physicians must be contacted, assuming an average response rate of 15% (1000/6667). Therefore, approximately 400 members of the German Sepsis Society and 250 physicians from the Knappschaft Kliniken GmbH who fulfill the inclusion criteria—(1) familiarity with adult medical care and (2) experience in intensive care medicine—are included. The sample is supplemented by randomly selected records of an address register. Based on the inclusion criteria, only addresses of physicians from the medical specialties of intensive care medicine, anesthesiology, orthopedics and trauma surgery, general surgery, visceral surgery, and internal medicine are selected. The Knappschaft Kliniken GmbH hospitals are excluded during the address data extraction process of the address register, as the hospital addresses are known and can be defined as an exclusion criterion to prevent duplicates. Furthermore, a duplicate check is conducted between the address register and the German Sepsis Society to avoid duplicates and to ensure that all physicians are not contacted twice.

In order to reach "offliners," it is possible to take part in the survey both online (LimeSurvey) and on paper. A pretest is conducted before the distribution of the survey in order to identify potential deficiencies and implement necessary modifications. A think-aloud protocol is used to ascertain the comprehensibility, manageability, completeness, and time required to complete the questionnaire [38]. In addition, the online version undergoes several functional tests for layout and usability.

Univariate or bivariate descriptive analyses are carried out as part of the evaluation of the second part of the questionnaire. Depending on the type of variable, frequency distributions, mean values, or medians are compared with simultaneous testing of statistical significance. Subgroup analyses are also conducted, for example, in relation to age or gender. The DCE (third section of the questionnaire) is expected to be analyzed using logit or mixed logit models. As both the absolute influence of the attributes and the relative influence of the levels are of interest, dummy coding is used.

Work Package 3

In work package 3, a white paper is developed. It includes (1) the final requirement profile for AI-based CDSS and (2) the determined health policy recommendations for action to reduce implementation barriers. Therefore, a preliminary requirement profile and health policy recommendations for action are developed (module 3.1), discussed with experts (module 3.2), and finally summarized in a white paper (module 3.3).

Derivation of a Preliminary Requirement Profile and Health Policy Recommendations for Action (Module 3.1)

The preliminary requirement profile for AI-based CDSS in the treatment of sepsis is developed based on the results of module 1.4 (summary of interim results and creation of a set of criteria for AI-based CDSS) as well as the results of the survey from work package 2 (second research objective). Furthermore, the identified barriers to the implementation and integration of AI-based CDSS in the German SHI system are used to develop targeted strategies for the removal and reduction of implementation barriers and translated into health policy recommendations for action (first research objective).

Expert Roundtable Discussion on the Requirement Profile and Corresponding Health Policy Recommendations for Action (Module 3.2)

In module 3.2 an expert roundtable is held. The aim of the discussion is to evaluate and optimize the preliminary requirement profile for AI-based CDSS as well as the corresponding health policy recommendations for action. In order to gain a comprehensive perspective, different stakeholders involved in the development and provision of AI-based CDSS are invited. In the context of the requirement profile for AI-based CDSS for sepsis care, the expert roundtable discussion focuses on input (data basis), output (presentation of decisions or recommendations), and setting (context of interaction between AI-based CDSS and user). Besides technical requirements, the results can include further requirements such as organizational, procedural, legal, or medical content.

The discussion is divided into four parts, after (1) introductory presentations, the (2) preliminary requirement profile for AI-based CDSS and (3) the health policy recommendations for action for the use of these systems in the German SHI system are presented. The workshop then provides an opportunity for (4) open discussion of the partial results of the requirement profile and the health policy recommendations. In addition, selected topics can be discussed in small groups with relevant experts, and the results of the discussions are presented in a plenum to reach a consensus among the stakeholders on the main issues.

A maximum of 30 stakeholders are invited to the workshop. In addition, there are at least 2 moderators and a technical and organizational staff member from the Institute for Health Care Management and Research from the University of Duisburg-Essen, as well as representatives from the University Hospital Knappschaftskrankenhaus Bochum and the German Sepsis Society. Discussions are led by a team of facilitators using prepared guidelines. The results of the workshop are recorded, transcribed, and subsequently analyzed.

Finalization of the Requirement Profile as Well as the Health Policy Recommendations for Action and Preparation of a White Paper (Module 3.3)

Based on the results of the expert roundtable discussion (module 3.2), the requirement profile for AI-based CDSS is finalized using the example of sepsis care. This enables a user-oriented development of AI-based CDSS in this context. Wherever possible, generic aspects are elaborated and presented in order to include indication-independent and therefore generalizable information in the requirement profile.

In addition, the health policy recommendations for action are concretized. It is discussed how to reduce or overcome barriers to the implementation and establishment of AI-based CDSS in clinical care and finally, proposals for legal adaptations are derived.

The results of both research project objectives, the requirement profile for an AI-based CDSS, and the health policy recommendations for action, are published in a white paper.

Ethical Considerations

In agreement with the ethical review committee of the Medical Faculty of the University of Duisburg-Essen, an ethics vote is not required as only physicians and experts are surveyed or interviewed within the project and no patient data is collected or used.

Results

The research project started in November 2022. The scoping review has been completed and the qualitative modules have been subjected to analysis.

As part of the scoping review, factors that pose barriers to the transition of CDSS into the health care system as well as solutions that reduce or overcome these barriers are analyzed. The review also sought to investigate the potential patient-relevant benefits of AI-based CDSS. The scoping review thus serves both to develop the guidelines for the qualitative modules and to derive potential problems for the survey (section 2 of the questionnaire).

The expert interviews, conducted between June and August 2023, aim to identify further problems and possible solutions for AI-based CDSS in the context of the German SHI system. The findings derived from the expert interviews are subsequently employed in the development of the survey (section 2 of the questionnaire).

The objective of the focus groups, conducted in June 2023, is to ascertain the preferences and requirements of health care providers with regard to the input, output, and setting of AI-based CDSS. The findings of the focus groups are used in the development of the DCE (section 3 of the questionnaire).

The conception of the survey, including the DCE, is finalized. It focuses on the preferences and requirements of physicians regarding the design of AI-based CDSS and the potential

problems associated with their implementation. The questionnaire is subjected to a series of comprehensive pretests. Furthermore, it is implemented on the web-based survey platform LimeSurvey (LimeSurvey GmbH) to facilitate digital participation.

Recruitment of the 6667 survey participants was initiated at the end of July 2024 and the results of the scoping review, and the qualitative modules are expected to be published at the end of 2024.

Discussion

Principal Findings

AI-based CDSS are developed for various diseases. These systems possess the potential to enhance the quality of care and thereby positively impact patient-relevant outcomes (such as a reduction of sepsis-related mortality, a reduced average hospital length of stay, or an earlier administration of antibiotics) [21,23,24]. Nonetheless, despite extensive development efforts, the majority of CDSS developed have not been adopted in standard care and do not make a significant contribution to improving care in their current form.

There may be 2 primary reasons for this. First, it is assumed that a technology push development is currently taking place, wherein AI-based CDSS are being developed without or only insufficiently considering the requirements and preferences of users [16]. Such requirements may relate to the complexity of the algorithm, with simpler algorithms potentially being preferred to more complex approaches that are incomprehensible and may be perceived as black boxes by users. Requirements related to the design and layout of AI-based CDSS may vary depending on professional experience or age. An analysis of current evidence reveals that other authors have identified various requirements for AI-based CDSS among health care providers in qualitative studies. These criteria include ease of implementation, predictive capability, and costs [39]. In addition, workload requirements [40] and the need for training programs [41] have also been highlighted.

Second, the implementation of such systems may face various barriers during the transition from the developmental phase to standard care, for instance, operational problems or regulatory uncertainties [4]. These and other hindrances may have a negative effect on the successful integration of AI-based CDSS and need to be identified and addressed before AI-based CDSS can be sustainably integrated into care.

Based on these 2 hypotheses it is necessary to analyze potential barriers, as well as the requirements and preferences of health care providers for AI-based CDSS. The results are summarized in health policy recommendations for action to reduce barriers and a requirement profile for AI-based CDSS in order to develop user-oriented systems and thereby optimize user acceptance.

Since the requirements for AI-based CDSS vary depending on the indication, the requirement profile is developed using the specific example of sepsis. Sepsis is a suitable subject for investigation due to its heterogeneity and complex pathophysiological processes, which pose challenges for health care providers in terms of diagnosis and treatment [10]. In addition, the intensive medical treatment and the continuous monitoring of patients with sepsis in the intensive care unit generate a large amount of data suitable for use in AI-based analysis.

The requirement profile for sepsis-specific AI-based CDSS, which is developed based on the requirements and preferences of health care providers, can help to ensure that future CDSS development is aligned with medical practice needs. Involving future users of such systems may counteract the current technology-push development and contribute to greater user acceptance. Following completion, the requirement profile is evaluated in terms of generalizability, and transferability to other indications. In addition, indication-independent health policy recommendations for action are developed based on the identified inhibiting factors for the implementation of AI-based CDSS.

Strengths and Limitations

The results of this multimethod research project, combining qualitative and quantitative research methods, represent the first attempt to create a comprehensive user-oriented requirement profile for the development of sepsis-specific AI-based CDSS. In addition, general recommendations are derived to reduce barriers to the development and implementation of such systems. Thus, this research project has the potential to promote future technology and facilitate the transfer of AI-based CDSS into standard care.

Despite the comprehensive design of the research project, it is not free of limitations. International literature is analyzed in the scoping review to provide an international perspective. However, all subsequent modules are limited to the perspective of health care providers and stakeholders in the German health care system, which may limit international comparability.

Qualitative and quantitative methods each have inherent limitations. Combining both is expected to leverage their strengths and mitigate their weaknesses. For instance, the predominantly qualitative findings from work package 1, which tend to be subjective and nongeneralizable, are tested for generalizability through the quantitative survey conducted in work package 2. However, not all nuances obtained through the qualitative approaches can be fully reflected in the quantitative survey. The combination of various research approaches—scoping review, expert interviews, focus groups, quantitative survey, and expert workshop—ensures that the project delivers comprehensive and well-founded results.

Furthermore, recruitment for the survey and the DCE may lead to selection bias. Although the majority of respondents are randomly selected from an address register, there is a risk of overrepresentation of physicians from the German Sepsis Society and Knappschaft Kliniken GmbH.

Dissemination Plan

The dissemination plan for this research project includes publishing the findings of the scoping review, the qualitative modules, the survey including the DCE, and the white paper in peer-reviewed open access journals dedicated to health

informatics, digital health, data science, and emerging health technologies. The results will also be presented at national and international conferences focusing on digitalization, sepsis, and health services research.

Conclusion

Based on the results of this research project, developers are provided with guidelines for the development of new AI-based CDSS or the revision of existing systems in order to make their products more user-oriented. In addition, the research project culminates in the development of health policy recommendations for action to reduce barriers to the implementation of AI-based CDSS. Ultimately, this enables AI-based CDSS to become a future standard in health care practice, providing benefits to patients.

Acknowledgments

This research is part of a wider research project (Multimethod Research Project on Requirements for Artificial Intelligence-Based Clinical Decision Support Systems Using the Medical Example of Sepsis (="KI@work")) funded by the German Federal Joint Committee (funding code: 01VSF22050 –KI@work). We acknowledge support by the Open Access Publication Fund of the University of Duisburg-Essen and Mr Björn Koos for his support in preparing the grant proposal.

The large language models ChatGPT (GPT-3.5) and DeepL (classic language model) were used exclusively to support the translation of the manuscript from German to English.

Data Availability

The datasets generated during and/or analyzed during this study are not publicly available for privacy reasons but are available from the corresponding author on reasonable request.

Authors' Contributions

Authors CA, GDG, JW, MA, HN, SM, NT, MT, FMB, and NB obtained the necessary funding and developed the design of the research project. All authors contributed to the organization of the research project. NB is responsible for project administration and supervision. PR drafted the study protocol. All authors reviewed, read, and approved the manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Timeline of the multimethod research project.
[PNG File , 58 KB - resprot_v14i1e62704_app1.png]

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Abbreviations

AI: artificial intelligence
CDSS: clinical decision support system
DCE: discrete choice experiment
PCC: Population, Concept, and Context
SHI: statutory health insurance

Edited by T Leung; submitted 29.05.24; peer-reviewed by A Staffini; comments to author 24.07.24; revised version received 21.08.24; accepted 31.10.24; published 30.01.25.

Please cite as:
Raszke P, Giebel GD, Abels C, Wasem J, Adamzik M, Nowak H, Palmowski L, Heinz P, Mreyen S, Timmesfeld N, Tokic M, Brunkhorst FM, Blase N
User-Oriented Requirements for Artificial Intelligence–Based Clinical Decision Support Systems in Sepsis: Protocol for a Multimethod Research Project
JMIR Res Protoc 2025;14:e62704
URL: https://www.researchprotocols.org/2025/1/e62704
doi:10.2196/62704
PMID:

Protocol

Prehabilitation Program for Lung and Esophageal Cancers (Boosting Recovery and Activity Through Early Wellness): Protocol for a Nonrandomized Trial

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Abstract

Background: Cancer is the leading cause of death in Canada, responsible for 28.2% of all deaths. Based on surgical candidacy and disease status, both lung and esophageal cancer are treated through surgical resection by a thoracic surgeon. Although surgery contributes to improved outcomes, the 30-day postoperative mortality risks are as high as 10% and 2.8%, respectively. Evidence has shown that prehabilitation is a way in which patients can have improved postoperative outcomes. Prehabilitation is multimodal, often including some form of movement, nutrition, stress management, and smoking cessation. Given the complexity of the health care system, pragmatic trials are important methodological tools to assess internal validity and improve current practice under real-world conditions. Concurrently, using community resources is imperative to keep people active in their community and create sustainable programming.

Objective: The Boosting Recovery and Activity Through Early Wellness (BREATHE WELL) study aims to explore the feasibility, implementation, and preliminary effectiveness of a clinically integrated, community-based, prehabilitation health coaching program. This includes nutrition, smoking cessation, sleep hygiene, and movement for individuals scheduled to undergo surgery for lung or esophageal cancer.

Methods: This is a pilot, nonrandomized, pragmatic, repeated measures, mixed methods trial. We will recruit 32 participants diagnosed with lung or esophageal cancer and are scheduled to undergo surgical resection into the prehabilitation program, with 32 additional participants who decline participation to act as a control group. Participants who agree will then go through an 8-week tailored prehabilitation program (in person or virtual), covering movement, nutrition, stress management, nutrition, goal setting, and smoking cessation. They will complete 6 sessions prior to surgery and then have 4 sessions, 1×/week following surgery. Following the completion of the program, they will have 3 booster sessions via phone or Zoom (Zoom Video Communications). The primary outcome is feasibility: (1) recruitment feasibility—recruitment rate (the number of participants referred per month), enrollment rate (the number of enrolled participants divided by the number of referred participants), reasons for declining, and prehabilitation window (time between consent and surgery); and (2) intervention feasibility—adherence to the movement intervention, attrition, safety, study completion rate, and adverse events. Secondary outcomes include measures of

preliminary effectiveness including patient-reported outcomes, such as well-being, fatigue, and functional measures. All measures will be assessed before, during, and after the prehabilitation program.

Results: Enrollment has begun in January 2025, with 2 participants enrolled in the health coaching program. The full study is expected to be completed in approximately 3 years and be published in winter 2027.

Conclusions: This study will inform the feasibility, implementation, and preliminary effectiveness of a clinically integrated, community-based, prehabilitation program in Nova Scotia, Canada, for people scheduled to undergo curative intent surgery for lung and esophageal cancer.

Trial Registration: ClinicalTrials.gov NCT06354959; https://clinicaltrials.gov/study/NCT06354959

International Registered Report Identifier (IRRID): PRR1-10.2196/60791

(JMIR Res Protoc 2025;14:e60791) doi:10.2196/60791

KEYWORDS

cancer; prehabilitation; physical activity; lung; esophageal; wellness; surgical; candidacy; feasibility; implementation; community-based; coaching program; Canada; lung cancer; esophageal cancer; surgery; nonrandomized trial; mixed method

Introduction

Cancer is the leading cause of death in Canada, responsible for 28.2% of all deaths [1]. Among these cancers, lung cancer is the most frequently diagnosed in the country, resulting in 25% of cancer-related deaths [2]. Esophageal cancer, while less common, presents unique challenges due to its effect on patients' nutritional status, its tendency to metastasize rapidly, and, consequently, its poorer prognosis [3]. Based on surgical candidacy and disease stage, surgical resection by a thoracic surgeon is a mainstay of treatment for lung and esophageal cancers. Although surgery contributes to improved outcomes, the 30-day postoperative mortality risk are as high as 10% and 2.8% for lung and esophageal cancers, respectively [4,5]. Postoperative complications (eg, pneumonia and pain) pose a significant risk to patients undergoing curative-intent, lung and esophageal cancer surgeries [6]. These events not only increase the length of hospital stay but also negatively impact the patient experience, decrease quality of life, and result in substantial financial burdens for health care [7-10]. Therefore, it has been proposed that completing a prehabilitation program prior to undergoing surgery may lead to improved postoperative outcomes for patients. Prehabilitation refers to assessments and interventions initiated prior to treatment to create a physiological and psychosocial buffer against anticipated deconditioning, complications, and other comorbidities that typically occur as a result of treatment [11,12]. Prehabilitation is multimodal, often including some form of movement, nutrition, stress management, and smoking cessation.

Previous research has found that older adults (aged 70 years and older; American Society of Anesthesiologist score III/IV) who participated in prehabilitation experienced 50% less postoperative complications relative to the control group; this type of intervention was safe and feasible and showed cost-savings of up to €800 (~US $833.62) per patient [13]. Although prehabilitation interventions have generally shown benefit [14], there is still little uptake into the standard of care. This could be due to a wide variety of factors, including the complexity of implementing programs in a health care setting. Therefore, there needs to be more consideration for clinical care pathways, delivery strategies, and infrastructure and personnel for the local uptake of these programs.

Given the complexity of the health care system, pragmatic trials are important methodological tools to assess internal validity and improve current practice under real-world conditions [15]. Concurrently, using community resources is imperative to keep people active in their community and create sustainable programming. Practice-based evidence is an emerging field that strives to ensure research is applicable to real-world settings [16,17]. Practice-based evidence is derived from implementation science research methods, which assess effective intervention in real-world settings and provide insights into the system's capacity and preparatory needs for dissemination and scalability [18]. The purpose of Boosting Recovery and Activity Through Early Wellness (BREATHE WELL) is to explore the feasibility, implementation, and preliminary effectiveness of a clinically integrated, community-based prehabilitation health coaching program, including nutrition, smoking cessation, sleep hygiene, and movement for individuals scheduled to undergo surgery for lung or esophageal cancer. Central to our research endeavor is the driving question: "How can a clinically integrated, community-based prehabilitation program be successfully implemented in the community, and can it lead to improved functional outcomes in patients undergoing surgery for lung or esophageal cancer?" This overarching question provides the study with its core focus and serves as a guiding force throughout the research process. The aim of this study is to investigate the implementation, feasibility, and effectiveness of BREATHE WELL, a community-based prehabilitation health coaching program specially designed for individuals scheduled to undergo surgery to address lung or esophageal cancer.

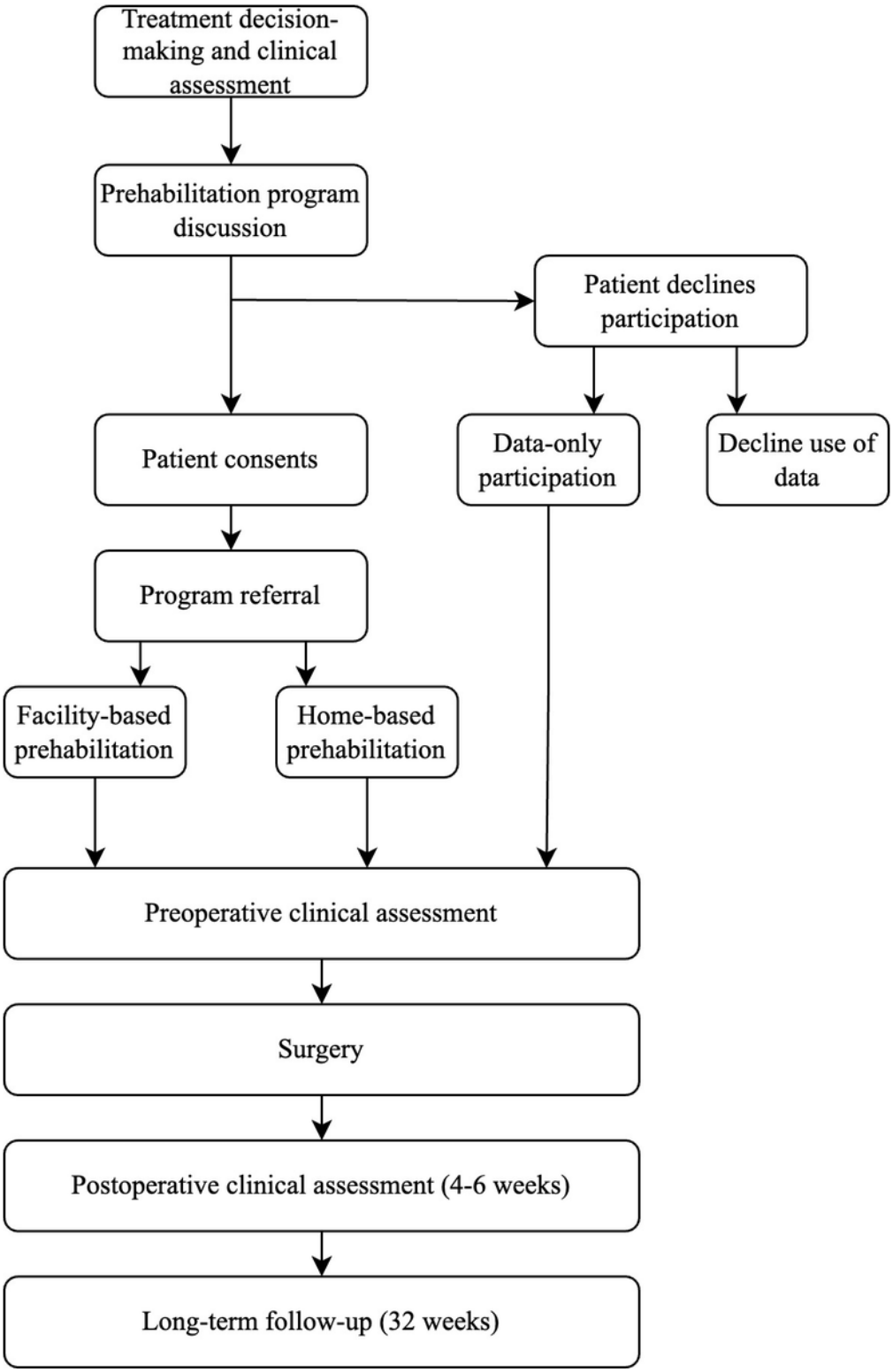
Methods

Design

This is a pilot, nonrandomized, pragmatic, repeated measures, mixed methods trial to assess the feasibility, implementation, and effectiveness of a clinically integrated, community-based, multimodal prehabilitation program for patients with lung and esophageal cancers in an urban academic health center in Halifax, Nova Scotia, Canada. Participant flow throughout the study is presented in Figure 1. This study aligns with the

TREND (Transparent Reporting of Evaluations of Nonrandomized Design) checklist (Multimedia Appendix 1) for nonrandomized trials [19].

Figure 1. Participant flow.



Participants

Based on a monthly surgical volume of 10 patients per month to the referring surgeon, assuming an enrollment rate of 25% while accounting for 20% attrition within a 16-month recruitment window, we will seek to recruit 64 participants (aged 18 years and older) diagnosed with lung or esophageal cancer (32 in the program and 32 who decline). This is based on the number of surgical candidates that the current surgeon sees in a 2-year period. Participants will be identified based on the following inclusion criteria: (1) confirmed diagnosis of lung or esophageal cancer; (2) treatment plan includes surgery (at least 2 weeks from the time of consent) [20]; (3) fluent in English; and (4) surgical oncologist approval. Exclusion criteria

include (1) unstable or symptomatic cardiac disease, musculoskeletal injury, or comorbid disease that precludes the ability to safely engage in physical activity or (2) significant cognitive limitations.

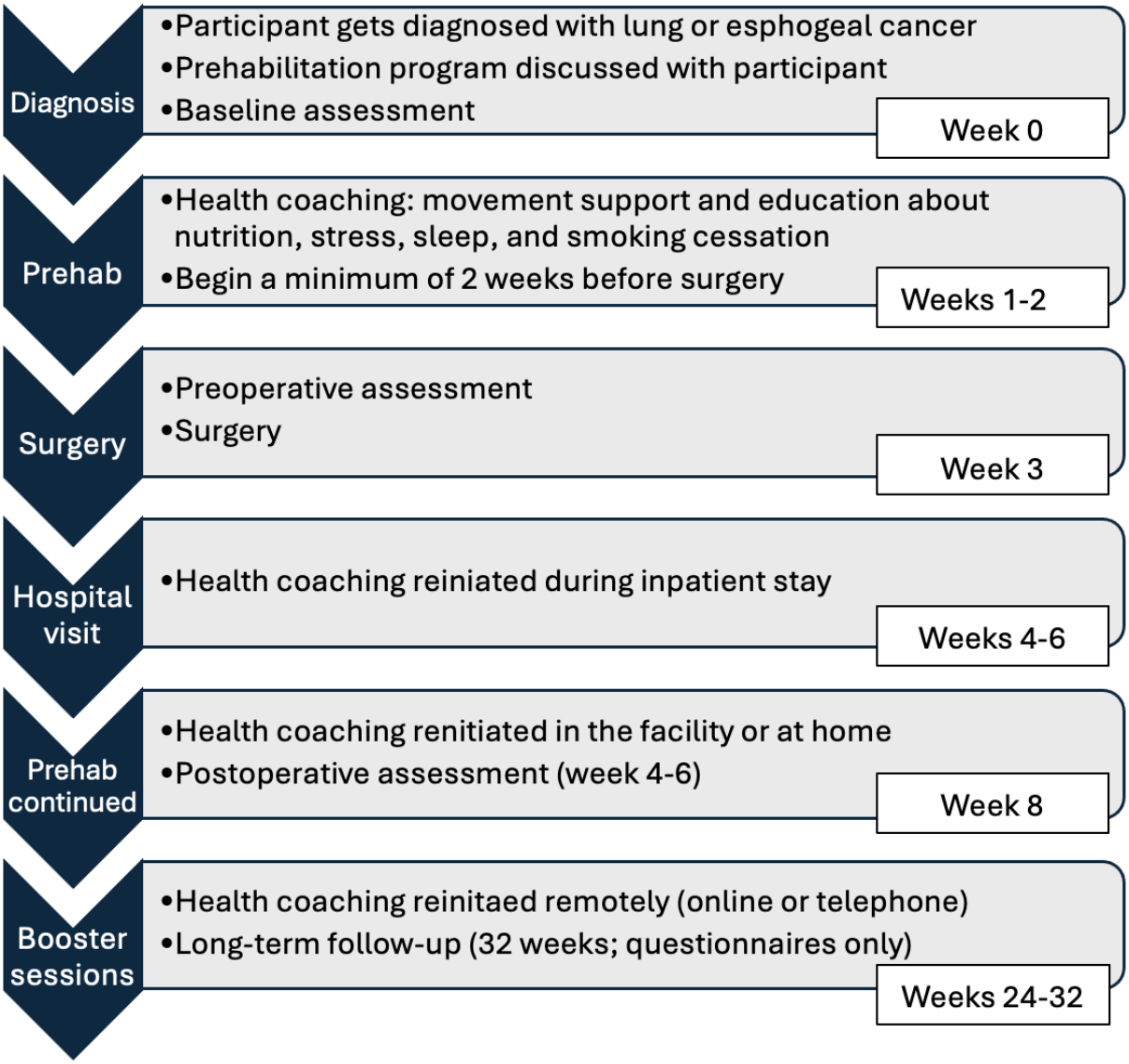
Enrollment and Assessment

Each potential participant will go through an assessment with the surgeon, including height, weight, blood pressure, heart rate, pulmonary function tests, grip strength, and a stair climb test as part of their clinical assessment. The thoracic surgeon will then raise the subject of prehabilitation with patients. At this point, patients will have the choice to participate in the prehabilitation program or not. If the participants do not agree to the study, they will continue with a standard of care. If a participant agrees to participate and provides written informed consent in accordance with the Nova Scotia Health Research Ethics Board, they will be referred to the research team and YMCA for immediate start of a prehabilitation program. Those who do not participate in prehabilitation will be used as a comparison group, through a waiver of consent; only those as part of the circle of care will pull these deidentified data for the research team.

Intervention

Participants will first have an appointment with a community-based, qualified exercise professional to discuss a tailored prehabilitation program. This will be dependent on a current functional fitness assessment (completed by the surgeon), goals of care, and surgery date. Participants will receive a handbook that will guide them through this process. The handbook will include a calendar of events, a guide to prehabilitation modalities (eg, movement, nutrition, sleep hygiene, stress management, and smoking cessation), publicly available resources (eg, Canada's Food Guide, CSEP 24-Hour Movement Guidelines, and Smoking Cessation guidelines), and helpful worksheets and other resources (Tobacco Free Nova Scotia Quit Line and mindfulness webinars). Participants will have the choice of delivery modality: either at home, virtual via Zoom (Zoom Video Communications), or at the nearest community-based YMCA. Both in-person and virtual programs will run in the same fashion. All participants will be given 2 resistance bands to assist with their at-home exercises. The intervention will last a total of approximately 8 weeks (Figure 2), depending on the time of surgery and postoperative follow-up. The intervention follows a tailored design, whereby the first 2-3 weeks provide more support, followed by weekly support and then biweekly support. This approach will help contribute to the autonomy of each patient. Following each counseling session, participants will engage in tailored movement sessions.

Figure 2. Timeline of prehabilitation intervention. Note that the "Prehab" phase may be longer than 1-2 weeks depending on the time from diagnosis to surgery. Prehab: prehabilitation.



Health Coaching

Participants will work with a qualified exercise professional who is trained in motivational interviewing (MI) to promote positive lifestyle habits. Participants will meet virtually or in person for counseling and movement sessions. Participants will receive 6 health coaching sessions prior to surgery (approximately 3×/week), with 5 additional wellness sessions after surgery (1×/weekly in the first month), and a follow-up (approximately 4-6 weeks after surgery). Health coaching will last 10-15 minutes, and the aim of these MI-informed behavioral counseling sessions is to develop personalized goals. Through MI techniques, qualified exercise professionals will use a shared decision-making approach with participants to promote evidence-based lifestyle modification, while using publicly available, evidence-informed resources to educate the participant on healthy and positive lifestyle behaviors. Following health coaching, the coach will lead the participant through a 15-45-minute movement routine. The booster sessions will provide health coaching over the phone or via Zoom only (Table 1).

Table 1. Overview of health coaching sessions.

Session	Week	Topic	Goal of session
Before surgery			
1	1	What to expect?	The goal is to have a clear understanding of what to expect from the diagnosis, surgery, and health coaching program. The qualified exercise professional will work with the participant to create a list of questions to discuss with their surgeon prior to their next visit. The qualified exercise professional will also start the process of what resources participants might need during their treatment, including Cancer Patient Pharmacare (which covers prescription cessation aids for example), Canadian Cancer Society patient supports (transportation supports), and other potential supportive services.
2	1	Understanding your body	The qualified exercise professional will go through how participants know their body the best, and things to look for when doing more movement. Key concepts of this session will be a rating of perceived exertion, use of our environment, and history of physical activity.
3	1	Movement + me	Participants will work with qualified exercise professionals to better understand what movement looks like for them and what type of movement they enjoy. Finding movement enjoyable is key to successful long-term movement.
4	2	Smoking cessation or sleep hygiene	If a participant reports current tobacco use, the qualified exercise professional will help the participant to understand the importance of smoking cessation as they prepare for surgery. This will include providing information about Tobacco Free NS and assisting with steps to access appropriate cessation resources. As well, participants will discuss sleep quality and the importance of sleep in preparation for and recovery from thoracic surgery.
5	2	Mindfulness	The qualified exercise professional will go through basic mindfulness attitudes, including patience, acceptance, and trust. The qualified exercise professional will review techniques for stress reduction and breathing.
6	2	Prepping for surgery	The qualified exercise professional will go through a reminder about things to bring with them to the hospital and talk about what to expect in the next few days. Participants will be reminded of the work they have done this far and be given a hospital date for their meet-up.
Surgery			
7	3	How are you feeling now?	The qualified exercise professional and participant will discuss how they are feeling and what supports the qualified exercise professional can offer to facilitate the transition from hospital to home setting.
8	4	Movement at home	The qualified exercise professional will assist the participant in better understanding movement at home and how they can make small movements as part of their everyday life. The focus of this session will be on doing small movement “snacks” and listening to their body.
9	5	Goal setting	Qualified exercise professionals will go through SMART[a] goals with the participants. This will include long- and short-term goals with an understanding of upcoming treatment and how that will affect goals.
10	6	Nutrition	The qualified exercise professional will assist the participant in the understanding of food as a whole and how important nutrition is when undergoing treatments for cancer, this will include tips from Canada’s Food Guide. If needed, the qualified exercise professional will also have resources for the food bank and how to access these types of services in their community.
11	8	Long-term planning: what is next?	The qualified exercise professional will discuss a long-term plan for the participant to sustain healthy lifestyle habits. They will go through their movement notes together and find a movement plan that will work for this participant, whether that be at home, at a local gym, or a more structured program.
Follow-up appointment with surgeon			
12	16	Booster session: where we are now?	The qualified exercise professional will discuss how the participant is feeling now and revisit goals. If participants require further support, the qualified exercise professional will also do anything within their scope and also refer to the Community Health Team resources, which offer support on many wellness topics and are free to all Nova Scotia residents.
13	24	Booster session: where we are now?	The qualified exercise professional will discuss how the participant is feeling now and revisit goals.
14	32	Booster session: where we are now?	The qualified exercise professional will discuss how the participant is feeling now and revisit goals.

[a]SMART: Specific, measurable, attainable, realistic, time orientated.

Movement Programming

All movement programming will be tailored to each individual participant’s current health status, goals, interests, and abilities. Each one-on-one movement session is expected to last 15-45 minutes and will include time for both warmup and cooldown. Participants will be instructed to begin at a light-to-moderate intensity (ie, 3-6 on a 10-point Borg Scale); systematically

progress (ie, periodized); and combine aerobic and resistance training programs for 15-45 minutes, 3 days/week. Should a participant feel that any movement is beyond their comfort level or ability, they will be instructed to inform the qualified exercise professional so that the movement can be modified to better suit their needs (Table 2).

Table 2. Outline of a movement programming[a].

	Description	Frequency	Intensity	Type	Time
Warmup	All sessions begin with a 5-minute warmup to gently increase heart rate and mobilize major muscle groups (RPE[b] 1-3/10).	—[c]	—	—	—
Aerobic	—	3-7× per week (3 supervised and 0-4 unsupervised)	MICT[d] (3-6 RPE) or HIIT[e] (7-9/10 RPE)	Rhythmic repetitive movements (eg, walking, marching, cycling)	10-15 minutes
Resistance	—	3× per week	4-7/10 RPE	Targeting major muscle groups including: • Legs (eg, sit to stand) • Back (eg, horizontal row) • Chest (eg, wall pushups) • Core (eg, dead bug) • Shoulders or arms (eg, shoulder press or bicep curl)	2 sets of 6-15 reps; 10-15 minutes
Balance	—	3-7× per week (3 supervised and 0-4 unsupervised)	4-7/10 RPE	Examples include single leg balance and tandem stance	2 × 30 seconds; 5 minutes
Flexibility	—	3-7× per week (3 supervised and 0-4 unsupervised)	4-7/10 RPE	Examples include hip flexor or quad stretch, hamstring stretch, and chest openers	2 × 20 seconds; 5 minutes
Locoregional	—	3-7× per week (3 supervised and 0-4 unsupervised)	4-7/10 RPE	Surgery-specific resistance and flexibility exercises (eg, swallowing exercises for esophageal participants)	2 × 20 seconds; 3-5 minutes
Cooldown	All sessions will conclude with a 5-minute cooldown to gently return heart rate to resting values (RPE 1-3/10).	—	—	—	—
Progression—aerobic	Sessions will begin at the lower limit of the desired range (eg, 3 sessions at 40% HRR[f]) and progress to the upper limit of the desired range (eg, 7 sessions at 70% HRR) as tolerated.	—	—	—	—
Progression—resistance, balance, and locoregional	Sessions will begin at the lower limit of the desired range (eg, 4/10 RPE) and progress to the upper limit of the desired range (eg, 7/10 RPE) by modifying repetitions, sets, or difficulty of exercises as tolerated.	—	—	—	—

[a]All programs will be tailored to each individual based on their functional level and environment.

[b]RPE: rating of perceived exertion.

[c]Not applicable.

[d]MICT: moderate intensity continuous training.

[e]HIIT; high intensity interval training.

[f]HRR: heart rate reserve.

Qualified Exercise Professional Training

Multiple YMCA-qualified exercise professionals will be trained in health coaching and MI to complete this study. This training will include (1) Thrive health services exercise oncology training [21], an exercise oncology-specific asynchronistic training module; (2) Health Coaching Certification [21], an evidence-based training that focuses on empowering health behavior change; and (3) completion of a full-day workshop on study protocol and MI techniques, including talks from experts in the field, individuals with lived experience of lung or esophageal cancer, and other health care professionals. Each counseling session will have a checklist and protocol for qualified exercise professionals to use outlining the targets and goals for each session. All qualified exercise professionals will be overseen by the YMCA clinical exercise physiologist who will offer advice and guidance on movement programming and health coaching sessions.

Outcome Measures

Feasibility (primary outcome) will include (1) recruitment feasibility—recruitment rate (the number of participants referred per month), enrollment rate (the number of enrolled participants divided by the number of referred participants), reasons for declining, and prehabilitation window (time between consent and surgery); and (2) intervention feasibility (adherence to the movement intervention, attrition, safety, study completion rate, and adverse events). The feasibility target for recruitment is a 25% enrollment rate. The feasibility target for adherence is 70% or more, measured by attendance to movement sessions with the qualified exercise professional. The feasibility target for attrition is 20% or less [22]. A timeline of feasibility measures is available in Table 3.

Table 3. Timeline of program measures[a].

	T0 (baseline)	T1 (before operation)	Surgery	T2 (after operation; weeks 4-6)	T3 (long-term follow-up; week 32)
Feasibility and acceptability					
Referral rate	✓				
Referring provider enrollment	✓				
Referred patient	✓				
Enrollment rate	✓				
Adherence		✓		✓	✓
Prehabilitation window		✓			
Safety	✓	✓		✓	✓
Reasons for decline	✓				
Attrition	✓	✓		✓	✓
Patient characteristics					
Demographic information	✓				
Cancer (type and stage)	✓				
Treatment Status	✓				
Surgery type	✓				
Resting, physical fitness, and patient-reported outcomes					
Height	✓	✓		✓	
Weight	✓	✓		✓	
Vitals	✓	✓		✓	
Pulmonary function	✓	✓		✓	
5TST[b]	✓	✓		✓	
Stair-climb test	✓	✓		✓	
Grip strength	✓	✓		✓	
FACT-L[c] or FACT-E[d]	✓	✓		✓	✓
FACIT-F[e]	✓	✓		✓	✓
Clinical outcomes					
Clavien-Dindo Surgical Complication (grade)			✓	✓	
Postoperative hospital LOS[f]			✓	✓	
Readmission and ED[g] visits			✓	✓	
Mortality			✓	✓	

[a]Pulmonary function test consists of tidal volume, forced vital capacity, vital capacity, and functional residual capacity. Vitals consist of blood pressure and pulse rate.

[b]5TSTS: 5 times sit to stand.

[c]FACT-L: Functional Assessment of Cancer Therapy—Lung.

[d]FACT-E: Functional Assessment of Cancer Therapy—Esophageal.

[e]FACIT-F: Functional Assessment of Chronic Illness Therapy—Fatigue.

[f]LOS: length of stay.

[g]ER: emergency department.

Participant outcome measures will include demographic information (age, sex, gender, socioeconomic status, race, marital status, educational level, and health knowledge), anthropometric measurements (height, weight, and BMI), medical information (surgery type, diagnosis, date of diagnosis, treatment status, and other chronic conditions), and patient-reported outcomes (PROs) that include quality of life (Functional Assessment of Cancer Therapy–Lung or Functional

Assessment of Cancer Therapy–Esophageal) [23,24] and fatigue (Functional Assessment of Chronic Illness Therapy–Fatigue) [25]. Both the Functional Assessment of Cancer Therapy–Lung or Functional Assessment of Cancer Therapy–Esophageal and Functional Assessment of Chronic Illness Therapy–Fatigue have been extensively validated and are reliable and widely used tools in the oncology setting [23]. Participants will have the option of completing surveys using the web-based (REDCap [Research Electronic Data Capture]; Vanderbilt University) database or using a pen and paper–based survey. A comprehensive assessment of functionality will be conducted in person in the clinic by the surgeon. Functional assessments are based on the Canadian Society of Exercise Physiology's Physical Activity Training for Health Protocol and include height, weight, resting heart rate and blood pressure, 5× chair sit-stand, stair climbing test, and grip strength. As part of standard of care, participants will undergo pulmonary function tests; these measures include tidal volume, forced vital capacity, vital capacity, and functional residual capacity.

The participants will be interviewed prior to the commencement of the program to better understand their perception of prehabilitation health coaching and to better understand their history with movement and healthy lifestyle behaviors. This will include questions that are based on past behaviors and future goals. This interview will be audio recorded and transcribed verbatim. A content analysis will be done using the Behavior Change Wheel and Theoretical Domains Frameworks [26,27]. This will aid in better understanding the behavior and barriers or facilitators to engage in the behavior. For sustained behavior change, participants need to have the Capability, Opportunity, and Motivation to perform the behavior [27]. Participants will also be interviewed at the end of the program to better understand their satisfaction with the program. This will also aid in understanding participants' perceptions of where they are regarding long-term behavior change. Postprogram interviews will be conducted to better understand their perspective on the program and how or if they found the program beneficial; these interviews will probe the understanding of sustained health behavior change and program satisfaction.

Postoperative outcomes include length of hospital stay and postoperative complications. The severity of complications will be graded according to the Clavien-Dindo classification [28,29]. Return to the emergency department within 90 days after the operation and 90-day mortality will also be assessed.

Statistical Analyses

The statistical analysis for this trial will be conducted with R (R Foundation for Statistical Computing). Participant characteristics will be summarized using descriptive statistics (mean, SD, frequency, and percentage). We will report on reasons for exclusion, attrition, and adverse events with frequency and percentages for each group. Safety will be determined by examining the total number of adverse events that occur over the duration of the program. Adherence to movement sessions will be summarized as a percentage (the number of movement sessions attended divided by the number of available movement sessions).

Baseline demographic and disease-related variables will be compared between prehabilitation and data-only participants using 1-way ANOVA for continuous variables and a chi-square test for categorical variables. The effectiveness analysis will include a linear mixed model to assess the difference in physical fitness and PROs from baseline (T0) to the preoperative (T1), postoperative (T2), 4-6 weeks postoperative (T3), and 32-week long-term follow-up (PROs only) time points, where the time point is the fixed effect and the individual participant is the random effect. A sensitivity analysis will be performed adjusting for sex, surgical type, and age. Linear mixed effect models will also be used to determine between-group differences. An α of .05 will be considered statistically significant. Point estimates and 95% CIs will be calculated for changes in the physical function and PROs at each timepoint and will also be used to provide important information for future sample size calculations. A Poisson regression will be used to estimate differences between groups for postoperative outcomes (ie, length of hospital stays, postoperative complications, return to emergency department, and mortality). Missing outcome data will be imputed using multiple imputation effects. Conclusions will be drawn using comparisons of each time point relative to the baseline.

Qualitative description is used to describe rather than interpret phenomena. Content analysis, the process of making sense of the meaning in the data will also be used during our thematic analysis. The research assistant will work with an experienced qualitative researcher to conduct multiple reviews of the transcripts and tapes (step 1) to familiarize themselves with the data. The analysis will be initiated as soon as the first interview is completed and continued concurrently with data collection. The analysis will examine what individual, structural, cultural, and institutional contexts are hypothesized to affect success. Additional codes will emerge to develop a thematic framework (step 2) that reflects the language and experiences of participants. An audit trial will be used to document the decision-making process. Sections of the transcripts will be charted into themes (step 3). Codes will be combined into themes during a series of research team meetings in which the relationships between behavior and the patient's capability, opportunity, and motivation to do said behavior will be explored and summarized. Analysts will review the codes and associate themes multiple times to check for potential biases, to ensure they reflect participants' words, and to improve and validate the interpretation (step 4) of the interviews. Additional interviews may be added when new themes emerge. Initial findings will be shared with a group of participants to help with interpretation and generate meaning from the data.

Ethical Considerations

This prehabilitation study includes human participants and was ethically approved by the Nova Scotia Health Research Ethics Board (REB# 1030020) in April 2024. All participants will go through a written informed consent procedure and will be aware that this study is completely confidential and voluntary. Participants will be given a small amount of money to offset the price of gas and parking when participating in an in-person program.

Author Reflexivity

This study brings together a multidisciplinary team with extensive expertise in research and clinical practice within the field of exercise oncology (JEL, DS, JC, and MRK); exercise measurement, evaluation, and prescription (JEL, DS, JC, and MRK); medical oncology (SS and AW); thoracic surgery (AW); policy implementation (LH and JP); and care experience (SS). The study team has a history of collaboration and has brought in key knowledge users to assist with the implementation of this project after the completion of research funding.

Results

Enrollment has begun in January 2025, with 2 participants enrolled in the health coaching program. It is estimated that it will take approximately 24 months to recruit all participants and collect all measures; analyses will take approximately 6 months; and writing the final manuscript will take approximately 6 months to complete. The full study is expected to be completed in approximately 3 years and be published in winter 2027.

Discussion

Principal Findings

The current standard of care for patients undergoing surgery does not include prehabilitation, although multiple randomized controlled trials have shown the efficacy of these programs [9,10,20,30]. Evidence is growing for the use of prehabilitation in standard of care, yet its implementation in clinical settings is still limited. BREATHE WELL will inform clinicians and knowledge users how structured prehabilitation programming using community settings and resources can bridge the gap between health care and the community. To maximize care pathways, it is imperative that those suited for community programs are triaged accordingly. Further, it is important to ensure that community-based resources are well equipped and trained to work with patients in prehabilitation to allow for sustained health behavior change and safe movement programming. Individuals living with and beyond cancer during and after treatment benefit from engaging in movement; however, they often lack the knowledge, resources, and guidance on how to do so safely and effectively [31-35]. By using an "exercise and educate" model focused on MI and health coaching, the emphasis will be on empowering participants to see the long-term benefits of behavior change and increase overall well-being for individuals. Also, previous community-based physical activity interventions with individuals living with and beyond cancer do see a longer-term increase in physical activity [11]. This could be due to familiarity with the environment and having increased support upfront, which can lead to better physical activity adherence. This study builds on previous evidence that prehabilitation is efficacious, yet its uptake into the standard of care is still lacking [14].

As part of this study, the intentional engagement of knowledge users including key health system partners, clinical care programs, and patients as team members will ensure high-quality evidence. It also provides an excellent infrastructure for rapid dissemination of findings into policy, practice, and clinical care. Knowledge translation initiatives will be ongoing throughout this research, including integrated and end-of-grant knowledge translation. We will regularly engage with all research team members, which includes key knowledge users (JP and LH) and patient partners (SS). The preliminary findings will be shared, when necessary, at team meetings, and interim research summary reports will be circulated via email and existing webinars and continuing education infrastructure established through our team members and collaborators. To support the further development of this project, we will generate an end-of-study summary report of key findings to policy and clinical partners. Findings will be disseminated to lung and esophageal cancer–specific audiences in Canada and internationally through conferences (eg, Canadian Association of Thoracic Surgeons Annual Meeting, American Association of Thoracic Surgeons Annual Meeting, Canada Cancer Research Alliance Annual Meeting, Canadian Society for Exercise Physiology Annual Meeting, and American Society of Clinical Oncology) and will be published in open access journals (eg, *BMC Health Services Research*) to enhance accessibility and potential for global reach and impact. This research will also be disseminated to patients and lay audiences through infographics to increase accessibility to a wider nonacademic audience.

There are several strengths to this study: (1) a pragmatic design allows for a deeper understanding of implementation and feasibility, which will aid in further understanding of prehabilitation in real-world settings; (2) the use of community-based facilities allows for a strong likelihood of not only system-level sustainability but also greater confidence for individuals to adhere to physical activity upon completion of the prehabilitation program; and (3) the use of a standard-of-care comparator group allows for preliminary effect estimates to understand if prehabilitation improves quality of care. However, this study is not without limitations. First, we have limited our sample to patients who have undergone thoracic surgery, which may not be generalizable to other populations with cancer. Second, the prehabilitation window is short (2-3 weeks), which precludes physiological changes. This is due to constraints from the diagnosis to the surgery date; if participants do have a longer window, they will be offered a longer presurgical program. However, with continued support after the surgery, participants will be supported to create long-term positive lifestyle changes and habits. Finally, this is a nonrandomized trial, which may decrease internal validity. However, the focus of this study is pragmatic in nature and the primary outcome is feasibility.

Conclusions

Prehabilitation is a key health intervention for those undergoing cancer surgery, with growing efficacy in the literature, yet the implementation of prehabilitation in real-world settings is lacking. BREATHE WELL will contribute to implementation science regarding approaches to support prehabilitation for surgical patients in a sustainable way that leverages the strengths of the health care and community setting.

Acknowledgments

The research team would like to acknowledge the continued support from the many administrative staff, Nova Scotia Health, and Dalhousie University, for their assistance in getting this research study off the ground. The study was funded by the Department of Surgery, Dalhousie University. The funder was not involved with the study design. The research team is focused on integrated knowledge translation and has used key support from patient partners (SS) and knowledge users (JC, JP, and LH) in the design, implementation, and dissemination of the study.

Data Availability

The original contributions presented in the study are included in the paper. Any further inquiries can be directed to the corresponding author. There are no data in the protocol paper.

Authors' Contributions

JEL, DS, JC, MRK, SS, JP, SS, and AW participated in conceptualization and funding acquisition. JEL, DS, JC, and AW collaborated on methodology. JEL wrote the first draft of the manuscript with assistance from DS and AW. All authors reviewed the final manuscript. AW supervised the full project.

Conflicts of Interest

None declared.

Multimedia Appendix 1
TREND (Transparent Reporting of Evaluations of Nonrandomized Design) checklist.
[PDF File (Adobe PDF File), 1832 KB - resprot_v14i1e60791_app1.pdf]

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Abbreviations

BREATHE WELL: Boosting Recovery and Activity Through Early Wellness
MI: motivational interviewing
PRO: patient-reported outcome
REDCap: Research Electronic Data Capture
TREND: Transparent Reporting of Evaluations of Nonrandomized Design

Edited by A Schwartz; submitted 23.05.24; peer-reviewed by C Urch; comments to author 10.09.24; revised version received 22.10.24; accepted 14.01.25; published 10.03.25.

Please cite as:
Langley JE, Sibley D, Chiekwe J, Keats MR, Snow S, Purcell J, Sollows S, Hill L, Watton D, Gaudry AE, Hashish I, Wallace A Prehabilitation Program for Lung and Esophageal Cancers (Boosting Recovery and Activity Through Early Wellness): Protocol for a Nonrandomized Trial
JMIR Res Protoc 2025;14:e60791
URL: https://www.researchprotocols.org/2025/1/e60791
doi:10.2196/60791
PMID:

Protocol

Sustainable Implementation of Digital Assistive Technologies in Health Care Through a Simplified Interaction and Control Platform: Protocol for a Cocreative Feasibility Study

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Abstract

Background: With the expected increase in the number of people needing care and the increasing shortage of skilled care workers, new care concepts are required. Therefore, digital assistive technologies (DATs), especially robotics, can improve the situation of people with different needs and create opportunities for participation. For a human-technology interaction to have a high level of usability, DAT's meaningfulness and effectiveness must be accessible to end users. Significant barriers to the use of DATs in health care are the lack of controllability and adaptivity, as well as control functions that are too complex.

Objective: The objective of this paper is to develop an interaction and control platform that is understandable to a layperson and has a programming interface for DAT interactions. The innovation consists of the expansion of usage and interaction options for carers of existing DAT in a more individual manner. This is to be achieved by combining modern interactive media, a modular software architecture, and already available DAT.

Methods: The project is planned as a mixed methods study with a longitudinal design, with multiple user involvements and measurement times in collaboration with 3 care facilities in Germany. When assessing technologies, the satisfaction of the basic human needs of competence, connection, and autonomy plays an important role in the actual use of the technology. These needs can be measured in the form of usability (System Usability Scale), intention to use (Technology Usage Inventory), and satisfaction with the carers' needs (Technology-Based Experience of Need Satisfaction). In the qualitative assessment, user experience is recorded using the think-aloud method and focus groups in order to obtain information about potential improvements of the platform.

Results: The EduXBot (Educational Exploration Robot Application Platform) project was initiated in January 2023 and is scheduled to conclude in December 2025, at which point the project's final results are expected to be available. The initial results were attained in the summer of 2024 when the final concept for the platform prototype was developed. In November 2024, an initial prototype of a functional platform for the simplified interaction and control of DAT was evaluated.

Conclusions: It is expected that the open DAT system architecture enables caregivers without any previous technical knowledge to assemble their individual DAT functional portfolio. The results of the project will provide low-threshold access to interaction options for existing DAT as well as expand the usage of such technologies in an individual and patient-centered way.

Trial Registration: Deutsches Register Klinischer Studien DRKS00034195; https://drks.de/search/de/trial/DRKS00034195

International Registered Report Identifier (IRRID): DERR1-10.2196/63089

(JMIR Res Protoc 2025;14:e63089) doi:10.2196/63089

KEYWORDS

digital assistive technologies; human-technology interaction; mixed methods; cocreation; user-centered design; health care; intention to use; feasibility study; long-term care

Introduction

Digital assistive technologies (DATs) have long been discussed as a way to address pressing health care challenges. On the one hand, these challenges are related to the aging of society and the associated increasing need for care services. On the other hand, the acute and future shortage of nurses makes it difficult to provide care for older adults and those who are sick [1-3]. The digital transformation of health care and the use of DAT could be an opportunity to address these challenges [4]. As the health care system in Germany is under pressure to respond to increasing care needs, one measure is to promote the digital transformation of the health care system [5-7]. However, preliminary work shows that DAT, such as mobile apps, telemedicine systems, and robotics, have not yet been implemented in care processes as sustainably as expected [8,9]. However, when used correctly, DAT can provide opportunities to reduce the burden on caregivers [10-13].

The term assistive technology is a generic term for assistive, adaptive, and rehabilitative devices, which, according to the World Health Organization [14], includes all assistive devices, such as crutches, bedpans, or wheelchairs. For the purposes of this study, the term is expanded to include digital technologies such as augmented or virtual reality technologies or robotic systems. A generally valid definition of DAT is difficult to formulate, however, because DAT can develop potential in different areas [15-17], the effects of which would then have to be demonstrated in a specific application.

Nursing can be described as a complex situation in which the patient must be approached individually and according to the situation. The advent of DAT presents a challenge to health care professionals, who must adapt these technologies to the diverse and individual needs of the patients they care for and integrate them into care processes that must be planned individually. Thanks to their training and professional experience, professional nurses are able to quickly understand these complex situations and make appropriate decisions. It is difficult for nurses to imagine that an algorithm-based system can learn their rules and principles and have the flexibility to know when to modify those rules or not apply them at all. Apart from this, nurses recognize that DAT could reduce the error rate for routine tasks that require high concentration, such as medication preparation or documentation [18].

In addition, ethical concerns play an important role in nurses' reluctance to use DAT. An aspect of the discussion is the change in the workflow that occurs with the integration of DAT. Nurses fear that the logic of the devices, which is different from their own, will cause additional stress or even make them feel influenced by others. Nurses also fear losing their jobs as technology takes over their activities. Last but not least, there is a fear of losing interpersonal contacts. A change in the psychosocial component of nursing work goes hand in hand with a reduction in the attractiveness of the profession for nurses and should, therefore, be avoided [18,19].

Previous work shows that technology development research has been approached from a technology-centered perspective. Reference to user interests is often only made in the context of raising awareness among target groups, identifying needs in the testing phase, or for a finished technology [20-22]. Participatory design approaches such as cocreation are a solution to foster usability and user acceptance. Cocreation is defined as a collaborative approach that involves end users and relevant stakeholders in all phases of a project [23]. Early involvement of end users can increase acceptance and have a positive impact on patient satisfaction and quality of care [24,25]. In addition, cocreation can increase the successful implementation of evidence-based interventions and policies through equal and deep involvement of end users [26,27].

In order for DAT to unfold its potential, it is necessary, on the one hand, to provide services that are tailored to the respective functional limitations of those in need of care so that the use of DAT can be planned and problem oriented [28,29]. This means that nurses also play a crucial role in the widespread use of DAT. According to a study by the Bertelsmann Foundation, the acquisition of knowledge about existing technical systems is a prerequisite for the use of DAT in care settings, as is the development of application skills on the part of nursing staff [30]. Preliminary work also shows that application knowledge and skills, as well as the opportunity to use DAT in relation to care problems, are beneficial for nurses' willingness to use DAT [31-34].

To fill this research gap, the EduXBot (Educational Exploration Robot Application Platform) project aims to develop and evaluate a technology-based interaction platform with a reduced complexity control interface as part of a cocreative, exploratory approach to facilitate the control of existing DAT by caregivers. The goal is to provide formal caregivers with a simplified way to use DAT to support caregiving. The aim of this feasibility study is to investigate to what extent a prototype for simplified control of already available DAT changes the willingness of nurses to use them in the nursing process. The collaborative project brings together developers from the field of technology research, nursing scientists, and business partners from the fields of project management for digital work environments and the development of digital formats for knowledge transfer. The cocreative nature of the project means that in addition to the scientific project staff, nurses will be involved as end users in every phase of the project. This ensures that the project goals are better achieved in terms of user needs and technical feasibility.

Methods

Conceptual Framework

The project aims at the participatory development and evaluation of a platform to promote the applicability of DAT in care settings. A feasibility study with a longitudinal design will be conducted based on a mixed methods approach. The main goal of the platform is a simplified application of DAT to support care processes. The development will be carried out in a participatory manner as a user-centered design (UCD) based on the suggestions of the "Motivation, Engagement, Thriving in User Experience" (METUX) model [35], which takes into account the expectations and experiences of the end users and promotes the intention to use (ITU) and thus the usability, relevance, and creativity of the platform, thus concretizing the overall implementation concept.

In practical implementation, the project is based on the theoretical model of UCD and follows the suggestions of the cocreative design cycle [36]. The UCD approach is used to cocreatively develop a more needs-based and more tailored end product based on the nurses' expert knowledge and to take possible consequences of implementation into account [36-38]. Positive effects are promised in terms of improving the identified outcomes as well as greater usability and user acceptance of technical products [39,40]. The cocreative design cycle is the process by which all relevant stakeholders are involved in the design and development of technologies. End users are actively involved in the design and development of solutions that meet their challenges. The result of the process is innovative and creative solutions that are useful, effective, and user centered, thereby promoting their actual use [41].

The user-centered and cocreative approach used in this study integrates 3 cycles (Figure 1) that incorporate the realities of end users (relevance cycle) and the scientific knowledge base (rigor cycle) into the development of technical products (design cycle) [42-45]. With this chosen approach, it is better possible to theorize, collect, and ultimately practically map the requirements for the technologies used in the study in the sense of determining needs. At the same time, collaboration between scientists and end users is more possible. Furthermore, end users can be more actively involved in product evaluation over the course of the test cycle. This ensures the functionality and, ultimately, the success in terms of improved applicability of a platform.

In the first step (relevance cycle), needs, functionalities, and application scenarios of and with nurses as end users are identified through focus groups. The selection of the DAT used in the project is based on the conditions of the cooperating institutions and the needs of the nursing staff. In order to clearly define nursing problems in the context of the learning scenarios, the concept of nursing need (see §14 Sozialgesetzbuch XI [Social Codebook XI]) is used. Based on this concept, DATs are selected that are already available and ready for use. These should cover a wide range and variety of technologies (from a mobile telepresence system to a complex humanoid robot).

Based on the results of this procedure, concrete scenarios will be outlined that are necessary for the implementation of a first demonstration model of the platform. In the next steps, the prototypes will be developed in 4 iterations with respect to usability, user acceptance, and satisfaction of basic psychological needs of the end users until the first prototype can be tested under simulated and real conditions in the facilities. The development of the prototype takes place schematically in 4 steps (Figure 2).

Figure 1. User-centered and cocreative design of the platform development (according to Farao et al [36]). DAT: digital assistive technology.

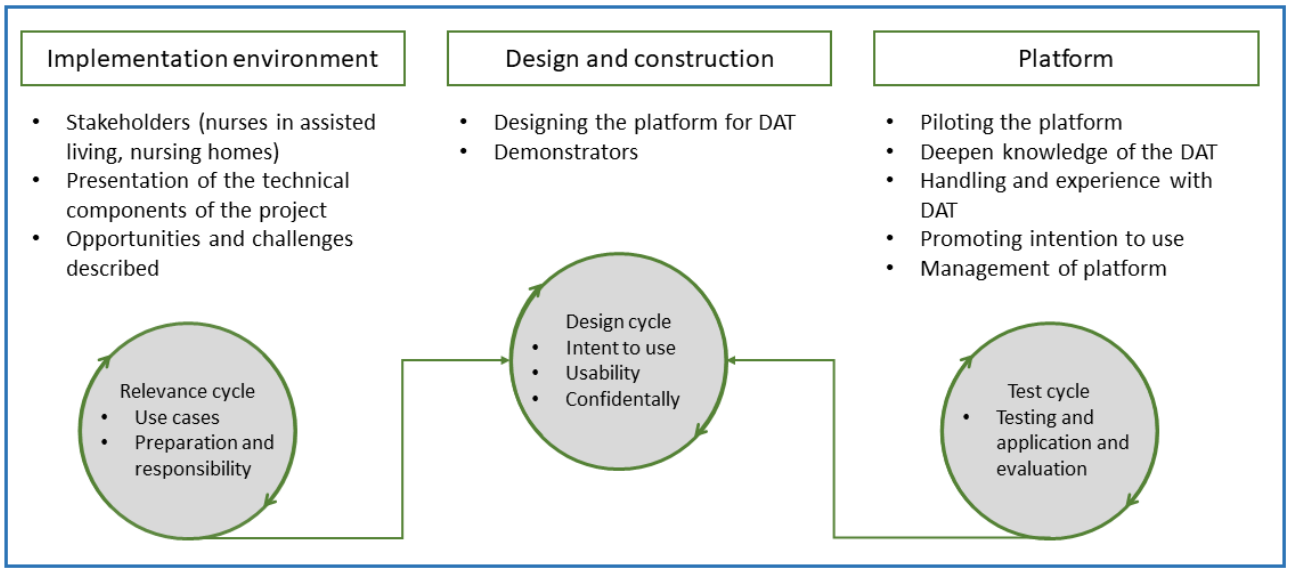
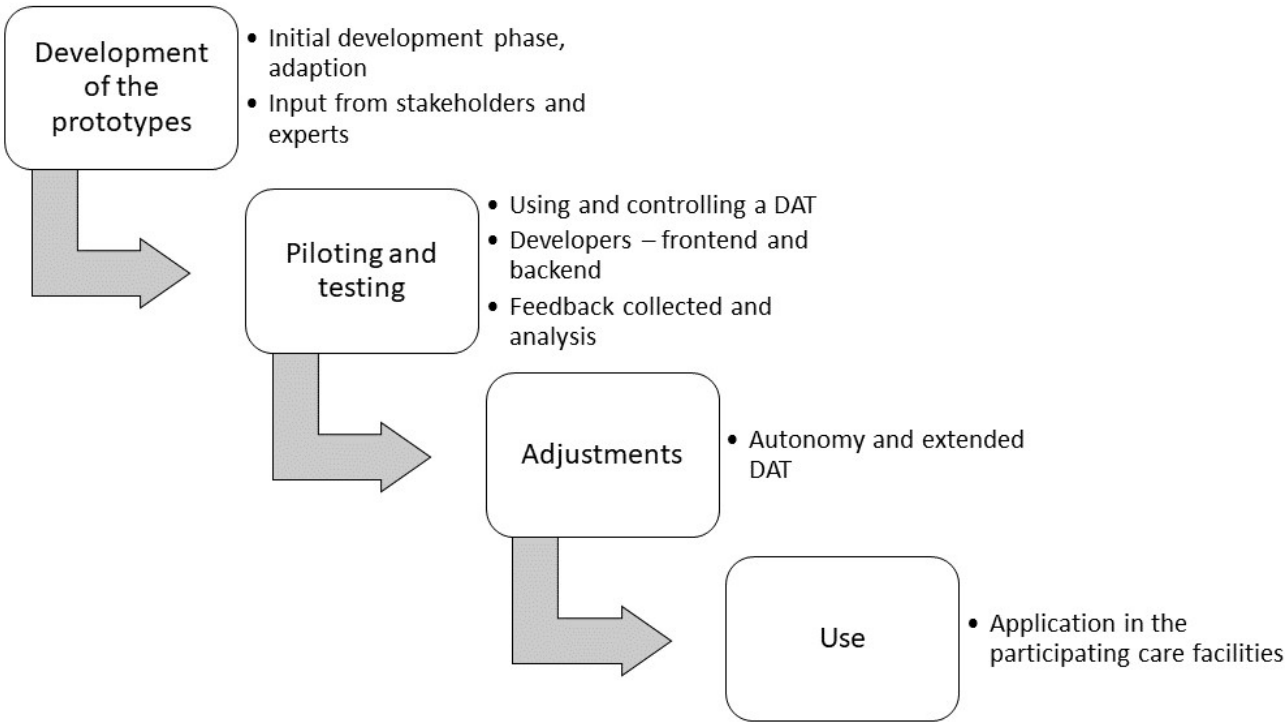


Figure 2. The development of the platform takes place in 4 steps. DAT: digital assistive technology.

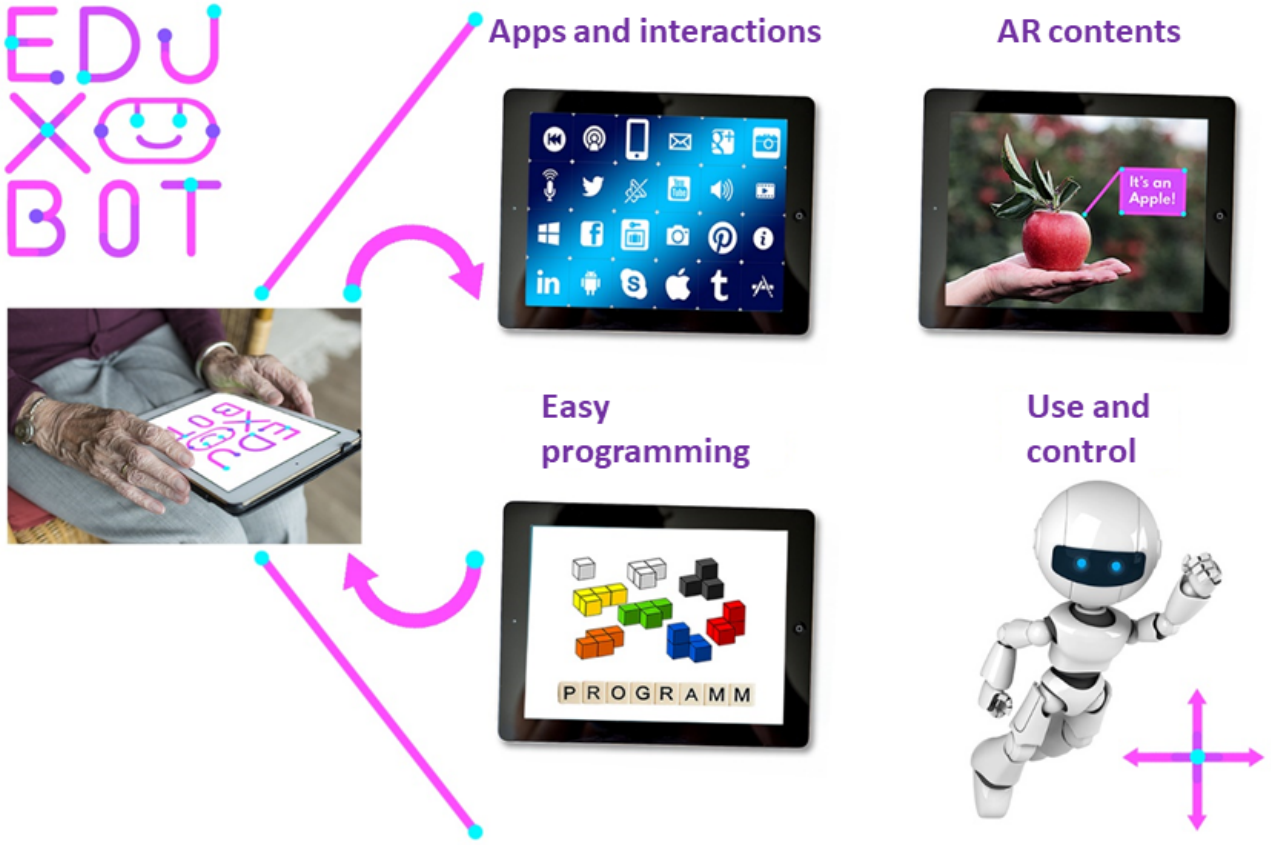


Technical Description

The innovation of the project does not lie in the development of new DAT per se but in the creation of extended usage and interaction possibilities for already available DAT. By combining modern interactive media and a modular software architecture, EduXBot aims to achieve the next level of DAT use in the care of people with disabilities, forced isolation, or restricted movement. The DAT should also promote an individual, programmable user interface for caregivers in an easier way to better meet the needs of those in need of care. EduXBot represents an experience and learning platform with 4 main functions (Figure 3): (1) programming (simplest type of programming), (2) community platform ("widget platform," users can share their apps), (3) using and controlling (easy way to interact, control, and use the DAT), and (4) augmented reality (AR) experience (experience and learn through AR content).

The multipart concept for using the platform then allows people with diverse previous technological knowledge to use DAT. That means EduXBot leads to the development of a layperson's iteration with the intention of human-technology interactions, which is developed in the form of a cocreative process together with the end users. EduXBot does not focus on the development of new care technologies that replace caregivers per se but rather on creating supportive interaction options that could relieve the burden on caregivers. The flexible and open system architecture of the platform supports this by keeping different DAT, sensors, and interaction systems available for different usage options. With the help of the development of low-threshold digital access options through an intuitive user interface with community and operator connections, informal support and supply networks are also strengthened as they enable participation in social networks.

Figure 3. The 4 main functions of the EduXBot platform. AR: augmented reality.



Study Design

Overview

EduXBot is a longitudinal feasibility study based on a mixed methods approach. The mixed methods approach combines aspects of quantitative and qualitative research in order to examine the research topic from different perspectives and to answer questions that could not be answered by a purely quantitative or purely qualitative study [46]. The researchers initiated the study with a quantitative phase, which was followed by a second qualitative phase that provided a more in-depth explanation of the initial results [47].

A total of 3 care institutions (1 inpatient, 1 outpatient, and 1 life-sustaining) that support people in their health care and daily life were recruited to participate in the project. The institutions were contacted as partner institutions in previous DAT research projects and agreed to participate in this project. Therefore, it can be assumed that the participating nurses are generally aware of the topic of DAT in nursing. The facility managers will be informed in detail about the project and will be asked to act as gatekeepers to motivate the nurses and relatives in their facility to participate in the research project.

Participants are invited to take part in the study as test subjects by the facilities with which they are affiliated. The participants are as varied as possible in terms of age, gender, length of professional experience, and so forth [48]. The inclusion of nurses from diverse backgrounds within the facilities serves to enhance the heterogeneity of the study sample, thereby contributing to the study's overall value. It should be noted that some participants may be unable to commit to the study due to scheduling conflicts or other commitments, while others may choose to withdraw (Textbox 1). It is essential to emphasize that no financial compensation is provided for participation in the study. However, those who elect to take part receive certain benefits, including complimentary refreshments during the workshop sessions and, upon request, recognition of their institution and name in the project acknowledgments.

Textbox 1. Description of the inclusion and exclusion criteria of the participants.

Inclusion criteria:

- The participants could be nurses
- The participants could be the support staff
- Currently in a facility that belongs to the project's practice partner
- Sufficient in written and spoken German

Exclusion criteria:

- Those who do not want to participate at the beginning or withdraw later

In the context of research involving human participants, it is imperative to consider pragmatic factors such as financial resources and the maximum feasible number of participants in accordance with the guidelines for designing and evaluating feasibility pilot studies [49]. According to the guideline, achieving saturation in a study occurs at 30 participants. Statistical principles suggest that 30 individuals are sufficient to ensure the normality of the sample size [50,51]. Therefore, the objective is to recruit a minimum of 30 caregivers. It is important to acknowledge that the implementation of blinding is not a viable option in this context, as the participants are required to actively engage with the technologies under study.

The primary objective of this study is to design the human-technology interaction between the platform and users in a manner that ensures a high level of usability for all users. The objective is to assess whether the accessible platform alters the intended use of DAT by offering a simplified application option for caregivers. This inquiry seeks to ascertain the potential for DAT to be integrated as a supplementary resource in the planning of individual care processes. The central question guiding this study is whether the EduXBot platform offers an interface that enhances the autonomy of caregivers' DAT use. The objective is to enhance usability by a minimum of one level over the course of the study. The primary objective is to ascertain the extent to which the platform affects the usability of DAT (System Usability Scale [SUS]), the intention to use it (Technology Usage Inventory [TUI]), and the satisfaction of caregivers' needs through technology (Technology-Based Experience of Need Satisfaction [TENS]).

The secondary objective is to develop a multilevel benefit concept for EduXBot. This will provide caregivers with different affinities for electronic media, as well as different levels of technical expertise, and will offer them windows of opportunity to use and experience the platform. The objective is to conduct a direct assessment of the EduXBot platform by the participating nurses and to evaluate the platform with the aim of continuously improving the content and application options of the platform. A secondary objective is to record user satisfaction in order to obtain information on potential improvements to the platform through the analysis of structured feedback. The collection of qualitative data will be facilitated through the implementation of think-aloud (TA) and focus group methods. The aim is to empower caregivers to articulate their subjective experiences and perceptions regarding the utilization of EduXBot in an unstructured manner.

The third objective is the long-term evaluation of the EduXBot platform, encompassing not only its readiness for implementation but also its potential for long-term integration, utilization, and management of DAT. A further objective is to examine the interrelationship between the perceived ITU, usability, and user acceptance of the platform, which is currently being developed for the application. The tertiary target variable is the long-term willingness to use DAT in a sustainable manner and to integrate the digital assistive support offering into the existing care provision framework.

The measurement times are based on the development process shown in Figure 2. This allows changes in improving ITU to be measured. Since there are different versions with different application scenarios, especially at TUI, Table 1 is intended to provide an overview of the measurement times and evaluation methods used.

Table 1. Different questionnaires are used at different measurement times.

Measurement time	Evaluation method
T0: Identification of functionalities and application scenarios	• TUI[a] original questionnaire (pre-post version) • Focus group
T1: Development of the prototypes	• TUI II parallel questionnaire (complete version) • Focus group
T2: Piloting and testing	• TUI II parallel questionnaire (complete version) • SUS[b] • TENS-Interface[c] • Focus group
T3: Adjustments	• TUI II parallel questionnaire (complete version) • SUS • TENS-Interface • Focus group
T4: Use	• TUI II parallel questionnaire (complete version) • SUS • TENS-Interface • Focus group

[a]TUI: Technology Usage Inventory.

[b]SUS: System Usability Scale.

[c]TENS-Interface: Technology-Based Experience of Need Satisfaction–Interface.

Quantitative Evaluation

The TUI is a valid measuring instrument that is based on the established Technology Acceptance Model [52] and its further developments [53]. It comprises 9 subscales, encompassing a total of 33 questions. These questions facilitate the estimation of technology use based on technology-specific and psychological factors. Each scale comprises 3-4 items, which are answered using a 7-point Likert scale. The intention to use scale uses a visual analog scale with a length of 10 cm. The subsequent Table 2 offers a comprehensive overview of the TUI scales.

Table 2. Description of the Technology Usage Inventory (TUI) scales according to Kothgassner et al [53].

Scale	Description
Curiosity	Curiosity and inquisitiveness of a person regarding a specific technology.
Technology anxiety	Independent of specific technology. Overwhelm, fear of using technology.
Interest	Independent of specific technology. Interest in technology and willingness to obtain information independently.
Usability	Perceived user-friendliness of a specific technology.
Usefulness	Perceived usefulness of a specific technology. Refers to support in everyday life.
Skepticism	Mistrust of a person regarding the use of a specific technology. Assessment of risk, danger, and disadvantages.
Accessibility	Perceived accessibility (in the sense of availability, procurability) of a specific technology.
Immersion	Can only be specified in connection with the corresponding technologies.
Intention to use	Intention to actually use a specific technology.

The internal consistencies of the scales can be rated as good overall (Cronbach α=0.70 to α=0.89). Furthermore, the TUI scales (with the exception of accessibility) have been found to be valid indicators of stress and relaxation based on heart rate and heart rate variability [53]. The wording of the individual questions can be adapted to the specific technology being evaluated, with the exception of the technology anxiety and interest scales. The TUI's modular design allows for the exclusion of individual scales contingent upon the investigative objective. For this study, for instance, the immersion scale was excluded, as no technology aimed at immersion was used.

This study uses the questionnaire at each measurement time (Table 1). Before the development of the platform, the original TUI questionnaire pre-post version was used to assess the caregivers' needs, functionalities, and DAT application scenarios. The "pre" version is administered before the introduction of the DAT, with the objective of collecting data on technology usage tendencies. The "post" version is administered after the introduction of the DAT, with the objective of establishing a baseline for measurement. Subsequent to these measurements, the TUI II parallel questionnaire (complete version) will be administered in its entirety. The

measurement enables the formulation of statements regarding changes in the ITU.

For the purpose of evaluation, a cumulative value was formulated for each scale. The cumulative value commences at 3 or 4, representing the lowest level of the construct, and, contingent on the number of items, ranges from 21 (3 items) to 28 (4 items) at the highest level. The ITU scale constitutes an exception in this regard. The scale is evaluated by measuring the distance from the right endpoint (full rejection) to the answer at the intersection of the line. The distance in millimeters was ascertained and added to all 3 items. The maximum scale value that can be attained is 300. The interpretation of test values is facilitated by the scale description. A high test value is indicative of a high level of the respective construct. In instances where the data does not conform to a normal distribution, it is advised to use stanines (standardized calibration scale with a minimum of 1 and a maximum of 9) and percentile ranks (relativizing the test characteristic value in relation to the reference population) [53]. Standard tables have been developed for this purpose (Table 3). Consequently, a statement regarding the proportion of participants who attained the same or lower values is attainable.

Table 3. Percentage ranks and stanines.

Percentile rank	Stanine	Percentage (%)
0-4	1	4
>4-11	2	7
>11-23	3	12
>23-40	4	17
>40-60	5	20
>60-77	6	17
>77-89	7	12
>89-96	8	7
>96-100	9	4

The SUS assesses the usability of a system as perceived subjectively by the user and is proven to be technology-independent; that is, it can be used for a wide range of systems and technologies [54,55]. The 10 items are divided into 5 positive and 5 negative statements and are each represented on a Likert scale from 0 to 5. The participants' answers result in the SUS item score, which must then be converted into the SUS overall score (from 0 to 100) [56].

The calculation of the overall SUS score entails the subtraction of 1 from the raw value of all odd items in the initial step, whereas the raw value of 5 is to be subtracted from the raw value of all even items. To illustrate this calculation, consider the following example. If item 1 had a raw score of 4, the calculated score would be 3 (obtained as 4 minus 1). For item 2, if the raw score was 2, the score was 3 (derived as 5 minus 2). Subsequently, the sum of these scores was calculated and multiplied by 2.5 to derive the overall SUS score [56].

The average overall score of all studies (68) can be used to interpret your overall score [55,56]. Bangor et al [57,58] also introduced a rating scale using adjectives and letters analogous to the American school grading system as an aid to interpretation (Table 4).

Table 4. Adjective scale of the System Usability Scale (SUS) overall score [54,55].

SUS[a] overall score	Area of acceptance	Adjective scale
90-100	Acceptable	Best imaginable
80-89	Acceptable	Excellent
68-79	Acceptable	Good
50-67	Marginal	Ok
35-49	Not acceptable	Poor
0-34	Not acceptable	Worst imaginable

[a]SUS: System Usability Scale.

Deci and Ryan's [59] assertion posits that the use of the platform is contingent upon the satisfaction of specific fundamental human needs, including autonomy, competence, and connectedness [35]. Psychology posits that the more fundamental psychological needs are met through interaction with the system, the more end users engage with technology [60]. The objective of the TENS-Interface questionnaire is to ascertain the extent to which direct interaction with a technology fulfills the fundamental psychological needs for autonomy, competence, and connectedness [35]. The questionnaires, initially developed in English, underwent translation into German under the guidance of a professional linguist for their

usage within the project. The translation process was guided by the "Translation Guidelines and Translation Documentation of the European Social Survey (ESS, 2020)" [61] with a focus on maintaining the validity and comprehensibility of the translation.

In the TENS-Interface, the items are each assigned to the basic needs of competence, autonomy, and relatedness. However, they are presented randomly in the questionnaire. The objective is to ascertain the extent to which direct interaction with a technology fulfills the fundamental psychological needs for autonomy, competence, and relatedness [35]. The application is designed to be universally accessible, ensuring autonomy of action, competence in handling, and a connection with the technology facilitated through the EduXBot platform interface. The collected data are then subjected to evaluation according to these objectives.

The descriptive statistics of the quantitative data are presented depending on the distribution, such as mean or median. Categorical data describing the sample are presented as absolute and relative frequencies. In order to answer the main question about the change in ITU, the difference between the measurement times of the individual test subjects, the facilities, and the overall sample is described as an absolute and relative mean difference. Possible further group differences are examined using the parameters "qualification" and "work experience." IBM SPSS is used as a tool for data management and data analysis.

Qualitative Evaluation

The TA methodology is used to qualitatively evaluate the platform. The idea is to ask subjects to express their thoughts and emotions out loud while testing the prototype in order to document them [62,63]. The advantage of this method is that it collects problems with the technology that has been tried by the end users, as retrospective surveys can lead to incomplete information about the problems with a technology. This means that TA protocols are helpful in understanding the thinking strategies of end users [64].

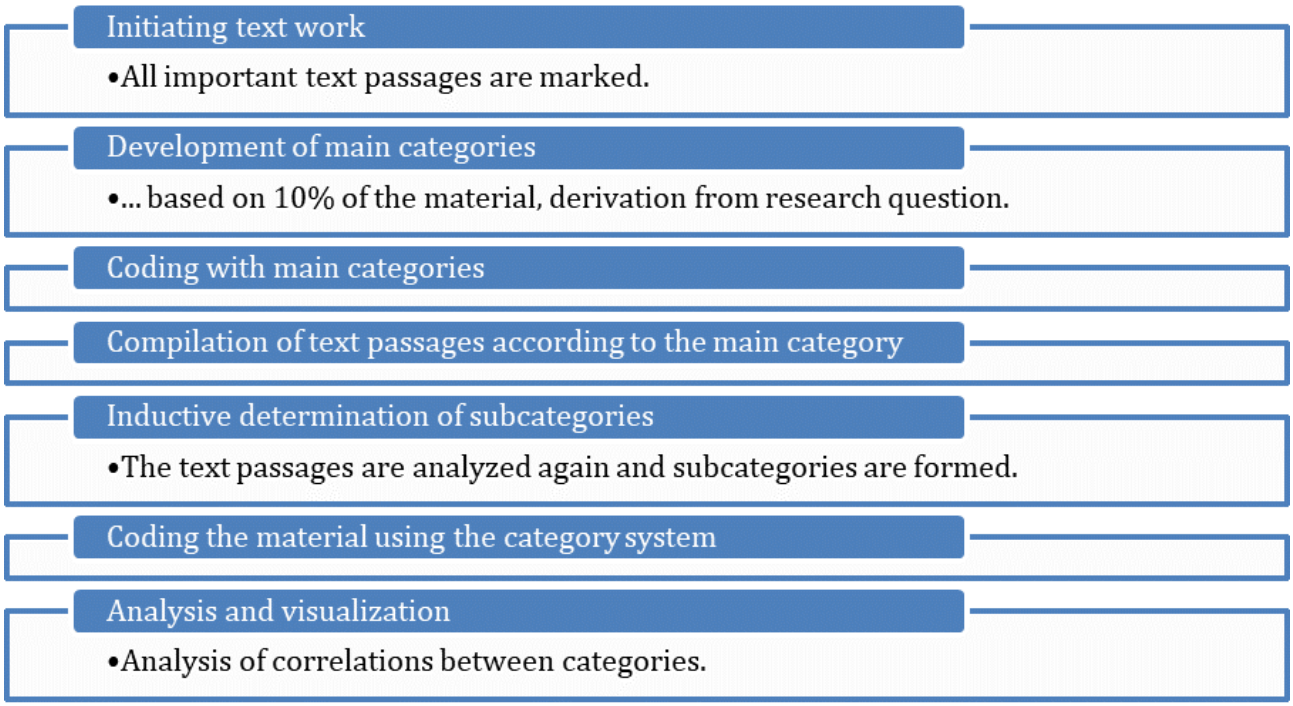
Testing sessions can be conducted on participants' own equipment or in a controlled environment. In protocols, participants think out loud as they complete a series of predetermined tasks. Participants are asked to say anything that comes to mind as they complete the task. This may include what they see, think, do, and feel. Sessions are often audio and video recorded so that developers can review what participants did and how they responded. Raw data comprise the verbalization of the thoughts, perceptions, and feelings that participants articulate as they complete a defined task. In a formal research protocol, all verbalizations are transcribed and then analyzed. In the context of usability testing, observers are asked to take notes on what participants say and do without trying to interpret their actions and words, and in particular, to note where they encounter difficulties [65].

The focus groups conducted during the iteration loops are partially structured with the help of guidelines Multimedia Appendix 1. The overall goal is to generate specific knowledge to answer the research question during the development process. The main factors that play a role are the adaptation of the selected application scenarios to the respective facilities as well as aspects of control and usability.

The composition of the focus groups is specifically based on theoretically based preselection in the sense of theoretical sampling according to the indicator caregiver [66]. In addition to these criteria, the most important thing is the willingness to talk about the respective needs and needs in the context of the platform development. No further criteria are defined in advance, but after the sample pool has been generated, the composition is determined exactly with regard to the contrasting of the groups. The number of participants in the focus groups is limited to 6 to a maximum of 10 people [67,68]. The selection of queries takes place according to the principle of theoretical sampling; achieving statistical representativeness is not intended [69].

All qualitative data were subjected to Kuckartz and Rädiker's [70] qualitative content analysis, which provides a structured framework for the content (Figure 4). Given the project's position within an emerging field of research, the material was coded inductively. This entailed the creation of categories based on the TA protocols and focus groups, thereby facilitating an exploratory evaluation of the material. This methodological approach enabled the systematic organization of the data material according to its content-related characteristics.

Figure 4. Steps of qualitative content analysis according to Kuckartz and Rädiker [70].



Ethical Considerations

All procedures involving human participants or human tissue will be performed in accordance with the ethical standards and principles of the institutional and national research committee of the 1975 Helsinki Declaration [71] and its later amendments or comparable ethical standards. Informed consent will be obtained from all participants. This study was approved by the Ethics Committee of the Medical Faculty of the Martin Luther University Halle-Wittenberg (approval 2023-190 of August 31, 2023). The study was registered in the German Register of Clinical Studies (DRKS00034195).

Results

The EduXBot project is funded by the Federal Ministry of Education and Research for a period from January 2023 to December 2025. During the summer of 2023, the practice partners were introduced to the project, and the application scenarios for a prototype design of the platform were cocreatively defined. The initial results were attained in the summer of 2024 when the final concept for the platform prototype was developed in collaboration with the target group. A total of 2 workshops were held in February and July 2024. An initial prototype of a functioning platform for the simplified interaction and control of DAT was evaluated in November 2024. The project is scheduled to conclude in December 2025, at which point the final results will be available. To ensure methodological quality, the Transparent Reporting of Evaluations with Nonrandomized Designs (TREND) statement [72] will be used for reporting the results.

Discussion

Principal Findings

The objective of this study is to design the human-technology interaction between an interaction and control platform and nurses in such a way that a process is created that ensures the high usability of DAT in nursing care. The central question guiding this study is whether the low-threshold platform changes the intended use of DAT through the simplified application options for nurses in order to integrate DAT as possible supplementary resources into individual nursing process planning. The objective is to assess whether the platform offers an interface that enhances the autonomy of nurses in using DAT. The evaluation will yield both quantitative and qualitative data, providing insights into the requirements of nurses as end users of DAT. The objective is to enhance the usability of the platform by at least one level over the course of the study.

Strengths and Limitations

The strengths of this study include the triangulation of quantitative and qualitative data. The potential for DAT to streamline individualized interventions in nursing care has implications for its intended use, which, in turn, affects its actual use in everyday work. The findings of this study will encompass practical, scientific, and societal ramifications, thereby paving the way for subsequent studies and interventions aimed at reducing nurses' workload. However, the study is not without limitations.

First, the number of participants is limited. For feasibility studies, the Guidelines for Designing and Evaluating Feasibility Pilot Studies [49] recommend basing the number of participants on practical factors such as availability and financial resources. In the event that the targeted number of 30 participants is not

attained, the evaluation will be conducted by combining quantitative and qualitative data in accordance with the methods outlined by Creswell and Plano Clark [47].

Second, the participating practice partners have previously engaged in other research projects, have been informed about the digital transformation, and have had experience with DAT. Conversely, participation in this study is voluntary, suggesting that nurses who are generally open to the topic are more likely to participate. The number of participating care facilities is limited to 3, which may limit the generalizability of the findings. While the inclusion of other professional groups, such as support staff, could be considered a valuable addition to the study, future research would benefit from the involvement of a more extensive range of care facilities and health care professionals to enhance the generalizability of the findings.

Conclusion

A scoping review of the state of the art of robotic interaction and control platforms in health care [73] reveals that only a limited number of feasibility or user studies have addressed the interaction and control of DAT by end users in a cocreative manner. The studies emphasize the necessity of end-user engagement to mitigate ethical concerns and ensure the relevance of the developed technologies to their intended beneficiaries [74-76]. A notable limitation of the existing studies is their exclusive focus on home care settings, resulting in a paucity of empirical findings for the domain of long-term inpatient care. In this context, the EduXBot project has been initiated to address this knowledge gap.

The implementation of technologies in nursing care practice is predicated on nurses' perception of their meaningful use. The generalization of the care process into standardized procedures is a challenging and complex scenario. The integration of individualized interactions further complicates the scenario, making it challenging for technical developers to meet the requirements and needs of the target group without the involvement of nursing professionals in the development process [77,78]. Caregivers play a pivotal role in research endeavors. Their expertise in the field, stemming from their in-depth understanding of diseases and their impact on patients, positions them as pivotal potential end users. By incorporating their insights, nurses can influence the development of technologies to align with their needs and requirements for interaction and control [79].

The dearth of development expertise among caregivers precludes them from programming the technologies independently. A potential solution to the usability issues of DAT is the development of a platform that provides an interface for nonprogrammers to create individual interventions using everyday controls and a few intuitive steps. This approach has the potential to ensure the sustainable implementation of DAT. EduXBot signifies an inaugural endeavor in this direction.

Acknowledgments

This work was created as part of the TDG (Translationsregion für digitale Gesundheitsversorgung)—project EduXBot (Educational Exploration Robot Application Platform) funded by the Federal Ministry of Education and Research via the WIR!—Wandel durch Innovation in der Region under funding FKZ 03WIR3118B. We acknowledge the financial support of the Open Access Publication Fund of the Martin-Luther-University Halle-Wittenberg.

Data Availability

The datasets generated during and/or analyzed during this study will be made publicly available upon completion of the study and can be obtained from the corresponding author on reasonable request.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Focus group guideline (draft).
[DOCX File , 15 KB - resprot_v14i1e63089_app1.docx]

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Abbreviations

AR: augmented reality
DAT: digital and assistive technology
EduXBot: Educational Exploration Robot Application Platform
ITU: intention to use
METUX: Motivation, Engagement, Thriving in User Experience
SUS: System Usability Scale
TA: think-aloud
TENS: Technology-Based Experience of Need Satisfaction
TREND: Transparent Reporting of Evaluations with Nonrandomized Designs
TUI: Technology Usage Inventory
UCD: user-centered design

Edited by A Schwartz, T Leung; submitted 10.06.24; peer-reviewed by J Walsh, S Goyal; comments to author 23.12.24; revised version received 27.12.24; accepted 26.02.25; published 18.03.25.

Please cite as:
Müller P, Hofstetter S, Jahn P
Sustainable Implementation of Digital Assistive Technologies in Health Care Through a Simplified Interaction and Control Platform: Protocol for a Cocreative Feasibility Study
JMIR Res Protoc 2025;14:e63089
URL: https://www.researchprotocols.org/2025/1/e63089
doi:10.2196/63089
PMID:

Protocol

Assessment of Community Stakeholders' and Health Educators and Professionals' Needs for the Continuous Enhancement of Sexual and Reproductive Health and Rights in Mali (Project CLEFS): Protocol for a Convergent Mixed Methods Study

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Abstract

Background: In Mali, a lack of qualified human resources in primary health care and sexual and reproductive health and rights (SRHR) is one of the greatest barriers to the population's access to standard health services. Frontline professional training must be strengthened to respond to the needs of the population, particularly those of women and girls. Training must be conducted using an interdisciplinary and adapted approach to promote gender equality.

Objective: This study aims to identify the SRHR training needs among the community, educational actors, and primary health care providers.

Methods: A concurrent mixed methods design was adopted, using 2 methods. A quantitative method, through a cross-sectional analytical survey, will be conducted at the community level with university community health centers (CSCom-U) users and adolescents in CSCom-U health areas, as well as at the health education institution and community health centers levels with teachers, students, and interdisciplinary professional groups within the CSCom-U and district hospital maternity. Descriptive and inferential analyses will be conducted to process quantitative data. This research is at the stage of data analysis and interpretation. A qualitative method, based on 3 sources of data (focus groups, individual semistructured interviews, and document analysis), which involved the same targets as the quantitative component, with additional community actors such as Community Health Associations (Associations de santé communautaire) and Women's Service User Communities. A thematic analysis of the qualitative data using a mixed deductive and inductive method will be performed.

Results: *:* Field data collection took place from March to April 2022. Quantitative data from 3153 participants are being analyzed using SPSS. Qualitative data from 11 interviews and 27 focus groups were processed with Qualitative Data Analysis Miner. Data analysis is still ongoing.

Conclusions: This study will provide a better understanding of adolescents and SRHR user's service needs in terms of health services availability and quality and SRHR knowledge, issues related to student training quality, the level of adequacy between the training offered and the actual needs of the service recipients, and the level of preparation and ability of teachers to provide quality teaching taking gender equity into account. The recommendations drawn from this assessment will propose concrete actions to improve women and girls' health services provided by professionals, and to better adapt the future health professionals' profiles to the needs of communities, particularly those of women and girls.

International Registered Report Identifier (IRRID): DERR1-10.2196/64796

(JMIR Res Protoc 2025;14:e64796) doi:10.2196/64796

KEYWORDS

mixed methods study; protocol; sexual and reproductive health and rights; Mali; primary health care providers; women and girls' health needs

Introduction

In Mali, the health system does not yet have sufficient capacity to meet the health needs of the population, especially those of women and girls. Primary health care (PHC), considered to be the foundation of sexual and reproductive health and rights (SRHR) service delivery, remains poor [1]. Each year, 33% of pregnant women give birth outside of a health facility, and the maternal death ratio is 440 out of 100,000 births [2]. Although 24% of Malian women aged between 15 and 49 years report having unmet family planning (FP) needs, only 15% of them use modern contraceptive methods [3]. Among women with unmet FP needs, 17% are oriented toward pregnancy spacing [3].

In rural areas, where approximately 75% of the Malian population live, access to PHC services is more difficult, thus creating substantial inequities [4]. There is a significantly higher fertility rate (6.8 vs 4.9 in urban areas), a lower proportion of prenatal care visits (37% vs 67% in urban areas), a higher proportion of deliveries outside a health facility (39% vs 7% in urban areas), as well as more limited access to FP (contraceptive prevalence rate for sexually active women not in a union is of 27% vs 44% in urban areas) [3]. This highlights that women and girls have poor access to nonstigmatizing SRHR services and information as well as insufficient bargaining power regarding their sexual and reproductive health [5,6]. In addition, gender-based violence (GBV), including domestic violence, is also widely common as 45% of women aged 15-49 years are survivors of physical or sexual violence [3]. However, this violence remains poorly documented due to several barriers such as low institutional commitment to integrating this issue, particularly in health reporting. There is also a lack of health professionals training and clinical screening tools for mental health problems, particularly for postpartum depression, GBV survivors, and people affected by armed conflict [7].

Health education institutions in Mali lack the human, material, and financial resources to fulfill their role in teaching PHC and SRHR care [8]. The gaps in undergraduate and continuing education contribute to the lack of skilled human resources in PHC and SRHR, particularly in rural areas [9]. Skills of frontline professionals need to be strengthened at the level of both institutional management and training, to respond to the population's needs using an interdisciplinary approach, to promote gender equality (GE), and, ultimately, to offer training tailored to the needs of the labor market.

To address these concerns, the Canadian consortium—which is composed of Santé Monde, the Cégep de Saint Jérôme and the Centre interdisciplinaire de développement international en santé from University of Sherbrooke and funded by Global Affairs Canada—has implemented the Local Teaching Communities for Healthy Women and Girls (Communautés locales d'enseignement pour les femmes et les filles en santé [CLEFS; French]) project. This project will operate for a 5-year period (2020-2025) in 5 different regions of Mali (Kayes, Koulikoro, Ségou, Sikasso, and the district of Bamako). The CLEFS project was developed in partnership with the Malian Ministries of Health, Higher Education, and Women's Promotion and with health training institutions in Mali (Faculty of Medicine and Odontostomatology [FMOS], National Institute for Training in Health Sciences [Institut National de Formation en Science de la Santé [INFSS]], and private schools), women's user committees, persons in charge at Community health associations (Associations de santé communautaire [ASACO]) for university community health centers (CSCom-U), as well as the Malian district hospitals to which the CSCom-U are attached. CSCom-U is a first-level health center in community settings offering a minimum package of health care. As community health centers with a university orientation, they also offer delocalized internships for medical students.

This project is based on the principle that health education institutions in Mali must fully integrate PHC and SRHR concepts into their curricula and pedagogical approaches to fulfill their social responsibility toward women's and girls' needs. This process involves collecting and analyzing data on the unmet needs of the beneficiaries, as well as those related to training and frontline health care system actors. In this context, the CLEFS project supported the Malian health training institutions (INFSS and FMOS) in conducting a participatory evaluation.

Methods

Research for the Continuous Improvement of PHC and SRH Training Programs

Improving care in SRHR requires going through all the steps of the training engineering process to ensure continuous improvement of health care services and related training. A key step is conducting a participatory evaluative study to identify the SRHR needs of the communities served by the CSCom-Us, with a focus on women and girls, as well as those of the various actors involved in training and in the provision of PHC services [10,11] to assess the adequacy between the real needs of the communities and the targeted output profiles in SRHR.

SRHR training needs for front-line care providers are those focusing on essential services such as comprehensive sexual health education, FP, antenatal, intrapartum, and postnatal care including emergency obstetric and newborn care, prevention and treatment of HIV and other sexually transmitted infections (STIs), postabortion care, and prevention, immediate services and referrals for cases of GBV, and finally prevention, detection, and management of reproductive cancers [12]. Training needs encompass a patient-centered approach that respects individual gender considerations and human rights.

This participatory approach will allow a better involvement and ownership of the needs assessment methodology by Malian professionals, as well as a better acceptance and use of the resulting findings. The results will reflect a concerted and consensual identification of SRHR needs and therefore an appropriate definition of the expected output profiles at the level of both undergraduate and continuing education.

Study Objectives

Overview

The main objective of this study is to depict the real and differentiated needs of Malian actors and primary care users related to SRHR to improve the training programs and services offered in this area.

This translated into the following specific objectives as follows: (1) to identify the SRHR needs of community actors and beneficiaries (adolescents and CSCom-U users); (2) to identify the SRHR training needs of students, trainers, and health professionals involved in training in terms of SRHR capacity building; and (3) to improve the curricula of nursing and obstetric practitioners in accordance with the needs of the health care professionals and specific needs of the populations served, in particular those of women and girls.

Overall Study Design

Using a participatory approach, this needs assessment adopts a concurrent mixed methods research design combining quantitative and qualitative methods [13]. It is based on the convergence of the analytical results performed for each method with all the actors concerned [14,15].

Method 1: Quantitative

Quantitative Study Design

Cross-sectional surveys were conducted in the 5 project intervention zones, namely the cercles of Sikasso, Kolokani, Baraouéli, Kayes, and Bamako in the regions of Sikasso, Koulikoro, Segou, Kayes, and Bamako. Note that a cercle is the second administrative division of Mali. Mali is composed of 8 regions and 1 capital district (Bamako), with each region divided into 49 cercles.

Three levels were considered as follows: (1) community level: targeting CSCom-U users and adolescents in the CSCom-U health areas; (2) health education institutions level (FMOS and the main INFSS and its regional branch schools [called Annex]) and CSCom-U targeting teachers, students/trainees as well as; and (3) groups of interdisciplinary professionals from CSCom-U and the maternity ward of district hospitals supported by the CLEFS project.

Participant Inclusion Criteria

The study participant inclusion criteria are as follows.

1. Female users: women of childbearing age between 15 and 49 years old who have resided in the household during the last 6 months before the survey.
2. Male users: male heads of household aged 20 years and older or their legal representative aged 20 years and older who have stayed in the household during the last 6 months.
3. Adolescents: unmarried girls and boys aged 15-19 years.
4. Interdisciplinary professional groups: consist of physicians, clinical supervisors, midwives, and obstetric nurses practicing in CSCom-U and district hospitals maternity units for at least 6 months prior to the survey.
5. Teachers: lecturers and supervisors on a temporary or contractual basis in the nursing care and obstetrical care programs at the INFSS or Annex schools and in the family/community medicine programs at the FMOS, who have been teaching for at least 1 year before the survey.
6. Students: students in the nursing care/obstetrical care streams of the INFSS and its Annex schools, as well as those of the Specialized Studies Diploma in Family/Community Medicine programs, from the 2nd year of teaching onwards—including trainees—with a proportional distribution between men and women and between the different years of study.

Sample Size and Techniques

Sample sizes of the different community targets and intervention zone were calculated separately based on the total number of households in the health areas and the size of the population targeted by the survey. Sample size was, considering the proportion of the phenomenon studied, at 50% and the CI at 95% [16]. The choice of 50% value allows us to have a sufficiently large sample to make inferences, regardless of the true value of the phenomenon studied in the real population. It was calculated using Epi Info7 software (Centers for Disease Control and Prevention) and was distributed proportionally to the size of the households in the selected villages.

Student and teacher sample size was calculated separately based on the total number of students in the nurse and obstetrical care stream at INFSS and its Annex schools and the number of family/community medicine and teachers involved in these streams at the 2 institutions. The calculation was done using the same method and the same software as the community-level actors in a separate way for the INFSS, the INFSS Annexes, and the FMOS. Thus, the calculated sample size (teachers and students) at the Annex schools' level was proportionally distributed based on the number of teachers and students in the different Annexes.

At the Community Level

A multistage sampling technique was used for selecting study participants (stratified random, clusters, and simple random).

Stratified random sampling was performed in the villages or sectors of the CSCom-U health catchment areas considered as natural strata (4 per CSCom-U). The lists of villages in the health catchment areas were established by CSCom-U. Strata were randomly drawn considering proportionality in this population by applying the systematic random method with a sampling step calculation. Once these strata were randomly drawn, the households within these villages or sectors were grouped into clusters (composed of a maximum of 40 households) using the segmentation method for each one. Thus, clusters were randomly selected, and the survey was conducted among the households in these clusters.

Another simple random draw was then conducted within households to select one woman of reproductive age in each household (if there are several) to answer the user survey questions. The head of the household or his/her representative who is 20 years or older was surveyed to answer questions about users. Adolescents (male/female [M/F]) meeting the criteria in the selected households, were also surveyed after a random draw if numerous. If the number of households expected to be surveyed was greater than the number of households in the selected cluster, another cluster was randomly selected to complete the total number of samples required for the survey.

At the Educational Institutions and CSCom-U Levels

A simple random draw without replacement was made from a list of all teachers of the Specialized Diploma of Family Medicine/Community Medicine and the INFSS and Annex schools to obtain the required sample size. Another simple random draw without replacement was also carried out based on the list of the students of the cycles and the level of teaching concerned to obtain the required sample size. The sample size was segregated by gender/level/profession. Randomly selected students were contacted to participate in the survey after obtaining their consent. If a student refused to participate in the survey, another number was randomly drawn to replace him/her until the total sample size was reached.

For the interdisciplinary focus groups in the CSCom-U and district hospitals, as the number of staff is not large, all physicians, midwives, and nurses with a role in SRHR who were available at the time of the team's visit and who gave their consent to participate were surveyed.

There is a low number of professionals in CSCom-U and maternity care. Therefore, all available and willing physicians, midwives, and nurses were solicited for the CSCom-U and district hospitals interdisciplinary professional focus groups.

Quantitative Data Collection and Management

To carry out the data collection, teams of external interviewers and trained supervisors were deployed on site. The interviewers were external individuals with expertise in conducting surveys and were recruited by the project team for the period of the data collection. They were responsible for carrying out the surveys among users, adolescents, and students. Due to the sensitivity of sexual and reproductive health issues, female interviewers conducted the surveys among female respondents and male interviewers among male ones.

Supervisors made up of members of the State's Technical Services and members of the FMOS, INFSS, and Association of Private Health Schools were responsible for verifying the conformity of investigators' work and supporting them when necessary. Their involvement strengthened the process of ownership of the continuous quality improvement approach from data collection to the presentation of evaluation results. This approach ensured the transfer of acquired skills to other stakeholders and replicated the continuous quality improvement process in their respective regions, with little or no outside technical assistance. Supervisors were also responsible for conducting the qualitative component.

The FMOS experts (Mali), in collaboration with the INFSS (Mali) and supported by the CLEFS project team (Canada), developed and customized questionnaires tailored to the various survey targets. These questionnaires were subsequently distributed to all stakeholders involved in the training needs assessment process for review, appropriation, and validation of the tools. Once validated, the tools were created on the Kobocollect platform (KoboToolbox software) and then deployed on tablets or smartphones to collect data. This method offers several advantages such as quickness, error avoidance, the obligation to answer all questions (better completeness of data), and reduction of outliers. All data collected on-site were sent daily to the Kobocollect account and extracted in an Excel file to be reviewed during the data collection.

Prior to data collection, a 3-day training was conducted for the entire evaluation team. This was followed by a 1-day pretest in an area outside of the project's intervention regions to assess its clarity and comprehensibility and to enable the methodology to be adjusted if needed.

Quantitative Data Analysis

Since the data were collected with tablets or smartphones, data entry was instantaneous. Data were extracted from the KoboCollect platform in Excel format, then processed, cleaned, and finally analyzed using Excel (Microsoft Corp) and SPSS software (version 27; IBM Corp).

Data analysis and interpretation are still ongoing. According to our research protocol, we will conduct descriptive analyses, such as examining proportions, averages, and SDs, to gain insights into sociodemographic characteristics. This includes

examining levels of knowledge, attitudes, practices, and perceptions regarding various aspects of SRHR, specifically FP, sexuality, STIs, HIV, prenatal care, childbirth, and GBV. The level of satisfaction and challenges related to the use of CSCom-U will also be analyzed. Access to information for CSCom-U users and adolescents regarding SRHR will also be measured.

The evaluation will also include an assessment of the satisfaction levels of students with the SRHR programs attended, the training environment and internships including safety aspects; students' sense of preparedness to face professional life; level of preparedness of teachers and health professionals to respond to the needs of students and interns and to train students able to respond to community needs.

Several inferential statistics will be used. For example, chi-square tests will be used to compare the proportions of the variables of interest and the student *t* test will be used to compare mean scores. Gender analyses will also be performed to understand gender specificities. The statistical significance level will be set at 5%. Multivariable regression analysis will be conducted afterwards if significant associations are found in bivariate analyses.

Method 2: Qualitative

Qualitative Study Design

Three groups (ie, multidisciplinary teams, community stakeholders, teaching teams, and students) were targeted for the qualitative component, which was conducted using 3 sources of data: focus groups, semistructured individual interviews, and a literature review.

Participant Selection and Method

Community Actors

Community actors mainly included the project's implementation partners, that is, ASACO members, women's user communities, youth groups, and community relays. This phase also reached users, adolescents, traditional birth attendants, traditional therapists, and community leaders. Targets were chosen according to a purposive sampling and snowball strategy until data saturation was reached according to the inclusion criteria previously identified in the sample of the quantitative component. To ensure a better representation of this population, we aim to select a variety of profiles in terms of age, gender, number of years in office, and as members of different associations.

At the community level, 6 focus groups were conducted as well as semistructured interviews per health area as follows: a mixed focus group (M/F) with members of each ASACO (8 to 12 people); a women's focus group with communities of women users (8 to 12 people); a mixed (M/F) focus group with youth groups, provided that heterogeneous youth groups exist in the localities. If not, or depending on cultural realities, homogeneous groups were conducted; a mixed focus group (M/F) with community relays of 8 to 12 people; a homogeneous focus group with women users of the SRHR services of the CSCom-U; a mixed focus group (M/F) with adolescents; and individual interviews with a traditional birth attendant or rural maternity officer and a traditional therapist per village/area, if available.

CScom-U and District Hospital Maternity Units' Multidisciplinary Teams

These multidisciplinary teams were composed of medical doctors, midwives, and obstetric nurses involved in the SRHR services. CSCom-U and maternity technical staff were not numerous and therefore all of them were involved.

Concerning the data, a mixed (M/F) focus group was organized at each CSCom-U and district hospital maternity unit to explore the following elements: the clinical skills of health professionals, the challenges, and issues they face in providing quality SRHR services to women and girls, their level of ability (training, tools, and equipment) to provide quality SRHR services as well as mental and environmental health issues. Discussions also focused on their ability to provide support and respond to the needs of trainees, including safety issues, and harassment.

Educational Institutions Actors

Overview

Two groups of actors were targeted at this level: teachers and students. They were chosen according to a purposive sample strategy and until data saturation was reached, according to the inclusion criteria already identified in the sample of the quantitative component. To ensure a better representativeness of this population, we selected a variety of profiles in terms of gender, seniority, level of study, teaching field, and type of teacher (lecturer and supervisors).

For the Teachers

Three mixed (M/F) focus groups (1/nursing, 1/obstetrical, and 1 family or community medicine specialty diploma) of 8 to 12 teachers were organized. Our objective was to better understand the level of preparation of the teachers in terms of pedagogy, teaching SRHR, their expectations, and the difficulties they face in teaching in the continuous improvement of programs.

For Students

A heterogeneous focus group for the nursing stream, a homogeneous focus group for the obstetrical stream, and a heterogeneous focus group for the family or community medicine specialty diploma of 8-12 students was organized. Our objective was the following: to identify the main challenges and issues related to the quality of training, the adequacy between training and the needs of the populations, the training environment, GBV, security aspects, and the consideration of their specific needs by teachers. To obtain quality information, students were selected from the 2nd year of training.

Document Analysis

In addition to the literature review, a documentary analysis was conducted and covered: the CSCom-U supervision reports, maternal death audits, CSCom-U and district hospitals activity reports, previous evaluation reports, etc. These reports helped to determine the needs already identified by the national or regional level at the CSCom-U and to understand the underlying problems related to SRHR.

Qualitative Data Collection and Management

Overview

Focus groups and individual interviews were conducted using interview guides tailored for each target group. They were developed by the project team in collaboration with key partners from FMOS and INFSS and validated by all stakeholders in the needs assessment process. The guides were inspired and adapted to the context and needs of the project based on existing guides such as the Demographic and Health Survey and covered the main themes explored (eg, SRHR knowledge and services offered) according to the actors of each target. The various individual interviews and focus groups were conducted by the survey supervisors, who are the project's supporting partners, that is, agents of the government's technical services, but also key partners. For the focus groups, a minimum of 2 people conducted them. One was responsible for facilitating the discussion and the other for managing the recording, taking notes, and making observations of the participants. For individual interviews, 1 or 2 people conducted them depending on the number of supervisors, one of them was responsible for asking the questions, and the other for taking notes and managing the recording.

At the Community Level

For the recruitment and data collection, our evaluation team informed ASACOs leaders as well as the Technical Directors of the Center of the evaluation process, the date, and the participants to be met. They then informed the other members of the ASACOs, the communities of women users, the youth groups, and the community relays and set up a schedule of visits and meetings with the different participants. The different discussion groups were conducted in the ASACO offices. ASACOs, with the support of the evaluation team, made the necessary arrangements to ensure the involvement of the participants and to respect data confidentiality.

Guidebooks were written in French, but were administered in Bambara, the most widely spoken national language of Mali. The observer took notes directly in French. Each focus group lasted a maximum of 120 minutes and was recorded after obtaining verbal or written consent from the participants. Discussions were fully transcribed as they occur in verbatim form and translated by interpreters when needed.

Individual interviews were conducted with traditherapists, traditional birth attendants, and community leaders and occurred in the villages or areas selected for the quantitative survey. Interviews were held after the ASACO leaders had informed the customary authorities and obtained the free and informed consent of the participants. Interviews lasted 45 to 60 minutes at most. The interviews were conducted in Bambara and verbatims were translated into French.

At CScom-U and District Hospital Maternity Units' Levels

The evaluation team informed the technical directors of the center and the district medical officer, who in turn informed the technical staff of the objectives of the evaluation, the people to be involved in the process, and the schedule for the evaluation team's visit. In collaboration with their ASACO, they made the necessary arrangements to encourage the participation of the people concerned as well as confidentiality during the data collection.

At the Health Education Institution Level

Under the guidance of the evaluation team, the administration of these institutions informed faculty and students of the evaluation process, objectives, and schedule. Together they organized the recruitment of faculty and students who wished to participate in the interviews. They provided a room for the team to ensure the confidentiality of the interviews. At the school level, interviews were conducted directly in French and notes were taken in French. They were also recorded after obtaining participants' consent.

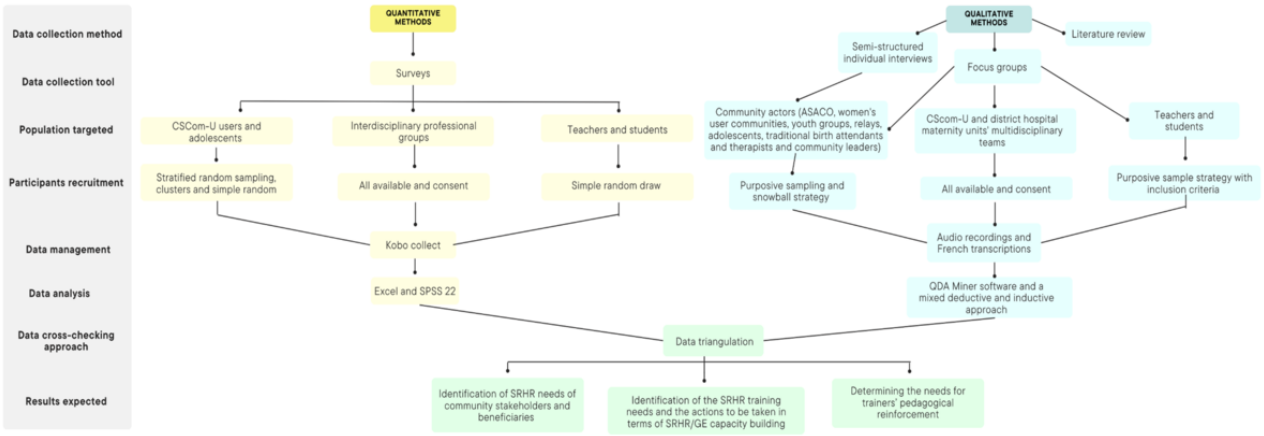
Qualitative Data Analysis Methods

Data analysis and interpretation are still ongoing. Qualitative data analysis will be conducted using an iterative process and will include the listening of audio recordings, successive readings of French transcriptions, team coding, team analysis, and participant validation. The project team will code the interviews using QDA (Qualitative Data Analysis; Provalis research) Miner software using a mixed deductive and inductive approach. This iterative method simultaneously makes sense of the data collected based on the state of knowledge, while potentially identifying new meanings. A brief list of initial codes based on the interview guides will serve as a coding grid a priori. It will be modified and enriched as the analysis proceeds. Coding will be controlled by a double coding technique performed by a member of the project team and the expert researchers. Parallel and independent coding will be done for the first few 4 interviews, followed by a comparison of the results. This process will be repeated until a consensus list of initial codes is obtained as well as intercoder fidelity greater than 90% [17].

Mixed Methods Integration

We will adopt a strategy using the matrix technique to summarize and present the QUAN and QUAL results [18]. First, the main statistical results (QUANT component) of the surveys will be presented by the participant group. Second, the themes emerging from the QUALI component (interviews and group discussions) will also be presented in a matrix by the participant group. This will enable us to look for similarities and divergences within and across participant groups, as well as patterns between different participant groups in each component of the study. Third, our integration strategy will focus on concordance as well as divergence between the main qualitative and quantitative findings [18,19]. Thus, we will develop a mixed methods matrix combining the main QUAN and QUAL results, organizing the data according to key themes and corresponding variables to enable comprehensive analysis and interpretation. This matrix will contain a row for each key qualitative theme (ie, needs related to GBV, FP, pregnancy and neonatal care, STI prevention and treatment, postabortion care, sexual health education, clinical support for GBV survivors, and SRHR capacity building needs for trainers), which will be compared or contrasted with the corresponding quantitative results for each theme (eg, knowledge and practice related to FP, STI prevention, and needs for trainers' pedagogical reinforcement; Figure 1).

Figure 1. Overview of the main stages of the research study. ASACO: Associations de santé communautaire; CSCom-U: university community health centers; SRHR: sexual and reproductive health and rights.



This approach is consistent with guidance on methods that advocate complementing quantitative analyses with in-depth data obtained from focus groups and individual interviews [20,21].

Evaluation Team Training and Formative Research

Overview

Prior to the data collection start-up, a 5-day training session on the use of the QDA Miner qualitative analysis software was organized for the evaluation team in Mali to strengthen their capacity to analyze qualitative data. This training was facilitated by a consultant supported by the University of Sherbrooke who was also in charge of making the software available.

A further 3 days' training on the KoboCollect software was provided to the evaluation team by the project's monitoring and evaluation technical advisor as required.

Prior to the teams' field deployment, a 4-day training session was held for all individuals involved in the needs assessment process. The training was provided by FMOS, INFSS, and the CLEFS project team and focused on the following.

Understanding the Roles and Responsibilities of Team Members

Following are the roles and responsibilities of the team members:

- The interviewer's responsibilities in terms of listening, paying attention, etc.
- The pitfalls to be avoided (nonjudgmental and noninterrupting)
- Setting up conditions to ensure data confidentiality
- Seeking free and informed consent to participation
- Respecting societal and cultural values.

Understanding and Translating the Different Tools to Be Used

The following will be ensured in understanding and translating the tools to be used:

- A detailed explanation of the tools to be administered
- An exchange to validate the translation of these tools into the national language so that any questions asked are understood and worded correctly.

Survey Methodology, Including On-Site Data Collection

The survey methodology involves the following:

- The process of identifying households and survey targets
- The process of obtaining participant consent and discussing the ethical aspects of the research process
- Data collection procedures, including digital data collection (eg, downloading, filling in and saving forms, and sending final versions).

Managing Sensitive Cases and Difficult Situations

Sensitive cases and difficult situations will be managed as follows:

- Training on how the evaluation team should act if respondents confide to us or seek our advice or support
- Following this 3-day theoretical training, a pretest was organized on the fourth day in a Bamako commune with a dozen people to identify and rectify any errors of understanding and phrasing before the team's deployment in the field.

Ethical Considerations

This study adheres to the ethical guidelines and principles relevant to human research. The ethical approval was granted by the Research Ethics Committees of the Malian FMOS (reference number: 20231 132 ICE/USTTB) and the University of Sherbrooke (reference number 2022-3261).

Prior to the teams' deployment, the ASACO's offices informed the local authorities in all villages or neighborhoods of the survey teams' presence. Once on site, the teams visited these authorities to obtain their approval to conduct survey activities in their villages or neighborhoods.

Informed consent to participate from all respondents was obtained at the beginning of the survey and all individuals were fully informed of the study's purpose, potential risks, and their right to refuse to participate, to withdraw at any time, or to not answer certain questions without any justification or prejudice.

If a participant wished to withdraw during or after the research, he or she had to contact the research team responsible whose contact details were provided on the consent form.

Confidentiality and anonymity of data were explained to the respondents. For minors, consent was also requested from parents or guardians. An informed consent form was developed outlining the objectives of the research, the voluntary and nonprofit nature of participation, data confidentiality and anonymity, and the approximate duration of participation. This form was shared by the collectors and its reading (in Bambara or French, as preferred) was mandatory and they were asked to devote time to explain it to the participants. The supervisors ensured that interviewers complied strictly with these instructions. All data are confidential and will be only used to achieve the project's results.

Identifiable information will not be disclosed in written publications and oral or poster presentations.

Results

Field data collection took place from March to April 2022. Quantitative data were collected using the KoboCollect application, and descriptive and bivariate analyses were carried out using SPSS software on a sample of 3153 participants. For qualitative data, 11 individual interviews and 27 focus groups were conducted and analyzed using QDA Miner software. Data analysis and interpretation are currently being finalized, and the first results should be submitted for publication in 2025.

Discussion

Overview

This research is one of the first to provide a holistic assessment and understanding of SRHR care needs across a continuum of services (from training, and provision to receiving care) covering the perspectives of various stakeholders at different levels (community, educational, and interdisciplinary health care professionals). It is also one of the first SRHR studies to be deployed in 5 regions (Bamako, Kayes, Koulikoro, Ségou, and Sikasso) across Mali.

Expected Findings and Outcomes

The results of the needs assessment will help us to better understand the needs of adolescents and users of SRHR services, not only in terms of availability, quality of services, and responsiveness of health care providers to their specific needs, but also in terms of SRHR information and knowledge.

Results will also help us gain a better understanding of the issues related to the quality of student training and supervision, and the adequacy between the training offered and the health care needs expressed by service users. They will also enable us to assess the readiness and skills of educators to provide quality SRHR teaching while considering GE.

Studies have demonstrated the effectiveness of training interventions in improving the attitudes and practices of health professionals regarding SRHR in low- and middle-income countries [11,22]. Therefore, recommendations resulting from this needs assessment will enable us to suggest concrete interventions for health care professionals and educators, allowing them to meet the community's needs—particularly those of women and girls.

Based on the results, we will design and implement a multifaceted strategy targeting the 3 levels (community, education, and health care providers).

In terms of training programs, the INFSS and FMOS will revise their curricula in line with the prioritized SRHR needs to fill the gaps in the existing modules. The plan is to integrate these needs into existing modules such as those concerning adolescent sexual and reproductive health, as well as care for GBV survivors and postabortion care, and to adopt interactive pedagogical methods to better prepare the future workforce in SRHR. In sum, the content of the existing curriculum modules will be repackaged to incorporate the priority needs and suggestions made by Malian participants and partners at the national, educational, and community levels.

Regarding the training needs, a package of interventions (training workshops and problem-solving exercises such as training on the management of GBV) will be developed, drawing directly on the results and recommendations of the study to enhance the teachers' and health care professionals' knowledge, skills and attitudes in providing SRHR services.

For community members, numerous interventions (eg, image kits, conferences, and training with peer educators on specific topics) will be codeveloped, prioritizing community involvement and ensuring that content will be oriented according to community acceptability and reflective of their needs.

Moreover, to bridge the gap between the study results and tangible impact in the field, the research findings will be disseminated through a variety of strategies and with numerous CLEFS project partners such as the relevant government actors, ASACO, community health centers, health professionals, and other community actors. This will enable key stakeholders to engage with the insights and facilitate the integration of the recommendations within their daily activities (practice and teaching).

This multifaceted strategy aims to ensure that the study results are effectively tailored to the Malian context and that they reach a wide range of stakeholders involved in PHC and in the provision of SRHR services. Having access to and using quality SRHR services are well linked to health care professionals' competencies, GE, and moreover to the well-being, community stability, and development [11,23].

Strengths and Limitations

Several strategies were used to ensure the credibility of this research as follows: triangulation of data sources (participants from 3 community levels, educational institutions, CSCom-U, and district hospital maternity wards), methods (document, focus groups, and interviews with different actors) and researchers (ie, triangulation of several analytical perspectives) to ensure consistency of the data and analysis; double coding for qualitative analysis; double member checking by sending preliminary results to participants belonging to the 3 target

groups to validate and rectify them if necessary; skeptical peer review by members of the research team who will question methods interpretations, and meanings throughout the process [24]; detailed, rich, and concrete description [25] of the study context to enable readers or research users to judge potential transferability to other contexts, as well as a detailed description of the methodological approach, including the research site and data collection methods; and sample diversification to promote a wider application.

The resulting recommendations will address multiple stakeholders' perceptions and needs, promoting alignment across various actors.

Finally, this research was developed through a collaborative and participatory approach, fostering an equitable partnership between research teams in Mali and the Canadian Consortium. Local researchers and partners led the selection of priority research questions and study design, ensuring that the research project reflected community priorities. Field researchers collected data while minimizing cultural bias, through an ongoing collaborative approach to interpretation between Malian and Canadian research teams. This approach involves local community representatives in several stages of the research process, including validation of tools, recruitment of participants and investigators, and validation of results analysis. To maximize the impact and accessibility of the research, results will be disseminated through many strategies. By focusing on local expertise and perspectives, this approach will promote greater ownership of the results by stakeholders.

However, some limitations were encountered during the data collection process. First, the inclusion criteria (15-19 years old and single) made access to adolescents in rural areas difficult. Most girls are already married by this age, and single girls often move to the city to work as domestic servants. Moreover, adolescents are rarely found at home, choosing instead to go to meeting places or sports activities. This required interviewers to seek them out in schools or conduct interviews in the evening. On the other hand, the availability of service users also posed a problem, requiring late-evening or late-day appointments. Finally, the complexity of the SRHR subject made the questionnaire lengthy, leading to a few complaints, although everyone completed the survey.

Conclusion

In summary, using a concurrent mixed methods study, this needs assessment will help provide essential knowledge on how to align the nursing and medical curriculum with the needs of different levels of stakeholders (community, education, and health care providers), increase the capacity of future and current health care providers to deliver appropriate SRH services, and ultimately address the needs of the Malian community, reduce inequities and promote social justice.

Acknowledgments

The authors would like to thank Massaba Kouyaté and Moussa Nianson Coulibaly for their contributions in the data collection stage. The authors would also like to thank the staff of the Centre interdisciplinaire de développement international en santé (CIDIS) at the Université de Sherbrooke for providing their expertise in the design of this protocol, as well as Global Affair Canada for its financial support.

Data Availability

The datasets generated and analyzed during this study are not publicly available due to ethical and privacy considerations but are available from the corresponding author on reasonable request, if approval is obtained from the relevant ethics committee and data sharing complies with institutional and legal guidelines.

Conflicts of Interest

None declared.

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Abbreviations

ASACO: Associations de santé communautaire
CLEFS: Communautés locales d'enseignement pour les femmes et les filles en santé
CSCom-U: university community health centers
FMOS: Faculty of Medicine and Odontostomatology
FP: family planning
GBV: gender-based violence
GE: gender equality
INFSS: Institut National de Formation en Science de la Santé

M/F: male/female
PHC: primary health care
QDA: Qualitative Data Analysis
SRHR: sexual and reproductive health and rights
STI: sexually transmitted infection

Edited by A Mavragani; submitted 31.07.24; peer-reviewed by MDM Fernández Álvarez, F Yang; comments to author 16.10.24; revised version received 29.01.25; accepted 20.02.25; published 01.04.25.

Please cite as:
Abou Malham S, Traoré D, Dicko F, Blouin Genest G, Boudreau J, Sidibé DM, Sidibé S, Goïta IS, Sangaré A, Togo M, Diarra D, Rietmann M, Maïga MM, Boulanger S, Grégoire AI, Milot DM, Berbiche D, Stecko S
Assessment of Community Stakeholders' and Health Educators and Professionals' Needs for the Continuous Enhancement of Sexual and Reproductive Health and Rights in Mali (Project CLEFS): Protocol for a Convergent Mixed Methods Study
JMIR Res Protoc 2025;14:e64796
URL: https://www.researchprotocols.org/2025/1/e64796
doi:10.2196/64796
PMID:

Protocol

Development of a Mobile-Based Personal Health Record for Pediatric Attention-Deficit/Hyperactivity Disorder Management: Protocol for a Study Based on Action Research Design

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Abstract

Background: Attention-deficit/hyperactivity disorder (ADHD) is one of the most widespread neurobehavioral problems during childhood. A child's personal health record (PHR) plays an important role in the controlled routine monitoring of ADHD symptom improvement. Along with the advantages, the convenience offered by mobile technology, and the ubiquity of smartphones in contemporary society, there is a compelling need for PHR to be available in the form of a mobile app.

Objective: This study aims to identify stakeholder needs, followed by designing, developing, testing, and evaluating a mobile-based PHR in the context of pediatric ADHD management.

Methods: This study will adopt an action research design structured into 4 stages: diagnosing, planning, taking, and evaluating action. Stakeholders, including parents, pediatricians, occupational therapists, clinical psychologists, and teachers, will participate actively. In stage 1, stakeholder requirements for the mobile-based PHR will be explored through in-depth interviews, focus group discussions (FGDs), and document reviews. Thematic analysis will be used to identify key needs and challenges. In stage 2, a systematic literature review will be conducted to enhance user requirements analysis by synthesizing insights from existing mobile apps for pediatric ADHD management. A mobile-based PHR prototype will be designed and developed based on user requirements enhanced with systematic review results. In stage 3, the prototype will undergo a 6-week trial with participants to evaluate its functionality and address any identified issues. In stage 4, both quantitative and qualitative methods will be used to assess the app's usability and quality. The System Usability Scale (SUS) and the User Version of the Mobile App Rating Scale (uMARS) will be used for quantitative evaluation, while interviews and FGDs will be conducted for qualitative evaluation.

Results: This study commenced in October 2024. As of December 2024, 13 participants (n=5, 38.5%, parents; n=2, 15.4%, pediatricians; n=2, 15.4%, occupational therapists; n=2, 15.4%, clinical psychologists; and n=2, 15.4%, teachers) have been enrolled, meeting the minimum participant requirements for stage 1. Stage 1 was completed at the end of 2024, with stage 2 expected to be completed by September 2025, stage 3 by December 2025, and stage 4 by February 2026. The findings from each stage will inform iterative refinements to the mobile-based PHR. The final results, including usability and quality assessments, are anticipated for publication by the middle of 2026.

Conclusions: This study protocol outlines a pivotal initiative to enhance the management of pediatric ADHD. By using an action research methodology and actively engaging stakeholders, the study aims to contribute significantly to the field. The iterative cycles of the research seek to develop a mobile-based PHR that is not only user friendly but also effective and uniquely attuned to the diverse needs of those involved in pediatric ADHD care.

International Registered Report Identifier (IRRID): PRR1-10.2196/60216

(JMIR Res Protoc 2025;14:e60216) doi:10.2196/60216

KEYWORDS

ADHD; attention deficit and hyperactivity; mobile app; personal health records; action research; pediatric

Introduction

Background

Attention-deficit/hyperactivity disorder (ADHD) is one of the most widespread neurobehavioral problems during childhood, with a worldwide prevalence of 5.29% [1,2]. The manifestation of ADHD occurs in 5.9% of youth and 2.5% of adults [3]. In the United States, an estimated 11%, equivalent to approximately 6.4 million children and adolescents aged 4-17 years, have received a diagnosis of ADHD [4]. Characterized by persistent patterns of inattention, hyperactivity, and impulsivity, ADHD manifests in various ways, affecting all aspects of a child's life [5,6]. The impact of ADHD extends beyond the immediate challenges of managing symptoms; it often disrupts academic performance, hinders peer relationships, and can contribute to emotional and behavioral difficulties [7-9]. Children with ADHD may face an increased risk of academic underachievement, low self-esteem, and a higher likelihood of engaging in risky behaviors [10-12]. Moreover, the condition places considerable stress on families and educators as they navigate the complexities of providing optimal support [13,14]. Recognizing the widespread prevalence and multifaceted impact of ADHD is crucial for developing targeted interventions and support systems that address the unique needs of affected children and related stakeholders.

Addressing the diverse needs of stakeholders in managing ADHD takes on added significance when considering the integration of personal health records (PHRs) into the care framework [15]. The PHR can serve as a central repository for health-related information, offering a comprehensive view of a child's medical history, treatment plans, symptoms improvement, and daily challenges associated with ADHD [16]. Within the context of pediatric ADHD management, routine and controlled monitoring of symptom improvement plays a pivotal role, and the PHR become instrumental in this process [17]. The PHR provides a structured platform for caregivers and related stakeholders to systematically monitor and analyze the child's response to therapeutic interventions [18]. By documenting the symptoms' progression, medication adherence, and the impact of various strategies, the PHR offers valuable insights that facilitate evidence-based decision-making [19]. Moreover, the ability to monitor symptoms in a controlled and consistent manner allows for a more nuanced and tailored approach to therapy adjustments, ensuring that interventions align closely with the child's unique needs [20]. The incorporation of the PHR into pediatric ADHD management not only enhances the accessibility of critical health information but also empowers stakeholders with a comprehensive tool for informed decision-making and the continual refinement of therapeutic strategies.

Although the idea of a PHR has historical roots in paper-based systems, health information technology now enables individuals to electronically store and manage their health information, granting them convenient access, whenever necessary [21]. In addition, with the ubiquity of smartphones in contemporary society, there is a compelling need for the PHR to be available in the form of a mobile app [22,23]. Furthermore, technological interventions for the assessment, monitoring, and treatment of neurodevelopmental disorders, including ADHD, are increasingly focused on mobile apps [24]. However, few apps related to ADHD provide information about their development processes, and none include evidence supporting their effectiveness [25].

The urgency to develop a mobile-based PHR specifically tailored for pediatric ADHD management stems from the growing demand for facilitating information sharing between stakeholders to promote the adoption of evidence-based practices in the management of children with ADHD [26]. The fragmentation of health care services, coupled with the dynamic nature of ADHD symptoms, necessitates a technological solution that can bridge communication gaps and empower those involved in the child's care [26,27].

Recognizing the imperative for a user-centric approach, the adoption of an action research methodology becomes paramount in the development of a mobile-based app [28-30]. Action research, designed to enhance the engagement of potential mobile app users in the entire research process, can foster awareness within the pediatric ADHD management stakeholders' context of how they experience and interact with technology [31,32]. This inclusive approach ensures that the resulting mobile app is not only technologically sound but also rooted in the practical experiences, preferences, and needs of those directly engaged in the daily challenges of pediatric ADHD management. Through iterative cycles, the action research methodology contributes to the development of an effective, user-friendly, and contextually relevant mobile-based PHR, ultimately advancing the landscape of pediatric ADHD management via the active participation of the stakeholders.

Objectives

The objectives of this study are to first identify the needs of stakeholders concerning the development of a mobile-based PHR for pediatric ADHD management. Based on the identified needs, a customized mobile app will be developed

collaboratively, with continuous input from the stakeholders to ensure the app addresses those needs effectively. Finally, the usability and quality of the mobile app will be rigorously tested and assessed, ensuring it aligns with the preferences and expectations of the stakeholders and functions as an effective tool for managing pediatric ADHD.

Methods

Study Design

This study will use an action research methodology in the form of a cycle with 4 stages (diagnosing action, planning action, taking action, and evaluating action), integrating both qualitative and quantitative designs [33,34]. The term "action research" in this paper refers to the same definition as "participatory action research," "participatory research," "interactive research," "collaborative inquiry/research," and "engaged scholarship" [35]. The action research design centers on doing "with" rather than doing "for" relevant stakeholders [36]. In this context, the participation of the relevant stakeholders becomes key to the implementation of action research.

Each stage in action research consists of an iterative process (plan, act, observe, reflect), involving the stakeholders at each step [37]. The stages of action research in this study can be succinctly observed in Figure 1.

Table 1 outlines the specific steps in each stage of action research, the measures used to track progress, and the timeline for each activity. Activities at each stage will be carried out, and their progress will be systematically monitored based on the table.

Figure 1. Stages of action research.

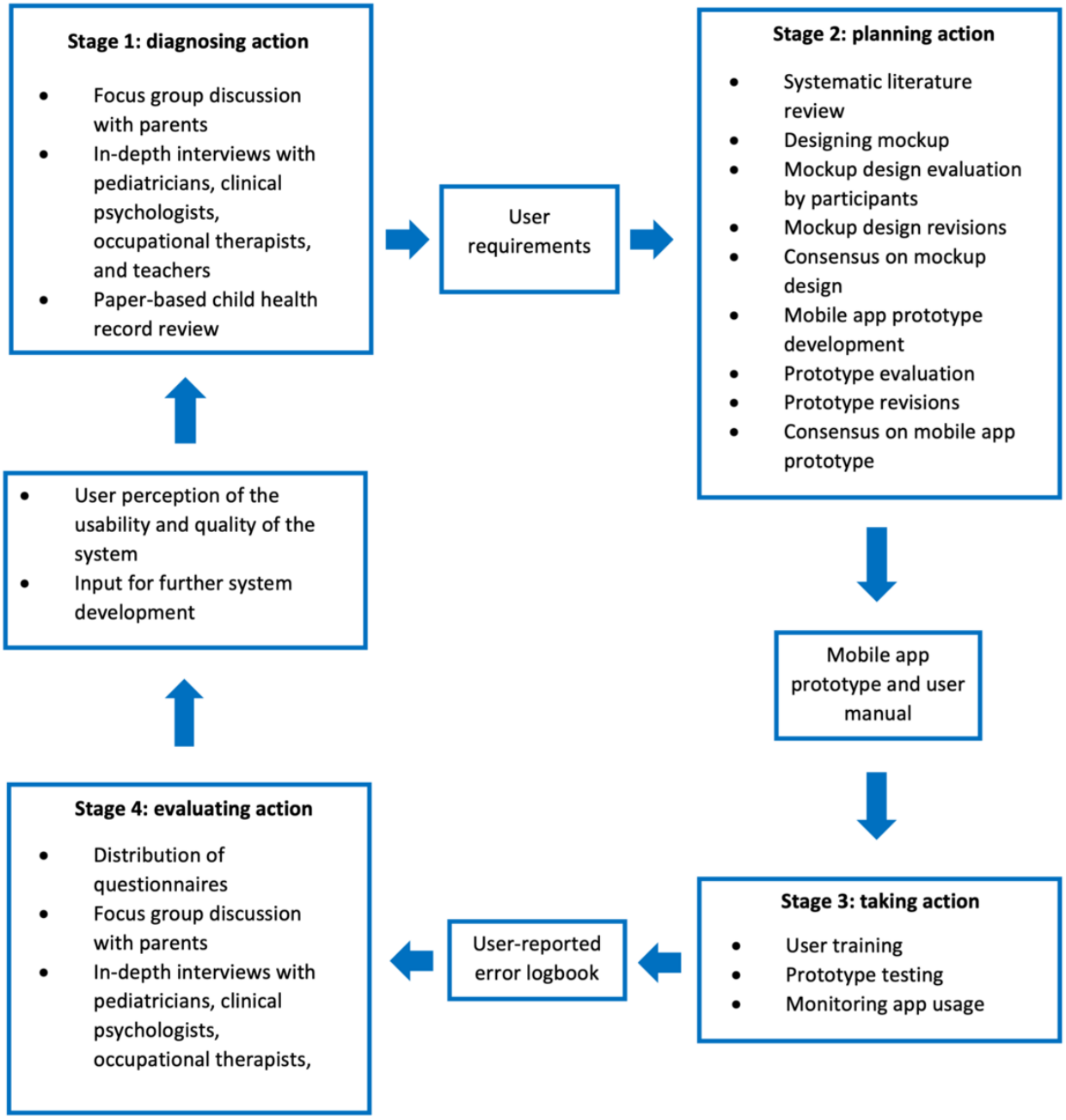


Table 1. Detailed steps and measures in each stage of the study.

Stage and steps	Measure(s)	Timeline
Stage 1: diagnosing action		
Conduct user requirement analysis through FGDs[a] with parents and interviews with pediatricians, occupational therapists, clinical psychologists, and teachers.	Number of participants, identified user needs	Months 1 and 2
Review paper-based documents managed by parents and related stakeholders.	Completeness of documentation analysis	Months 1 and 2
Stage 2: planning action		
Conduct a systematic literature review on the mobile-based app used for pediatric ADHD[b] management.	Number of reviewed studies, extracted key findings	Months 3-5
Design a mobile-based PHR[c] mockup.	Initial mockup completion	Month 6
Review and revise the mockup design based on participant feedback until consensus is reached.	Number of revisions, participant consensus	Month 7
Develop a prototype based on the final mockup design.	Initial prototype completion	Months 7-10
Review and revise the prototype based on participant feedback until consensus is reached.	Number of revisions, participant consensus	Months 11 and 12
Stage 3: taking action		
Conduct training and mentoring for participants on using the mobile-based PHR.	Participant attendance, knowledge gained	Month 13
Facilitate prototype trial usage among participants.	Number of users engaged	Months 14 and 15
Monitor app usage to identify challenges or technical issues.	Number of reported issues	Months 14 and 15
Stage 4: evaluating action		
Assess system usability using the SUS[d] questionnaire.	SUS score (range 0-100)	Month 15
Evaluate app quality using the uMARS[e] questionnaire.	Mean (SD) of uMARS scores	Month 15
Collect qualitative feedback via FGDs and interviews.	Identified feedback	Months 15 and 16
Summarize findings and provide recommendations for future development.	Final report completion	Months 17 and 18

[a]FGD: focus group discussion.

[b]ADHD: attention-deficit/hyperactivity disorder.

[c]PHR: personal health record.

[d]SUS: System Usability Scale.

[e]uMARS: User Version of the Mobile App Rating Scale.

Study Setting

This research will be conducted at Dr Sardjito Hospital, Special Region of Yogyakarta, Indonesia. This hospital was chosen as the research location because it is an educational and referral hospital with a pediatric health clinic specializing in social pediatrics and neurology, which is commonly referred to by patients with ADHD. As a tertiary hospital, it receives a significant number of pediatric patients with ADHD referred there each year. The hospital's comprehensive health care facilities and expertise in pediatric care, particularly in social pediatrics and neurology, make it an optimal environment for conducting this research.

This research will also be conducted in schools where children with ADHD receive formal education in Indonesia. These children are aged between 4 and 12 years [38]. Teachers who work with children with ADHD, including preschool and elementary school teachers, will be actively involved in the study. It is widely recognized that communication and active involvement of parents, health care providers, and teachers are essential for managing pediatric ADHD [39].

Stage 1: Diagnosing Action

Objective

The objective of stage 1 (diagnosing action) is to systematically identify and understand the diverse needs of stakeholders in relation to the development of a mobile-based PHR. This initial phase will be dedicated to diagnosing and comprehending the requirements of key stakeholders involved, including parents, pediatricians, occupational therapists, clinical psychologists, and teachers of children with ADHD. To develop high-quality apps, it is imperative to build the development process upon a comprehensive understanding of user requirements, derived from a methodology that actively involves users in the process [40]. Through a meticulous process involving document review,

focus group discussions (FGDs), and in-depth interviews, the stage will seek to uncover issues related to the recording of ADHD symptom development by parents and the PHR's role as a communication medium among parents, teachers, and health care professionals. The outcomes of this stage will include a comprehensive analysis of stakeholder needs, outlining specific requirements for the development of a mobile-based PHR.

Output

The output of this stage will be a document containing specific requirements for the development of a mobile-based PHR. These requirements include data needs, user groups and permissions, app features, functionalities, and expected technology specifications.

Participants

Stakeholders involved in the management of children with ADHD, including parents, pediatricians, occupational therapists, clinical psychologists, and teachers, will participate in this study [41,42]. Selection criteria for research participants are detailed in Table 2.

Involvement of parents or caregivers and teachers is related to the assessment of ADHD that requires evidence directly obtained from them regarding the core symptoms of ADHD, the duration of symptoms, the degree of functional impairment, and associated conditions [43].

We estimate that our study will need around 5 parents, 2 pediatricians, 2 occupational therapists, 2 clinical psychologists, and 2 teachers. This is the minimum number of participants; additional participants may be included during data collection until data saturation is achieved [44].

Table 2. Participant selection criteria.

Participants	Criteria
Parents	• Parents of children diagnosed with ADHD[a] (aged 4-12 years) who have received behavioral therapy and medication, with at least 1 year of experience in taking care of children with ADHD • Experienced in using mobile health apps • Own and actively use an Android- or iOS-based mobile phone with an internet connection
Pediatricians	• Pediatricians managing patients with ADHD whose parents are participating in the research, with a minimum of 2 years of experience in managing children with ADHD • Currently pursuing or have completed subspecialization in developmental pediatrics–social pediatrics or child neurology • Experienced in using electronic medical record systems or telemedicine or both
Occupational therapists and clinical psychologists	• Occupational therapists and clinical psychologists managing patients with ADHD whose parents are participating in the research, with a minimum of 2 years of experience in managing children with ADHD • Experienced in using electronic medical record systems or telemedicine or both
Teachers	• School teachers teaching children with ADHD whose parents are participating in the research, with a minimum of 2 years of experience in teaching children with ADHD • Own and actively use an Android- or iOS-based mobile phone with an internet connection

[a]ADHD: attention-deficit/hyperactivity disorder.

Data Collection

Data will be collected through a systematic approach, including FGDs with parents and in-depth interviews with pediatricians, occupational therapists, clinical psychologists, and teachers. The total number of interviews will be adjusted based on the number of participants involved. Participants will be selected using a purposive sampling method based on predetermined inclusion criteria to ensure representation of key stakeholders actively involved in managing pediatric ADHD. Comprehensive FGD and interview guides have been developed in Indonesian to facilitate semistructured sessions. The inquiry framework acknowledges the dynamic nature of discussions and interviews, allowing flexibility in question sequencing, particularly regarding follow-up inquiries, which may undergo alterations during the research [45]. The guides are designed to explore specific aspects described in Table 3.

The data collection process will follow a systematic procedure. Participants will be recruited through referrals from pediatricians specializing in ADHD to ensure a diverse and representative sample. In-depth interviews and FGDs will be conducted in a private and comfortable environment to encourage open and honest responses. Each session will begin with an introduction explaining the purpose of the study and obtaining consent for audio recording.

All interviews and FGDs will be audio-recorded with the participants' consent, and field notes will be taken to capture contextual details, nonverbal cues, and relevant observations during the sessions. Each in-depth interview session will be conducted for approximately 30-60 minutes, while each FGD session is expected to last from 60 to 120 minutes [46,47]. The semistructured nature of the interviews and FGDs will allow flexibility for follow-up questions and enable a deeper exploration of emerging themes during the discussions.

Table 3. Key aspects explored in stakeholder interviews and FGDs[a].

Aspect	Focus of exploration
Stakeholder needs	• Essential features required for a mobile-based PHR[b] • Information that needs to be recorded, monitored, and accessed (eg, symptom tracking, medication schedules, therapy progress)
Usability preferences	• Design expectations (eg, user-friendliness, interface layout) • Accessibility concerns, including navigation simplicity for parents and professionals
Data accessibility and security	• Preferences for access control (eg, who can input and view data) • Concerns about privacy and confidentiality of ADHD[c]-related information
Roles of stakeholders	• How each stakeholder envisions contributing to and using the PHR • Collaboration needs between parents, pediatricians, occupational therapists, clinical psychologists, and teachers in managing pediatric ADHD

[a]FGD: focus group discussion.

[b]PHR: personal health record.

[c]ADHD: attention-deficit/hyperactivity disorder.

As a methodological triangulation measure, paper-based child health records managed by parents will be reviewed to validate the essential data needs in the PHR [48]. Parents will be encouraged to present their manually recorded data, which reflects their needs in managing the care of children with ADHD. This will facilitate researchers in scrutinizing and documenting the various data types encapsulated within these records.

Data Analysis

Qualitative data from FGDs and in-depth interviews will be analyzed using thematic analysis following the 6-phase approach [49,50]: (1) familiarization with the data, where researchers immerse themselves in the data by reading and re-reading transcripts; (2) generating initial codes, involving systematic coding of significant features of the data across the entire dataset; (3) searching for themes, where codes are organized into potential themes; (4) reviewing themes to refine and ensure coherence and distinction between them; (5) defining and naming themes, focusing on capturing the essence of each theme; and (6) producing a report that involves a narrative that integrates the themes with supporting evidence from the data [51]. To address methodological rigor, aspects of reflexivity, confirmability, dependability, credibility, and transferability will be considered throughout the analysis process. Reflexivity will be addressed by creating fieldnote reflections, where researchers will document critical interpersonal dynamics affecting participants and their data, record and reflect on decisions made, and highlight moments of analytic insight to enhance transparency and self-awareness throughout the research process [52,53]. Confirmability will be ensured through detailed documentation of the analytic process, and peer debriefing dependability will be supported by maintaining a clear audit trail of the analysis process [54]. To enhance credibility, member checking with selected participants will be conducted, and investigator triangulation will be implemented with 2 researchers collaboratively reviewing and comparing the codes and resolving any differences through discussion for the same text unit [55]. Transferability will be facilitated by providing detailed descriptions of the study context and participant characteristics in this protocol [54]. The qualitative data will be organized using Open Code software version 4.03, ensuring systematic handling and transparency of the coding process [56,57].

Stage 2: Planning Action

Objective

Stage 2 (planning action) aims to design and develop a prototype of a mobile-based PHR that is agreed upon by all research participants. This stage will involve several key steps. First, a systematic literature review will be conducted on mobile apps used in pediatric ADHD management to enhance the user requirement analysis from stage 1 by thoroughly examining and synthesizing the existing literature. In the mobile app development process, understanding the efficient assessment of mobile apps, academic challenges, and other important aspects available in the existing literature is crucial [58]. The review will focus on identifying app features, purposes, target users, reported outcomes, and the measuring instruments used in previous studies. It will also address important considerations, such as the efficient assessment of mobile apps and academic challenges in the field. Next, a mockup design of the mobile-based PHR will be created based on the results of both the user requirement analysis and the systematic literature review. This mockup will be used to validate the user interface's usability [59].

Finally, a mobile app prototype will be developed based on the collective agreement of research participants on the finalized mockup design. The prototype will be developed in collaboration with a team of developers who will be recruited as part of the technical team for this study. The prototype will be built using Flutter, a framework that allows for the development of apps on both Android and iOS platforms, which together dominate the mobile app market [60-62].

Output

The outcome of this stage will be a mobile-based PHR prototype for both Android and iOS platforms, which has gained consensus

among all research participants and is ready for testing in the next stage. Furthermore, a user manual for the mobile app will be produced during this stage.

Participants

Participants in this stage will be stakeholders related to pediatric ADHD who have previously participated in stage 1. Participants in this stage will actively engage in the design and development process [63].

Data Collection

Data collection will involve several key steps. First, a systematic literature review will be conducted and documented following the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) 2020 guidelines [64]. To comprehensively explore the available literature on mobile apps for pediatric ADHD, a systematic search will be conducted across multiple databases, including PubMed, Scopus, Cochrane Library, and Google Scholar. The search strategy will involve a combination of MeSH (Medical Subject Headings) terms as controlled vocabulary terms and their relevant synonyms related to pediatric ADHD, mobile apps, and pediatric ADHD management stakeholders. MeSH terms used as keywords will include “parents,” “child,” “adolescent,” “family,” “caregivers,” “physicians,” “school teachers,” “pediatrics,” “mobile applications,” “smartphone,” “digital health” and “attention deficit disorder with hyperactivity.” The search strings will be tailored to the specific syntax and requirements of each database. The study/source selection process will follow a systematic and transparent approach. The process consists of 3 main steps. First, titles and abstracts of identified papers will be screened by 2 independent reviewers using predefined inclusion criteria. Any discrepancies will be resolved through discussion, and if necessary, a third reviewer will be consulted to facilitate consensus. Second, a full-text review of selected studies will assess their eligibility, with reasons for exclusion recorded and reported. Finally, relevant data will be extracted from the included studies. Subsequently, the data analysis will explore the apps’ features, purposes, reported outcomes, as well as variations in apps usage across different contexts and participant groups.

Information derived from the systematic literature review will be gathered and used to complement the results of the user requirement analysis, forming the foundation for the design and development of the mobile-based PHR. Next, the designed mockup will be presented to each participant for comprehensive feedback. Every discussion will be recorded, transcribed, and analyzed, with refinements made to the mockup design based on participant input. This iterative process will continue until a unanimous consensus is reached among all participants [65]. Finally, the approved mockup design will be transformed into a mobile-based app prototype. Similar to the mockup phase, the prototype will be discussed with each participant to gather further feedback The discussions will be recorded, transcribed, and analyzed, with subsequent revisions made to the prototype until a unanimous agreement is achieved among all participants.

Data Analysis

Data from the systematic literature review will be analyzed descriptively to map the user groups, as well as the apps’ features, purposes, and outcomes related to the implementation of mobile apps for pediatric ADHD. Additionally, participant feedback on the mockup design and prototype of the mobile-based PHR will be qualitatively analyzed, serving as a foundation for the continuous improvement and refinement of both the mockup design and the prototype.

Stage 3: Taking Action

Objective

Stage 3 (taking action) will involve the trial of the mobile-based PHR. The objective of this stage is for participants to actively use the mobile app in their daily activities while monitoring children with ADHD. Throughout this stage, technical challenges faced by users during the trial period will be identified to facilitate app improvements and refinements.

Output

The output of this stage will be a logbook document detailing the errors or technical challenges reported by users during the trial period. This logbook will serve as a comprehensive record of user feedback, documenting encountered issues and discrepancies. It will function as a crucial control document for the debugging process and for implementing necessary system refinements [66]. By systematically logging user-reported errors, the logbook will become a valuable resource for the iterative improvement process, ensuring that the mobile app prototype is continually enhanced and optimized based on real-world user experiences.

Participants

Participants in this stage will include individuals who have previously participated in stages 1 and 2, along with newly recruited parents of children diagnosed with ADHD. The number of newly recruited parent participants is anticipated to range between 20 and 80 individuals [67]. Eligibility criteria for participation require owning a smartphone compatible with either the Android or the iOS platform and having reliable internet access.

Data Collection

In this stage, participants will be asked to use the mobile-based PHR for 6 weeks before proceeding to the next stage [68]. During the trial period, app usage will be monitored, and users will be asked to report any system errors or technical issues encountered through the reporting form available in the mobile-based PHR. The reported data will be recorded and compiled into an error logbook. This monitoring will allow user issues to be addressed promptly, enabling the technical team to provide targeted support, as needed. To ensure participants use the mobile-based PHR consistently during the 6-week period and can test its entirety, they will be provided with detailed instructions during user training, as well as regular reminders and support throughout the period.

Data Analysis

The collected data will be descriptively analyzed by grouping similar types of errors or technical issues. Subsequently, app improvements and refinements will be implemented based on the analysis. Users will be informed of the implemented improvements and refinements through notifications in the mobile-based PHR.

Stage 4: Evaluating Action

Objective

Stage 4 (evaluating action) will focus on assessing the overall quality and usefulness of the mobile-based PHR from the user perspective. Unlike earlier stages, which focus on design, development, and refinement, this stage will primarily serve as a comprehensive evaluation of the outcomes of the previous stages. It will involve gathering feedback from participants on the effectiveness of the mobile-based PHR and identifying expectations for its further development.

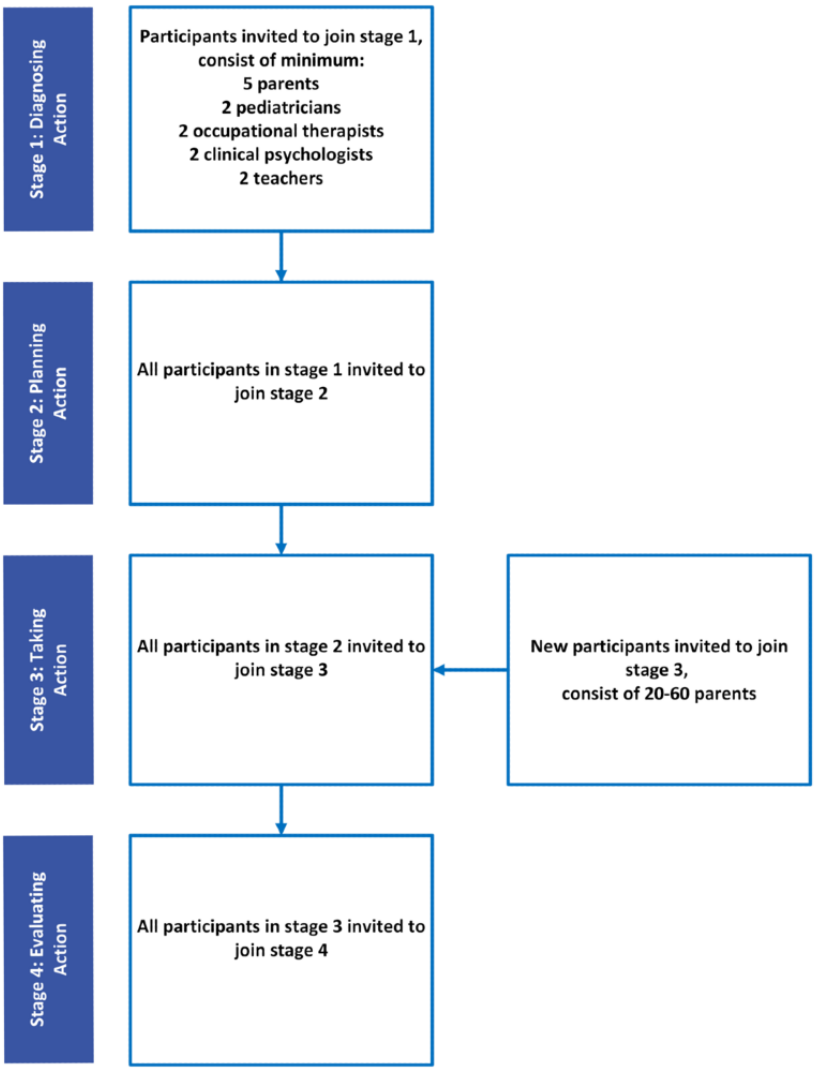
Output

The output of stage 4 will be a comprehensive evaluation report that summarizes participants' assessments regarding the usefulness and quality of the mobile-based PHR. Additionally, this stage aims to generate valuable feedback for future development.

Participants

The evaluation in stage 4 will involve both quantitative and qualitative assessments of the mobile-based PHR. Participants in stage 4 will consist of those who have participated from stage 1 to stage 3, as well as additional participants newly recruited in stage 3. Qualitative evaluations will be conducted exclusively with participants who have been involved from stage 1 to stage 3, as they can provide comprehensive and holistic feedback based on their entire experience. Meanwhile, quantitative evaluations in stage 4 will focus solely on parent participants, including both parents who participated from stage 1 to stage 3 and newly recruited parents in stage 3. The primary reason for focusing the quantitative assessment on parents is that they will be the main users of the mobile-based PHR, which is being designed to support the management and care of their children with ADHD. Figure 2 illustrates the sequential involvement of participants, starting from the initial recruitment in stage 1 through their continued engagement up to stage 4.

Figure 2. Participant flow diagram for the action research stages.



Data Collection

Quantitative data to assess the usefulness of the mobile-based PHR will be collected using the Indonesian version of the System Usability Scale (SUS) questionnaire [69]. The SUS consists of 10 statements, each scored on a Likert scale of 1-5, where a higher score indicates stronger agreement with the statement [70]. Additionally, quantitative data will be gathered to assess the quality of the mobile-based PHR using the User Version of the Mobile App Rating Scale (uMARS) questionnaire. The uMARS includes 20 items divided into 5 dimensions: engagement, functionality, aesthetics, information, and subjective quality. Each statement is scored on a 5-point Likert scale [71]. Qualitative data will also be collected through in-depth interviews and FGDs to gather comprehensive insights from participants' experiences during stage 3 (taking action). This approach will aim to uncover rich, contextual information regarding usability, satisfaction, challenges encountered, and participants' input and expectations for further development of the mobile-based PHR.

Data Analysis

Quantitative data obtained from the SUS questionnaire will be analyzed descriptively. The results will be summarized, totaled, and then multiplied by a coefficient of 2.5, yielding a final score within a range of 0-100 [70]. This score will be used to determine the percentile ranking. Data from the uMARS questionnaire will be analyzed through descriptive statistical analysis, calculating the mean (SD) to assess the quality of the mobile app. Scores ranging from 1 to 2 indicate "not acceptable," 2 to 3 indicate "poor," 3 to 4 indicate "acceptable," 4 to 5 indicate "good," and 5 indicate "excellent" quality [72]. Qualitative data from in-depth interviews and FGDs will be analyzed using thematic analysis [49].

Trustworthiness

The data in this research will be validated using the action research validation technique, which comprises coherence validation, discursive validation, and practical validation [35]. Coherence validation focuses on how various empirical, interpretative, and conceptual elements are integrated to mutually reinforce each other. The coherence validation technique that will be used in this research is triangulation, a method that will involve cross-referencing the results from FGDs and in-depth interviews regarding user requirements with the findings from the reviews of paper-based PHRs, particularly related to data that must be recorded in the PHR.

Discursive validation emphasizes dialogical and democratic validation in a forum. The discursive validation technique that will be used in this research is member checking, a method that involves returning the research findings to the participants for their review and validation. This iterative process will allow participants to confirm the accuracy and relevance of the data collected during in-depth interviews, FGDs, document reviews, and other research activities. By incorporating member checking, the study aims to ensure the credibility and trustworthiness of the research outcomes, as participants can provide feedback and insights, contributing to the overall validation and refinement of the research findings.

Practical validation focuses on testing in a real environment so that specific knowledge claims can gain sufficient trustworthiness. The practical validation method that will be used in this research is participant engagement, providing participants with an opportunity to actively use the mobile app prototype. Unlike a passive observation approach, participants will be directly involved in navigating and interacting with the prototype, offering insights into the user experience from a firsthand perspective. This hands-on engagement will ensure a more practical and realistic assessment of the mobile app's functionality and usability. By allowing participants to explore the prototype independently, the study aims to gather authentic feedback on the user interface, features, and overall performance, contributing to the refinement and enhancement of the mobile app based on the practical experiences of the end users.

The summary of the action research activities in each stage including output, activities, instrument, variable, participants, and validation methods are presented in Multimedia Appendix 1.

Ethical Considerations

The study has been approved by the Ethics Committee of the Faculty of Medicine, Public Health, and Nursing, Universitas Gadjah Mada (approval no: KE-FK-1257-EC-2023). To maintain ethical standards, we will provide comprehensive information regarding the study protocol to all potential participants. We will outline the purpose, procedure, and potential risks and benefits of their participation, especially in the context of action research [73]. Once they agree to participate, they will be required to provide signed informed consent. Confidentiality and privacy will be rigorously conducted throughout the research process, with measures in place to anonymize and secure sensitive information [74].

Results

This study was initiated in October 2024, with the research process divided into 4 distinct stages:

- Stage 1 (diagnosing action) will focus on identifying user requirements and challenges in managing ADHD care through stakeholder interviews, FGDs, and document reviews. As of December 2024, 13 participants were enrolled, comprising 5 (38.5%) parents, 2 (15.4%) pediatricians, 2 (15.4%) occupational therapists, 2 (15.4%) clinical psychologists, and 2 (15.4%) teachers, meeting the minimum target for participant numbers. This stage was completed at the end of 2024, providing key insights to guide subsequent stages.
- Stage 2 (planning action) will include a systematic literature review, user requirement validation, mockup design validation, and prototype development. The prototype development will be conducted in collaboration with a technical development team. This stage is projected to conclude by September 2025, delivering a finalized prototype for usability testing.
- Stage 3 (taking action) will focus on implementing and testing the prototype with participants during a 6-week trial

period. During this phase, system usage data, user feedback, and error reports will be collected and analyzed to refine the prototype. This stage is anticipated to be completed by the end of 2025.

- Stage 4 (evaluation action) will involve both qualitative and quantitative assessments of the mobile-based PHR. Qualitative evaluations will gather in-depth feedback from participants who have engaged in all stages, providing comprehensive insights into the user experience. Quantitative evaluations, targeting all parent participants, will assess the usability and quality of the mobile app through embedded questionnaires. This stage is expected to conclude in February 2026. The results of this study will be reported according to reporting guidelines provided for action research [75]. The final results are anticipated for publication by the middle of 2026.

Discussion

Summary

The landscape of future research in pediatric ADHD stands to evolve significantly, particularly in the development of effective electronic systems tailored for gathering crucial information to diagnose and monitor children and adolescents with ADHD [76]. As an innovative response to this research avenue, this study will contribute to this domain by using an action research approach that engages the stakeholders in pediatric ADHD management in all stages, including diagnosing, planning, taking, and evaluating action [77]. To the best of our knowledge, this is the first study that involves active participation and engagement with stakeholders, including parents, medical providers, and nonmedical providers, in the development of a mobile app related to pediatric ADHD management. This dynamic methodology will ensure that the mobile app developed is technologically effective, user-friendly, and contextually relevant.

The insights gleaned from this research will underscore the intricate challenges associated with managing pediatric ADHD and emphasize the critical role of collaborative and patient-centric interventions. These principal findings will pave the way for more targeted and contextually relevant interventions, fostering a deeper understanding of the intricacies involved in pediatric ADHD management.

Limitations

The scope of the study is confined to addressing the needs of stakeholders directly involved in the routine care of children with ADHD within tertiary hospital settings. Although this focus provides valuable insights into the specific challenges faced in such contexts, the findings may not be fully representative of the broader spectrum of ADHD management, especially in community or primary care settings. Additionally, the study's outcomes may be influenced by the regional or institutional characteristics of the selected tertiary hospitals, potentially limiting the generalizability of the results to a more diverse health care landscape. Despite these limitations, the study remains dedicated to refining and optimizing the care of children with ADHD within tertiary hospital environments, with the anticipation that the insights gained can contribute meaningfully to the broader discourse on pediatric ADHD management.

Conclusion

This study protocol outlines a pivotal initiative to enhance the management of ADHD in pediatric populations. By using an action research methodology and actively engaging stakeholders, including parents, medical providers, and nonmedical providers, the study aims to contribute significantly to the field. The iterative cycles of the research seek to develop a mobile-based PHR that is not only user-friendly but also effective and uniquely attuned to the diverse needs of those involved in pediatric ADHD care.

Acknowledgments

The authors would like to thank the Doctoral Program on Medical and Health Sciences of the Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada, for support and facilitation during their doctoral study.

Data Availability

The datasets used and analyzed during this study will be made available from the corresponding author upon reasonable request after the completion of the study.

Authors' Contributions

DBS drafted the initial manuscript and finalized the manuscript. RS, DKN, and MSK provided feedback and contributed to revising the manuscript. All authors have read and approved the final version of the manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Summary of action research activities.
[PDF File (Adobe PDF File), 67 KB - resprot_v14i1e60216_app1.pdf]

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Abbreviations

ADHD: attention-deficit/hyperactivity disorder
FGD: focus group discussion
MeSH: Medical Subject Headings
PHR: personal health record
SUS: System Usability Scale
uMARS: User Version of the Mobile App Rating Scale

Edited by A Schwartz, T Leung; submitted 04.05.24; peer-reviewed by Q Dong, A Ahmad, R McAdams; comments to author 24.10.24; revised version received 19.12.24; accepted 30.01.25; published 10.04.25.

Please cite as:
Santoso DB, Kristanti MS, Nurputra DK, Sutomo R
Development of a Mobile-Based Personal Health Record for Pediatric Attention-Deficit/Hyperactivity Disorder Management: Protocol for a Study Based on Action Research Design
JMIR Res Protoc 2025;14:e60216
URL: https://www.researchprotocols.org/2025/1/e60216
doi:10.2196/60216
PMID:40208656

Protocol

Adaptation of the Stakeholders' Walkability/Wheelability Audit in Neighborhoods (SWAN) Tool for Individuals With Diverse Disabilities: Protocol for a Mixed Methods Study

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Abstract

Background: The prevalence of sensory, cognitive, and mobility disabilities in Canada underscores the need to address environmental barriers. This study adapts and validates the Stakeholders' Walkability/Wheelability Audit in Neighborhoods (SWAN) tool to assess the challenges the built environment poses for individuals with disabilities, aiming to inform policy changes for accessibility and inclusivity.

Objective: This study aims to (1) adapt the SWAN tool for those with hearing, vision, or cognitive disabilities; (2) validate SWAN tool for researching environmental barriers for people with disabilities, including older adults; and (3) offer insights for policy changes in the built environment, contributing to literature and guiding future research.

Methods: The study uses a community-based research approach, carried out over 4 phases within an 18-month period in British Columbia. Phase 1 includes adapting and pilot-testing of the SWAN tool. In Phase 2, street intersections are identified for data collection using Geographic Information System tools and consultations with municipal officials. Phase 3 involves recruiting participants across four disability categories. The final phase includes analyzing the data and disseminating findings.

Results: Data collection concluded in September 2024, involving 80 eligible participants across four streams in preidentified hotspots. The results are expected to be published in March 2025. To date, data collection is ongoing, and we are currently in the process of data analysis.

Conclusions: This study will contribute to the growing body of research on built environment accessibility by adapting the SWAN tool for individuals with diverse disabilities. By identifying key barriers in urban spaces, the study aims to inform policy changes that will lead to more inclusive, accessible, and safe urban environments for all individuals.

(JMIR Res Protoc 2025;14:e60553) doi:10.2196/60553

KEYWORDS

age and accessibility; disability experiences; community engaged research; inclusive urban design; user-led built environment audits

Introduction

Overview

The number of people living with sensory (hearing and vision), cognitive, and mobility disabilities is increasing in Canada. In 2019, approximately 5% of people aged 15 years and older had a hearing disability, and in 2020, a total of 567,000 people were living with a cognitive disability [1]. About a quarter (24.1%) of the population living with disabilities are aged 65 years and older [2].

Mobility restrictions are not typically the result of a single cause but arise from an interaction of risk factors in various domains, both individual and environmental [3]. Historically, disability research primarily relied on the medical model, emphasizing the individual and their specific impairments or conditions [4]. However, in more recent times, disability models have shifted their focus toward understanding the dynamic interplay between individuals and their surrounding environment [5]. Environmental characteristics are hypothesized to limit or promote an individual's ability to complete purposeful actions and fulfill role expectations, affecting physical functioning and disability [3]. Lawton [6] proposed several dimensions of environment that are important for older adults: personal environment (family and friends), suprapersonal environment (ie, neighborhood racial or age composition), social environment (norms or values related to society or culture), and physical environment (eg, built environment). The physical environment is defined as the human-made or human-altered space in which individuals live out their daily lives [7] and is the focus of this paper. The built environment has a profound impact on the mobility of older adults and people living with disabilities, which can affect their health and quality of life [3,8-11]. This aligns with the International Classification of Functioning, Disability, and Health, which posits disability and functioning as outcomes that result from the interplay between health conditions (such as diseases, disorders, and injuries) and contextual factors, including the built environment.

For instance, individuals who are deaf or hard of hearing (DHH) feel less safe when navigating the pedestrian environment as they struggle to hear traffic on the road [12,13]. Persons living with mild cognitive impairment (MCI) often experience challenges with navigation of their own environment, which is heightened when communities do not integrate sufficient green spaces and landmarks (such as large shops, libraries, community centers, and senior centers) to help reduce the stress of wayfinding [14]. Moreover, people using mobility assistive technologies (MAT) may find it challenging to navigate the built environment, especially during rain and snow because of inadequate drainage or snow removal [10]. People with vision impairment (VI) also face difficulties due to the lack of accessibility in public spaces and transportation systems [11].

Limited research exists on the role of environmental factors on mobility and social participation of individuals with disabilities, creating a gap in the literature [3,8-11]. Environmental variables that can affect the experience of being mobile in a place, fall into 2 broad categories: macroscale, consisting of structural features such as street interconnectivity and land use mix [15,16]; and microscale, or details, such as aesthetics and sidewalk design, and maintenance [17]. While much research has concentrated on macroscale variables that define walkability [18], investigating microscale features is also valuable for understanding the mobility experience [19-22]. Microscale characteristics of the built environment can often be modified at a lower cost and within a shorter timeframe compared with restructuring macroscale designs [23].

Various audit tools have been developed and tested to evaluate the microscale qualities of the built environment, particularly at the street level, through on-site visits [24]. The Stakeholders' Walkability/Wheelability Audit in Neighborhoods (SWAN) is a microscale, user-led audit tool designed to evaluate both objective and subjective aspects of the built environment that affect the lives of older adults and individuals using mobility assistive devices, persons who are DHH, and persons living with MCI including dementia [25,26].

The SWAN tool is an adaptation of the SWEAT-R tool that captures the perspective of persons with disabilities [25]. Moreover, the development of the SWAN tool included a comprehensive literature review and incorporated aspects of other user-led tools, such as the Microscale Audit of Pedestrian Streetscapes [23,27], the Built Environment and Active Transport Neighborhood Assessment [28], and Jane's Walk: Walkability Checklist [29].

Previous research using the SWAN tool was primarily done with individuals with mobility disabilities using MAT [30]. To incorporate a wider variety of disability experiences, the SWAN tool has been adapted to accommodate individuals' living sensory disability (hearing and vision) as well as those with cognitive disabilities, including early stages of dementia and MCI. This adaptation enables these populations to systematically evaluate their neighborhoods.

Using a community-based participatory research approach, the SWAN tool was developed in collaboration with a committee of individuals with lived and professional experience, ensuring that diverse perspectives and needs are integrated into the research process. This approach promotes self-advocacy among participants and facilitates policy changes that are reflective of community needs [31].

Objectives

This study aims to (1) adapt the mobility tool for individuals living with hearing or vision as well as cognitive disability; (2) validate the tool for researching barriers in the built and social environment for persons with disabilities, including those with vision, hearing, cognitive, and mobility disabilities (including older adults); and (3) provide insights for decision-making and policy changes in modifying the built environment.

This protocol paper aims to contribute to existing literature and guide future studies on how individuals with cognitive, sensory, or mobility disabilities navigate the built environment. The goal is to fill knowledge gaps and provide evidence-based results for municipalities and communities to implement necessary policy changes for a safe and accessible living environment.

Methods

Overview

The research will be conducted over 4 phases within an 18-month period in British Columbia. Advisory committees including individuals with a variety of disabilities have been created to ensure the consideration of inputs or concerns of these individuals in the research project through a participatory research approach. These committees include individuals with mobility, visual, and hearing disabilities and early-stage dementia. The committees meet 2 to 3 times a year to provide feedback on the ongoing phases of the research project, which are presented below.

The first phase involves conducting a literature review, tool consolidation, and pilot-testing. Phase 2 entails identifying street intersections for data collection using Geographic Information System layers and discussions with municipal officials. Phase 3 involves collecting data across various streams of disabilities. The fourth phase includes data analysis and knowledge mobilization efforts.

Ethical Considerations

This study has been reviewed and approved by the ethics boards of Simon Fraser University and the University of British Columbia (H21-01234). To protect identities, names and any other information that might identify a participant will be removed from transcriptions and field notes. Any photos taken as part of data collection that could potentially identify individuals will be blurred. All data will be collected, managed, and stored in accordance with university research ethics procedures, and all data will be anonymized. We perceive that the risks for physical or emotional harm to the participants associated with the proposed research are minimal. The time and effort required by participants is minimal, and there is no deception or other manipulation of participants. Given that participants might share difficult experiences, which may lead to emotional and/or psychological distress, the researcher will make clear at the beginning and throughout the interview that participation is voluntary, and participants can withdraw their consent at any time without harm. Participation in this study is voluntary, and participants can decide to opt out. An honorarium of CAD $75 (approximately US $53) will be provided to participants.

Phase 1: SWAN Tool Development Process

Overview

To conduct the walking/wheeling audits with DHH individuals and those living with cognitive and vision disabilities, the original SWAN tool (that is, SWAN for MAT users) was adapted through reviewing the literature and consultations with persons with disabilities or persons with professional experience. Involving persons with disabilities and professionals with relevant experience fosters a more inclusive approach, ensuring that the tool reflects the diverse perspectives within the community. The incorporation of findings from both academic and gray literature allows for evidence-based adaptations, increasing the tool's validity and reliability for the target populations.

Literature Review

Relevant concepts pertaining to DHH individuals and those living with cognitive and vision disabilities, focusing on their experiences and interactions with the safety and accessibility of the outdoor built environment, were taken from reviews done by our study team [10,25,32,33]. This allowed for collating similar concepts to pinpoint areas where the tool may need expansion or clarification to better support these specific populations.

Content Comparison and Tool Consolidation

After developing the newly adapted tools, they were charted in Microsoft Excel alongside the original SWAN tool for content comparison, sequencing of questions, and language simplicity and consistency. Upon review of all tools, they were finalized as the Hearing and Mobility Tool, the Dementia Tool, and the Vision Tool.

Pilots

To test the functionality of the tools in the field, 4 pilots were conducted with persons with disabilities from the 4 populations of interest. These pilots served as an opportunity to try the tools with participants and gather feedback on the questions, content, process, and flow of data collection. Since data collection involves a walking/wheeling method, both the research team and participants experience this process in the field, allowing for adjustments to be made accordingly. During the pilot sessions, particular attention was given to ensuring the clarity and comprehensibility of the terminology used in the tools. This was done to ensure individuals with different levels of abilities could easily understand the features being inquired about.

Following the pilot session with individuals with vision disabilities, substantial adjustments were implemented to improve the tool's readability. These changes encompassed modifications to align the tool with the Canadian National Institute for the Blind standards, ensuring adherence to best practices for accessibility in both design and functionality. These adjustments, informed by participant feedback and collaboration with the Canadian National Institute for the Blind standards, are aimed at fostering a more user-friendly and inclusive experience for individuals with vision disabilities during data collection.

Phase 2: Identification of Data Collection Locations Through Community and Research Project Partnerships

Overview

To identify areas for data collection, the research team undertook a stepwise approach, namely (1) generating prioritized sites and (2) hosting an interactive community forum to finalize locations.

Intersections for Data Collection

The research team identified data collection areas in 6 partner municipalities across Metro Vancouver using open-source data and ArcGIS. They focused on pedestrian-involved collisions data, integrating additional layers such as transportation hubs (eg, sky train stations) and city center locations to create maps and identify "hotspots" for data collection. The outcome was maps highlighting 7 to 10 intersections in each municipality. Subsequently, the team met with municipal officials to discuss and prioritize 3 to 4 intersections for the data collection per municipality based on their feedback and guidance.

SWAN Community Forum

The second step involved hosting an interactive forum with persons with disabilities, community partners from senior centers, and municipal officials. The goal was to understand challenges at intersections and surrounding areas, examining barriers and facilitators to mobility. The forum also explored designing interventions based on evaluating these areas in relation to municipal priorities and funding.

Phase 3: Participant Recruitment, Coordination, and Data Collection

Overview

Finalizing the tool and confirming selected intersections enables the research team to proceed with participant recruitment for the 4 populations: individuals with cognitive, mobility, hearing, and vision disabilities, starting with those living with cognitive disabilities. In this study, we aim to collect data from 80 participants across various disability categories. The minimum sample sizes for each category are as follows: 30 participants using MAT, 15 individuals with MCI, 15 individuals who are DHH, and 20 individuals with VI. These numbers are selected to ensure sufficient data for validity and reliability tests. The larger sample size for participants using MAT reflects their greater prevalence compared with the other groups, allowing for a more comprehensive analysis of the effects of MAT in our study. All data collection will be concluded by September 2024. While our recruitment methods are committed to diversity and inclusion, we recognize the importance of providing specific details on participant demographics. By including a diverse range of participants in terms of age, gender, ethnicity, and disability type, we aim to gain a comprehensive understanding of the barriers and facilitators present within the built environment.

Recruitment

The research team will recruit participants from community centers, relevant organizations serving persons with disabilities, and health care connections. This ongoing process targets DHH individuals, those with hearing and vision disabilities, those with early stages of dementia or MCI, and MAT users. To streamline participant onboarding, a researcher will act as the central administrator. This individual will verify eligibility, review study details, consent, web-based online tool training, and COVID-19 protocols with participants before scheduling data collection sessions. Sessions will be scheduled based on participant and research team availability. The lead research assistant (RA) for each session will maintain communication with participants and ensure all necessary documents (SWAN tools, consent forms, and equipment) are ready for the efficient completion of the audits.

On-Site Preparation Research Team

On the day of data collection, the lead and accompanying RAs will arrive in advance to assess the presence and accessibility of public washrooms. Additionally, they will identify either an indoor or covered location for the completion of the SWAN Secondary Observation Form (SOF). This form will be filled out in the format of a 15- to 20-minute qualitative interview.

On-Site Preparation Participant

Before starting the audit with the participant, the lead RA will review the consent form to ensure the participant understands the study objectives, the use of collected data, and their right to withdraw. Next, a demographic form will be completed to contextualize the participant's answers. The participant will be oriented on the path of travel using a map of the intersections to be covered. The lead RA will accompany the participant throughout the walking/wheeling audit, providing assistance as needed or taking a more active role by reading questions aloud, based on the participant's preference.

SOF Content

The SOF includes open-ended questions similar to those in the SWAN tool, encouraging discussion and reflection from the participant. Responses will be either audio recorded or handwritten based on the participant's consent choice. By incorporating the secondary observation interview guide, the SWAN tool gains a more comprehensive understanding of participants' interactions with their neighborhoods.

Home and Community Environment Survey

During the data collection phase, 2 complementary tools will be used: the Home and Community Environment (HACE) tool and the SWAN tool. Participants can either complete these tools themselves or have assistance from a secondary RA. This dual approach enhances the validation process, providing a more thorough assessment of the research variables.

The HACE tool, designed as a self-report measure, will be directly administered by the participants. It aims to evaluate various factors within an individual's HACE that might influence their level of community participation. In this study, the HACE tool serves as an additional validation measure for the effectiveness of the SWAN tool [34].

The initial HACE prototype consisted of 44 items assessing the physical, attitudinal, and political aspects of HACEs. Specifically, questions related to the community mobility domain will be included in the SWAN project's data collection process.

Sidewalk Accessibility Index

The Sidewalk Accessibility Index (SI) serves as an indicator to assess the performance of sidewalks and public spaces, focusing on the needs and expectations of wheelchair users to define accessible routes within urban road networks. It considers

various variables that contribute to the comfort and safety of wheelchair users, weighted according to their perceptions [35].

In the SWAN project, the SI will be used as a complementary tool for validation purposes. During data collection, a secondary RA completes the SI, which gathers data on 4 key aspects related to sidewalks: evenness, maintenance, width, and surface quality. However, the SWAN project focuses solely on these sidewalk-specific factors and does not inquire about the suitability of pedestrian crossings.

Sidewalks and public spaces should provide an environment that meets the needs of all users, ensuring comfort and safety regardless of physical limitations, whether temporary or permanent. The SI variables are designed to describe aspects of comfort and safety related to pedestrian movement along the block and crossing street intersections.

Finalization of Data Collection

The participant will then be provided with an honorarium for their time spent, and if required, a discussion of a second data collection will take place to complete any outstanding segments. The lead RA is responsible for ensuring the completion of all documents along with uploading and storing data collected appropriately. Finally, a reflection form will be completed by the researchers to reflect on the data collection.

Phase 4: Data Analysis

Overview

The analysis will focus on validating the SWAN tool, which collects both quantitative and qualitative data. Objective and subjective scores will be calculated for its 5 domains. In order to verify the validity of the SWAN tool, 2 additional audit tools will be used to collect data, including HACE [34] and SI [35]. Walk score results for the audited area will also be compared with the SWAN result for further validation. Details on tool validation methods can be found in the section on tool validity. Additionally, the interrater reliability (IRR) of the SWAN tool will be assessed. More information is provided in the IRR section.

Quantitative data from SWAN and other tools will be entered and organized in Microsoft Excel. This includes coding and scoring based on the codebook and calculating domain scores within Excel. For further analysis, the R programming language in RStudio (Posit, PBC) will be used for IRR and tool validity assessments. Qualitative responses from the SOF will be entered and analyzed in NVivo software (Lumivero). More details on SOF analysis can be found in the *Qualitative Data Analysis* section. The specific steps of data analysis are outlined in the following sections.

Data Cleaning and Reorganization

After data are entered and prior to moving forward with the analysis, certain questions will be moved to their original domains. The questions were moved to a different domain for efficient data collection. Although they were physically sequential on site, they are better organized in a separate domain for analysis. For example, questions about street safety features were placed in the function of the street crossing domain during data collection but belong to the safety domain.

Weighting of Scores

The primary step in calculating scores for street segments involves assigning weights to both the domains and subdomains, ensuring a total cumulative score of 100 for all domains. These weights are determined through a comprehensive literature review and expert recommendations.

For individuals who are DHH, use medical assistance technology, and have cognitive disabilities, the domain weights remain consistent. However, there is a slight variation in the vision stream weighting, reflecting the unique needs of individuals with visual impairments. Specifically, the “appearance and maintenance” domain is considered less critical. Therefore, the vision stream receives a weight 5 points lower than other streams, which is then added to the “sidewalk functionality” subdomain.

“Functionality” and “safety” are deemed the most crucial domains for neighborhood accessibility for individuals with disabilities. Consequently, each of these domains will be assigned the highest weight. As shown in Table 1, functionality is divided into crossing functionality (20 points) and sidewalk functionality (15 points in vision stream, 10 points in other streams). The same weights will apply to safety subdomains, traffic safety at 20 (covering pedestrian and vehicle interaction safety), and personal safety at 10 (focusing on subjective safety perceptions).

Table 1. Domain and subdomain weights.

Domains and subdomains	Vision stream	Other streams
Functionality	30	35
Crossing functionality	20	20
Sidewalk functionality	10	15
Safety	30	30
Traffic safety	20	20
Personal safety	10	10
Land use and supportive features	20	20
Appearance and maintenance	15	10
Social aspect	5	5
Total	100	100

The "land use and supportive features" domain, recognized as the second most critical, will receive a weight of 20. "Appearance and maintenance" will be weighted at 10 for vision and 15 for all other streams, due to overlapping questions within the land use and supportive features domain. In contrast, the "social aspects" domain, with a limited set of 5 questions focusing on subjective assessments, will have the lowest weight.

Subsequently, a detailed review of questions within each domain and subdomain will extract essential concepts and elements. The assigned weight will then be evenly distributed among these identified concepts and elements to avoid undue emphasis on specific concepts. For instance, the 20 points allocated to the subdomain of crossing functionality will be evenly divided among concepts (eg, curb ramp, crosswalk, and pedestrian signal) within that subdomain. Finally, the weight assigned to each category of questions will be equally distributed among all questions within that category to ensure a balanced weighting process.

Objective Scores

There will be 3 steps to calculate the objective score for each domain. First, responses to questions will be converted into numeric codes based on the code book. Second, these codes will be multiplied by the question's weight to calculate the question's score. Third, the scores for all questions within a domain will be summed and divided by the maximum possible score for that domain. To make the aggregated objective score easier to understand, it will be multiplied by 100% for each domain.

Some questions in the SWAN tool are reverse-coded to avoid confusion. For instance, a positive response to the presence of a certain physical feature indicating a barrier (eg, "transition from the curb ramps into the crosswalk causes problems") would be scored as "1," though it is not a facilitator in this context. These questions were reverse-scored as needed to ensure the total score includes only true "Yes" scores.

In addition to the final objective score for each domain, a total score for the SWAN tool will be calculated by averaging the scores for each domain. This total score will facilitate comparisons between different audited segments.

Codebook

In the SWAN tool, response options typically include "Yes," "No," "Don't Know," and "Not Applicable," as shown in Table 2. However, for individuals with vision disabilities, an additional option, "Cannot detect," is provided for cases where the participant cannot clearly see the object but is aware of its existence. When participants with vision disabilities choose this option, it is treated as equivalent to selecting "No," as the object is not detectable or functioning properly for the user. During the coding process, a value of "1" will be assigned for the presence of an assessed environmental feature that enhances walkability/wheelability, and "0" for its absence. Reverse-coded questions, such as "The outdoor patio(s) is/are an obstacle to walking/wheeling," will use "0" to represent the presence of this barrier and "1" to denote its absence.

Table 2. Different types of questions and scoring rationale (missing data: n=99).

Type of question and possible responses	Code
General questions	
Yes	1 (0 in case of reverse coding)
No (cannot detect, specifically in the tool designed for vision impairment)	0 (1 in case of reverse coding)
Not applicable	98
Don’t know	97
Both sides questions	
Both sides	2 (0 in case of reverse coding)
One side	1
Neither side	0 (2 in case of reverse coding)
Not applicable	98
Don’t know	97
Directional questions	
One-way	1
Two-way	0
Not applicable	0
Don’t know	0

For items referring to “one side or both sides” of a street segment, they will be grouped together as a scale. For example, “Are there curb ramps/cuts present?” will be coded as “2” if they are present on both sides, “1” if present on only one side, and “0” if not present at all. The same approach applies to items with a positive or negative impact on walkability/wheelability.

In addition to general and 2-sided questions, the SWAN tool includes questions about the direction of traffic, with responses like “one-way” and “two-way”. Through a disability lens, “one-way” responses will be coded as “1” and “two-way” as “0” since crossing one-way streets is less complex.

Responses like “not applicable” and “don't know,” based on the data collection area and participants’ familiarity, will be excluded from the scoring system to ensure it accurately reflects walkability/wheelability factors.

Subjective Ratings

Participants in the SWAN tool provide subjective ratings using a 5-point Likert scale at the end of each domain. This scale ranges from “poor” (scored as “1”) to “excellent” (scored as “5”), reflecting their subjective experience of the assessed domain. These ratings are averaged and converted into percentages to indicate participants’ subjective perceptions of the audited segment. Comparing these subjective scores with the objective scores may reveal interesting findings.

Qualitative Data Analysis

As indicated, the qualitative data will be collected using the SOF which contains open-ended questions based on the 5 primary domains, and 4 subdomains in the SWAN tool. Qualitative data gathered using the SOF is intended to capture detailed insights from the participants regarding the built environment and their lived experiences. For instance, within the personal safety subdomain, participants will be asked the following “Are there things that make you feel safe or unsafe when walking/wheeling during the daytime?” Collectively, the SOF data and the photo commentary build the qualitative dataset connected to the SWAN tool.

The qualitative data will be analyzed by using both Braun and Clark’s [36] seminal multistep thematic analysis process and by drawing on later advances in their methodological framework [37]. Their original analytical process consists of six integrated phases including (1) data familiarization and review, (2) code development and comparison, (3) code consolidation and early theme exploration, (4) theme confirmation and mapping, (5) theme refinement and name creation, and (6) research findings write-up (Braun and Clark [36]). While the open-ended questions contained in the SOF are grounded in the conceptual domains of the SWAN tool, the qualitative analysis process will be both inductive and reflexive [36,37]. Therefore, the analysis will be guided by the data itself [36] and will aim to identify insights and interpretations of the data beyond known built environment barriers and facilitators while also embracing the subjectivity of the research team members [37]. The research team will also independently and collectively engage in reflexive journaling practices and group discussions throughout the qualitative analysis process [38]. These practices will help the research team examine their subjectivity and understand its connection to their analysis [39]. Last, this will also contribute to the quality of the analysis; specifically, the adoption of these reflexive methods will contribute to the equitable and fair representation of all participant perspectives [38].

Step 1: Data Familiarization and Review

The raw qualitative data will undergo initial transcription and cleaning using Otter.ai. Subsequently, the transcriptions will also be verified by several RAs. This process will not only

ensure a clear and reliable dataset for analysis but will also help the research team familiarize themselves with the data.

Step 2: Code Development and Comparison

After the data have been transcribed and cleaned the coding process will begin. This will include the development of early/open codes and exploration of the codes across transcripts [36]. Coding will be undertaken by individual research team members, however, will be complemented by group discussions to allow for exploration of the research team's subjectivity and interpretation of the data.

Step 3: Code Consolidation and Early Theme Exploration

Following the coding of the transcripts, the research team will work to consolidate the existing codes and explore relevant themes identified within the data [36]. This process will be collaborative as all research team members will aid in collating existing codes, and in the development of a preliminary thematic map/diagram.

Step 4: Theme Confirmation and Mapping

After the potential themes have been identified, the research team will work to solidify the themes. This will involve examining if the preliminary themes fully represent and reflect the data [36]. This process will be iterative and will potentially involve revisiting the coding process. This stage will not conclude until all team members agree that the analysis fully captures the data, and a cohesive thematic map has been developed.

Step 5: Theme Refinement and Name Creation

The research team will then work to ensure each theme is well-defined and succinct [36]. This process will also be iterative and will work to identify the relevance of each theme in relation to the broader goals of the SWAN tool.

Step 6: Write-Up of Research Findings

In the final step, the team will elaborate on each theme, discussing their significance with evidence from the data, including quotes. This comprehensive write-up will aim to convey theme frequency, and importance, within the research context.

IRR Analysis

The reliability of the SWAN will be determined by calculating IRR using the paired observer method. The IRR will compare the objective scores of older adults or persons with disability and the secondary RA. This will be calculated both in percentage agreement and Cohen κ to compare the results [40]. Percentage agreement is a straightforward measure that calculates the proportion of agreement between 2 observers as a percentage of the total observations; however, in 1960, Cohen [41] critiqued the use of percent agreement due to its inability to account for chance agreement. He introduced the Cohen κ, developed to account for the possibility that raters actually guess on at least some variables due to uncertainty [40]. Cohen suggested the κ result be interpreted as follows: values ≤0 as indicating no agreement, 0.01-0.20 as none to slight, 0.21-0.40 as fair, 0.41-0.60 as moderate, 0.61-0.80 as substantial, and 0.81-1.00 as almost perfect agreement [41].

Tool Validity

To validate the SWAN tool, correlation analyses will be conducted between its domains and other environmental audit tools used in data collection: HACE, SI, and Walkscore. HACE and SI scores will be normalized using formulas outlined in their respective papers [34,35], while Walkscores for the audited area will be obtained via web. After examining data distribution, the appropriate correlation analysis method, Pearson correlation, will be applied to assess associations between scores from different tools. Pearson correlation lies between –1 and 1. Values near 0 mean no (linear) correlation and values near SD 1 mean very strong correlation. The negative sign means that the 2 variables are inversely related, that is, as one variable increases the other variable decreases. The following table gives a guideline on the strength of the linear relationship corresponding to the correlation coefficient value [42].

As no comprehensive audit tool similar to SWAN was identified in existing literature, each additional audit tool was purposefully selected to assess the validity of specific SWAN domains. Therefore, SI will be compared with functionality, HACE with safety, and Walkscore with land use and supportive features. The matrix in Table 3 illustrates which SWAN domains or subdomains will be compared with measures from HACE, SI, and Walkscore tools.

Table 3. Similarity between the Stakeholders' Walkability/Wheelability Audit in Neighborhoods (SWAN) domains and subdomains and other tools.

Extra tools and measures used for tool validation	Domains and subdomains of the SWAN tool						
	Functionality		Safety		Land use and supportive features	Appearance and maintenance	Social aspect
	Street crossing	Sidewalk	Traffic safety	Pedestrian safety			
SI[a] (sidewalks)							
Even		✓		✓			
Well-maintained		✓		✓		✓	
Surface condition		✓		✓		✓	
Width		✓					
Intersection	✓		✓	✓			
HACE[b]							
Uneven sidewalks		✓		✓			
Easy to use sidewalks		✓		✓			
Safe	✓	✓	✓	✓			
Places to rest							✓
Curb ramps	✓		✓				
Walkscore							
Access to amenities					✓		

[a]SI: Sidewalk Accessibility Index.

[b]HACE: Home and Community Environment.

Results

Data collection concluded in September 2024, involving 80 eligible participants across 4 streams in preidentified hotspots. The results are expected to be published in March 2025. To date, data collection is ongoing, and we are currently in the process of data analysis.

Discussion

Expected Findings

By focusing on a diverse group of participants, including those using MAT, those living with MCI and VI, and those who are DHH, the study aims to provide a comprehensive understanding of the barriers and facilitators present within the built environment using the SWAN tool. As there are no validated tools to capture this population perspective while navigating the built environment, the anticipated findings are expected to contribute to the existing literature by validating the SWAN tool in diverse disability categories. We hypothesize that similar to prior research, functionality and safety will emerge as key factors influencing accessibility across all disability groups. Past studies have consistently shown that features like sidewalk width, smoothness, and the presence of safe crossings are fundamental to pedestrian mobility [3,8-11]. However, our approach considers physical features, by integrating subjective participant ratings and qualitative data collected through the SOF to capture subjective experiences. This dataset should provide a more comprehensive view of how the built environment influences community participation and social participation for individuals with disabilities.

A key strength of this study is its comprehensive inclusion of multiple disability types. This research adopts a holistic perspective, capturing the full spectrum of disability-related accessibility challenges.

One important aspect that was not fully addressed in this study was the inclusion of individuals who are deaf-blind. This population, which experiences both vision and hearing impairments simultaneously, faces unique challenges that were not directly captured in this phase of the research. Due to the complexity of their needs, the lack of comprehensive accessibility tools for this group, and the potential for logistical difficulties in coordinating data collection with deaf-blind individuals, this population was excluded from this study. However, their experiences are equally critical to understanding how the built environment affects individuals with multiple disabilities.

To ensure that the findings from this study reach a wide audience and have a meaningful impact, we have developed a comprehensive knowledge mobilization strategy. A central element of this plan is the community forum, which will provide an interactive space for people with disabilities, urban planners, local government officials, and other key stakeholders to engage

directly with the research findings. This forum will facilitate the exchange of experiences and insights from individuals with disabilities, offering a platform to share their lived experiences navigating urban spaces. Through this collaborative dialogue, we aim to raise awareness and generate actionable recommendations for improving the accessibility of urban environments.

Additionally, as part of the knowledge mobilization strategy, we will develop multimedia resources including games and videos to engage both the disability community and the general public in the study's outcomes. The games will simulate the various mobility challenges faced by individuals with disabilities, offering an immersive experience for users to understand and empathize with the barriers these individuals encounter. These interactive tools will be used as educational resources in community centers, schools, and public awareness campaigns to foster greater understanding and empathy.

Conclusion

This study introduces a new approach to assessing urban accessibility for individuals with various disabilities using the SWAN tool; by adopting a community-based methodology, the research emphasizes the importance of including diverse disability perspectives in evaluating the built environment. The anticipated findings will provide valuable insights into the barriers and facilitators that impact mobility, safety, and overall accessibility in urban spaces.

While the study's limitations include the exclusion of individuals who are deaf-blind and the focus on specific urban areas, these gaps present opportunities for future research. Expanding the participant pool and environments will strengthen the generalizability of the findings.

This work contributes new knowledge to the field by offering a comprehensive framework for urban accessibility that integrates both subjective and objective measures. It underscores the importance of inclusive design and offers practical implications for urban planners and policymakers striving to create more accessible, inclusive communities.

Acknowledgments

This research was funded by a Social Sciences and Humanities Research Council (SSHRC) funded partnership grant.

Data Availability

The datasets generated or analyzed during this study will be available from the corresponding author upon reasonable request.

Authors' Contributions

RN collected and analyzed data, contributed to the interpretation of results, and wrote the manuscript. AM contributed to the study design and critically revised the manuscript for important intellectual content. BM contributed to the interpretation of results and critically revised the manuscript. All authors agree to be accountable for all aspects of the work, ensuring the accuracy and integrity of the research presented. All authors have read and agreed to the published version of the manuscript.

Conflicts of Interest

None declared.

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Abbreviations

DHH: deaf or hard of hearing
HACE: Home and Community Environment
IRR: interrater reliability
MAT: mobility assistive technologies
MCI: mild cognitive impairment
RA: research assistant
SI: Sidewalk Accessibility Index
SOF: Secondary Observation Form
SWAN: Stakeholders' Walkability/Wheelability Audit in Neighborhoods
VI: vision impairment

Edited by A Schwartz; submitted 21.05.24; peer-reviewed by SH Mousavi, OAA Yamini, U Sinha; comments to author 05.09.24; revised version received 16.11.24; accepted 05.12.24; published 10.04.25.

Please cite as:
Mahmood A, Rikhtehgaran F, Nasiri R, Hedayati N, Pandsheno S, Sharrock A, Mora DJ, Haji Hosseini S, Routhier F, Mortenson W Adaptation of the Stakeholders' Walkability/Wheelability Audit in Neighborhoods (SWAN) Tool for Individuals With Diverse Disabilities: Protocol for a Mixed Methods Study
JMIR Res Protoc 2025;14:e60553
URL: https://www.researchprotocols.org/2025/1/e60553
doi:10.2196/60553
PMID:

Corrigenda and Addenda

Correction: Evaluating the Effectiveness of a Multimodal Psychotherapy Training Program for Medical Students in China: Protocol for a Randomized Controlled Trial

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Related Article:

Correction of: https://www.researchprotocols.org/2025/1/e58037

(JMIR Res Protoc 2025;14:e71220) doi:10.2196/71220

In “Evaluating the Effectiveness of a Multimodal Psychotherapy Training Program for Medical Students in China: Protocol for a Randomized Controlled Trial” ([JMIR Res Protoc 2025 Jan 3:14:e58037.]doi:10.2196/58037) the authors noted one error.

In “Table 3,” the “Rating” for “Appraisal” appeared as follows:

> *“4=somewhat likely; 3=neutral; 2=unlikely; 1=not at all likely”*

This has been corrected as follows:

> *"5=very likely; 4=somewhat likely; 3=neutral; 2=unlikely; 1=not at all likely"*

The correction will appear in the online version of the paper on the JMIR Publications website on 05 Feburary 2025, together with the publication of this correction notice. Because this was made after submission to PubMed, PubMed Central, and other full-text repositories, the corrected article has also been resubmitted to those repositories.

Submitted 12.01.25; this is a non–peer-reviewed article;accepted 14.01.25; published 05.02.25.

Please cite as:
Pei T, Ding Y, Tang J, Liao Y
Correction: Evaluating the Effectiveness of a Multimodal Psychotherapy Training Program for Medical Students in China: Protocol for a Randomized Controlled Trial
JMIR Res Protoc 2025;14:e71220
URL: https://www.researchprotocols.org/2025/1/e71220
doi:10.2196/71220
PMID:

Corrigenda and Addenda

Correction: Auricular Acupressure Versus an Intermittent Low-Carbohydrate Diet in Children With Overweight or Obesity With Gastric-Heat and Dampness-Obstruction Syndrome: Protocol for a Randomized Controlled Trial

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Related Article:

Correction of: https://www.researchprotocols.org/2025/1/e59856

(JMIR Res Protoc 2025;14:e74014) doi:10.2196/74014

In "Auricular Acupressure Versus an Intermittent Low-Carbohydrate Diet in Children With Overweight or Obesity With Gastric-Heat and Dampness-Obstruction Syndrome: Protocol for a Randomized Controlled Trial" the authors noted 3 changes.

The author affiliation information has been changed from:

> *Wen Sun[1], MSc; Jingwei He[1], MSc; Wenqin Wang[1], MSc; Chen Lu[1], PhD; Yating Lin[1], BSc; Yalan Dou[2], PhD; Weili Yan[2], PhD; Jian Yu[1], PhD*
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to:

> *Wen Sun[1*], MSc; Jingwei He[1*], MSc; Wenqin Wang[1], MSc; Chen Lu[1], PhD; Yating Lin[1], BSc; Yalan Dou[2], PhD; Weili Yan[2], PhD; Jian Yu[1], PhD*
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An equal contribution footnote has also been added for authors Wen Sun and Jingwei He.

In addition, under "Participant Timeline in Methods", in Table 1, the entries for Auricular acupressure at t_1 1 month and t_2 3 months, and Intermittent carbohydrate restriction diet at t_1 1 month have been changed from:

> *"N/A"*

to:

"✓".

We intend to convey that the intervention duration for auricular acupressure is 3 months, while the intervention duration for dietary restriction is 1 month. It appeared incorrectly in the final published version.

The correction will appear in the online version of the paper on the JMIR Publications website, together with the publication of this correction notice. Because this was made after submission to PubMed, PubMed Central, and other full-text repositories, the corrected article has also been resubmitted to those repositories.

Submitted 16.03.25; this is a non–peer-reviewed article;accepted 24.03.25; published 28.03.25.

Please cite as:
Sun W, He J, Wang W, Lu C, Lin Y, Dou Y, Yan W, Yu J
Correction: Auricular Acupressure Versus an Intermittent Low-Carbohydrate Diet in Children With Overweight or Obesity With Gastric-Heat and Dampness-Obstruction Syndrome: Protocol for a Randomized Controlled Trial
JMIR Res Protoc 2025;14:e74014
URL: https://www.researchprotocols.org/2025/1/e74014
doi:10.2196/74014
PMID:

Protocol

Influence of Partnership Relationships on Long-Term Neurological Rehabilitation in Germany: Protocol for a Qualitative Retrospective Study

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Abstract

Background: Acquired neurological diseases entail significant changes and influence the relationship between a patient and their significant other. In the context of long-term rehabilitation, those affected collaborate with health care professionals who are expected to have a positive impact on the lives of the affected individuals.

Objective: This study aims to examine the changes in the relationship between the patient and their loved ones due to acquired neurological disorders and the influence of health care professionals on this relationship.

Methods: Through sociogenetic type building, we will identify different types of patient-caregiver dyads and their effects on health care professionals and vice versa. The results will then be integrated into a model based on the theory of symbolic interactionism and Baxter's Relational Dialectics Theory.

Results: This study is not funded and was approved by the ethics committee of the German Society for Nursing Science, and it complies with the Declaration of Helsinki. The data collection started in June 2024 based on narrative couple interviews and is running. We assume that patients and their relatives will demonstrate heterogeneity as individuals, as well as in their interactions within the dyad, regarding certain orientations such as coping with illness, motivation for therapy, and coping strategies.

Conclusions: Our findings address a biopsychosocial perspective that enhances treatment approaches in neurological long-term care. Understanding the influence of professionals on dyadic couple relationships can improve rehabilitation effectiveness by tailoring therapeutic approaches to various patient types, relatives, and dyadic relationship constellations. This fosters patient- and family-centered therapy in line with holistic care.

International Registered Report Identifier (IRRID): DERR1-10.2196/63949

(JMIR Res Protoc 2025;14:e63949) doi:10.2196/63949

KEYWORDS

neurological rehabilitation; neurological injury; therapeutic alliance; relationship building; caregivers; family; partnership; health professionals; neurological; therapeutic; Germany; retrospective study; narrative interview; biopsychosocial; family-centered

Introduction

Scientific and Practical Relevance of the Project

Rehabilitation is effective for any person with a long-lasting disability at any stage of the illness. A patient-centered biopsychosocial rehabilitation approach involving a multidisciplinary team is particularly essential for individuals with neurological conditions, as they frequently experience lifelong limitations and require comprehensive, individualized support to enhance their quality of life and achieve maximum independence [1].

Neurological damage is acquired through stroke, traumatic central nerve injury, or traumatic brain injury. The resulting sudden loss of independence often leads to irreversible harm and is one of the main causes of lifelong support and home care needs. Strokes cause a high economic and health burden [2]. For example, the cost of stroke to health care systems in 32 countries totaled US $28.2 billion in 2017 [3]. This is why the Stroke Alliance for Europe emphasizes the need for European countries to invest in cost-effective stroke interventions to improve rehabilitation and the quality of life of stroke survivors [3]. The number of patients with traumatic brain injury in 2016 in Germany was 419,507 [4]. More than 4000 patients become long-term care cases due to severe permanent injuries, resulting in high costs and limited ability to work [5]. The rehabilitation process for neurological diseases is highly complex, depends on numerous influencing factors, and is vague concerning the results. The effectiveness of rehabilitation is highly dependent on its integration within a biopsychosocial framework and requires an individualized, person-centered approach [1]. Functional, cognitive, and psychological challenges directly impact the ability to perform daily tasks independently [6]. Acquired neurological damage leads to a loss of social roles for those affected and requires adaptation to the new living conditions [7]. In the context of illnesses, the individual coping strategies used vary greatly across the different patients [8]. Life orientations, goals, ideas, and expectations about one's own life and future development represent a relevant aspect of rehabilitative cooperation and success. Relatives of those who are directly affected not only experience trauma but also deal with the illness and its lasting personal consequences for themselves [9]. Individual processes take place within partnership dyads and domestic cohabitation. This is particularly relevant for Germany where 63% of people in need of care are cared for exclusively by relatives in a domestic setting. Nursing homes care for only 16% of people in need of long-term care in Germany [10].

Family Change Processes and Relationship Dynamics

In the partnership dyad between the person affected and the caregivers, dual roles arise as a spouse, patient, or caring relative [11]. Changes caused by a sudden loss of independence and the need for assistance due to a family member's illness impact power dynamics, role distributions, tasks, and decision-making between patients and their relatives. On the one hand, relatives provide their resources while on the other hand, they need help themselves. Within the framework of the existing family system, relatives thus have to face new challenges [9,12]. In this context, the rehabilitation process after acquired neurological damage is associated with fears, worries, and adaptations for many patients and their caregivers [13].

The therapeutic relationship significantly influences the rehabilitation process of neurological diseases and is of paramount importance [14,15].

Family caregivers play a central role in providing care, therapy, and social support, particularly in the case of lifelong disability due to acquired neurological damage [16]. According to recent international studies, the psychosocial effects of neurological damage have already been described for patients [12,17] and family caregivers of affected persons [18]. Studies also explore the dynamics between patients and therapists, as well as the relationships formed in patient-therapist interactions [12,19]. However, given the importance of biopsychosocial aspects in therapy and the close interactions affecting the well-being of patients and their relatives, there is a lack of studies on the influence of health care professionals on the dyadic relationship between patients and relatives in different phases of rehabilitation.

Our study addresses the following questions:

1. How does the dyadic relationship between persons with acquired central nervous chronic impairment and their significant others change over time and what does it mean for the therapeutic process?

2. How do relationships and relationship aspects influence the rehabilitation process?

3. What is the influence on the dyadic relationship that affects persons and their life partners which attributes to the health care professionals?

Furthermore, we want to discuss how health care professionals should react to the different situations and dyads in the rehabilitation process to enable the best possible quality of life from the perspective of the affected person and their life partner.

Underpinning Theories and Theoretical Approach

The theory of symbolic interactionism (SI) is based on the fundamental idea that actors influence each other within the framework of interaction processes and the resulting ongoing interpretations [20]. In relation to the object of the study, this means that 2 people enter a relationship with each other based on a "self" resulting from their history of interaction. The "self" is called into question by the sudden injury that leads to a long-term need for help, is no longer connectable in the strongly changed interaction, and needs a challenging adaptation.

Building on the understanding of SI, Leslie Baxter's Relational Dialectics Theory (RDT) focuses on forming a meaningful relationship between partners [21]. The relationship between the patient and the caregiver is established in dialogue and is subject to continuous change. Examples of dialectics within the dyadic relationship are integration-separation, stability-change, or expression-nonexpression. According to the RDT, these dialectics are natural and unavoidable in any relationship, and they play a crucial role in shaping how individuals communicate and interact [22]. This is particularly relevant to understand the changes within the couple relationship of patient and relative over time.

From a theoretical perspective, this study aims to increase the knowledge on the influence of changes in the couple's relationship on the rehabilitation process and vice versa, and consequently on the quality of life of patients and caregivers. Different types of patient-caregiver dyads can be identified and empirically validated based on theoretical approaches. This approach makes it possible to link empirically identified types back to the theory of SI [20], and the RDT [21], to support them empirically or to change, refute, or expand them. A major novelty of the study lies in the theoretical foundation of the

reciprocal effects of relational changes in acquired central nervous damage in rehabilitative processes and interaction with health care professionals.

From a practical perspective, standardized types of dyads can be recognized, and various rehabilitative approaches can be postulated at the practice level on a sociopsychological basis. This enables the enhancement of individual care for affected individuals, with a focus on improving their quality of life.

Methods

The study follows the Standards for Reporting Qualitative Research [23].

Approach, Sampling, and Recruitment

Approach

We use a qualitative approach, exploring how individuals maintain and shape their relationships in response to changed life situations within a domestic environment.

Sampling

Our sample consists of people with similar neurological conditions. Within the scope of the study, we include adult couples in which one person is chronically affected by an acquired neurological injury. Within these cases, disturbances, social status, age, and duration of affliction should be heterogeneous to ensure a high degree of diversity.

The inclusion criteria are (1) people who had an acquired central nervous system injury at least 6 months before and their partners, (2) the partnership existed before the injury and still exists at the time of the survey, (3) partners live together in a household, (4) participants have the capacity to give consent, (5) participants exhibit sufficient visual and hearing ability in order to understand the questions during the interview, (6) residence in Germany, and (7) sufficient understanding of German language.

Recruitment and Field Access

We recruit participants by displaying notices and flyers in public areas, including doctor's waiting rooms and neurological rehabilitation centers. This approach promotes voluntary participation. The study aims to achieve theoretical saturation without relying on predetermined statistical methods. Participants and their partners may choose the location for the interviews, which can be either through video call or in a place of their preference. The decision regarding the interview setting (face-to-face or online) is made by the concerned family dyads to avoid complicating the caregiving situation. No payment or reimbursement of expenses is provided for participation.

Data Collection Instruments and Data Processing

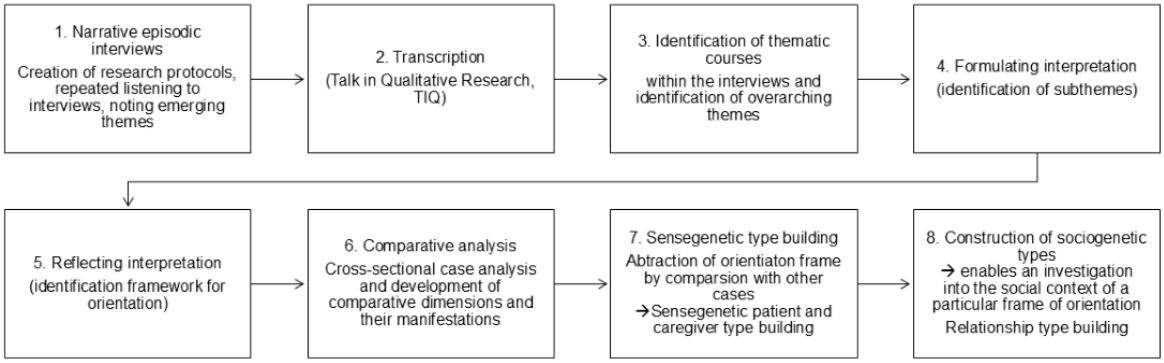
Narrative episodic joint couple interviews were conducted as part of this study. A deliberate decision was made to engage in dialogue with the spouses collectively, as this approach reflects the shared reality and facilitates negotiation processes between the individuals. Our research will deliberately consider the role of power dynamics within the interview setting, with a particular focus on the use of interruptions, attributions, accusations, and consents in relation to the discussed issues. This will be done in order to explicate the power structures and roles within the relationship and to analyze them in the context of the rehabilitation process. The couple's interviews will be recorded using an audio recording device. To meet the criterion of intersubjective traceability, the researcher will meticulously maintain posttranscripts and research diaries, which will document not only the content of the interview but also the researcher's personal feelings and reflections after each interview. This process will include active reflection on the researcher's role in the field, ensuring a transparent examination of potential biases and interactions.

The project uses the transcription system "Talk in Qualitative Research" for data processing, which was developed within the framework of the documentary method [24,25].

Data Analysis

The analysis of the narrative couple interviews is carried out according to Bohnsack's documentary method (Figure 1) [24]. The main researcher will systematically engage with the material, using a step-by-step immersion process to gradually extract insights and develop comparative horizons through case comparisons. This approach will ensure a thorough exploration of each case before proceeding to the next. The material and interpretations will be discussed with the research team using a 4-eyes principle and in workshops to gain diverse perspectives, validate findings, and enhance analytical rigor.

Figure 1. Methodical approach according to the documentary method.



Accordingly, the documentary method does not only remain at the level of an actor's reflexive knowledge but also allows access to practice-relevant action. This is pertinent in relation to the attitudes and behavior of those affected and their

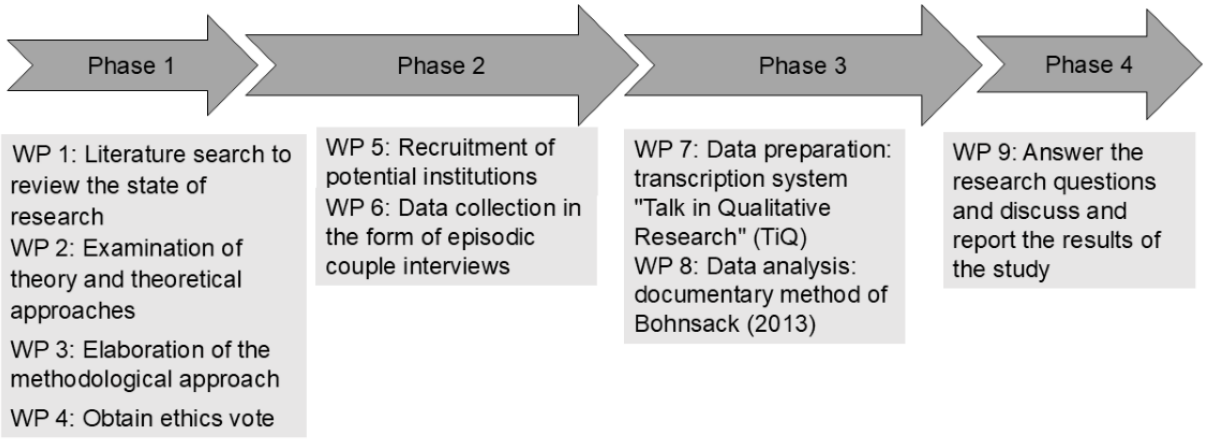
caregiving relatives. By examining dyadic relationships retrospectively, the research seeks to understand how the meanings and dynamics within these relationships have developed and changed over time. The formulating textual interpretation summarizes what has already been interpreted by the actors in the research field. This forms the basis for the reflexive interpretation, which consists of a formal and a semantic interpretation.

Comparative Analysis and Type Formation

The reconstruction of the habitus based on biographical narratives is conducted with the objective of determining the extent to which the habitus interpretations developed from the initial sequence can be confirmed, differentiated, or expanded through the analysis of subsequent sequences of this case. This is achieved through a comparative contrast with thematically similar sequences from other cases [26]. In a comparative analysis, the horizons of the respective cases within this study (eg, attitudes of patients and caregiving relatives) are compared and related to each other [25]. In sense-genetic type formation, we work out different orientation frameworks for dealing with a problem, for example, coping strategies for illness, and typify them [26]. Building on this, sociogenetic typing includes social contexts within the partnership and the relationship with health care professionals (Figure 1 [24]).

A flowchart of the study procedure and work packages is provided in Figure 2.

Figure 2. Flowchart of study procedures and work packages, own illustration. WP: work packages.



Ethical Considerations

The study was approved by the ethics committee of the German Society for Nursing Science (EK-23-018) and it complies with the Declaration of Helsinki. This study is not funded. Each participant provided both verbal and written informed consent to the first author before data collection commenced. During data collection, an initial review of the material is conducted to identify emerging themes within the interviews, enabling a deeper exploration of contrasts between them. Participants were advised that they could contact the interviewer at any time if they required further information or wished to reflect on the interview's impact. Due to the sensitive nature of discussing intimate relationship dynamics, particularly within the context of illness and rehabilitation, strict confidentiality must be upheld. Considering the emotional sensitivity of patients and their partners, the lead researcher undertook specialized training in sensitive interviewing techniques.

Anonymization and Data Security

We will anonymize all participant names, including their place of residence and treatment facility as well as names of workplaces and contact persons. We will manage and store the raw and analytical data (transcripts) and the code list in separate, password-protected data repositories. The data will be stored for 10 years in accordance with the data protection ordinance. No payment or reimbursement of expenses is provided for participation.

Results

The research question has been little explored and, in accordance with qualitative research principles, remains open to new and unexpected findings. The data collection started in June 2024 based on narrative interviews and is actually running. Currently, 15 dyads have been recruited and 7 have been interviewed. The current stage of the project is in work packages 6 and 7 (Figure 2). Due to the extensive procedures involved and the depth of reconstruction anticipated, we expect a sample size of up to 20 dyads. We anticipate that the study will be completed by June 2025, with data analysis concluding in the first quarter of 2025 and publication expected in the third quarter. We assume that patients and their relatives will demonstrate heterogeneity as individuals, as well as in their interactions within the dyad, regarding certain orientations such as coping with illness, motivation for therapy, and coping strategies. Furthermore, we expect that these orientations will manifest dynamically throughout the rehabilitation process and may therefore change over time.

Discussion

Overview

This study aims to enhance our understanding of how the relationships of affected couples evolve over the long term and how these changes impact the rehabilitation process. We propose that the nature of the relationship dynamics between patients and their partners varies based on the individual characteristics

of both the patient and the partner, significantly influencing the rehabilitation experience. These dynamics may affect how patients and their partners interact and adapt to the challenges of rehabilitation. Therefore, it is essential that intervention strategies are customized to the specific types of relationships in order to provide effective therapy.

From a biopsychosocial perspective, it is crucial to involve not only the affected persons themselves but also their social environment in therapy and rehabilitation [27]. The impact of a neurological impairment extends far beyond the individual and touches on the family members and friends. Incorporating health care professionals into the everyday lives of individuals with long-term illnesses signifies a significant shift for both the patients and their partners. Frequent interactions with health care providers, whether through medical appointments or therapies, have a direct effect on patients' health, their level of independence, and the dynamics of their shared lives.

A systematic review conducted by Weitkamp et al [28] suggests that couples dealing with chronic illness benefit from effective stress communication, supportive dyadic coping, and shared appraisals of their situation. We hypothesize that similar strategies will be identified in our study, as couples may use comparable communication techniques to manage stress and enhance mutual support. Furthermore, we expect to gain additional insights into coping strategies, including various communication patterns, and how these influence both the couple's relationship and the rehabilitation process. This variability in coping strategies underscores the intricate ways in which couples adapt to chronic illness. We anticipate that these findings will have implications for therapeutic approaches, emphasizing the importance of recognizing and supporting diverse communication styles and options for action.

Strengths and Limitations

The reconstruction method used in this study promises a significant gain in understanding through an in-depth analysis of the unique life worlds of the dyads. This approach aligns with Flick's [29] advocacy for narrative and reconstructive methods, which are instrumental in revealing deeper insights within qualitative data.

Through nationwide recruitment, we aim to minimize one-sided outcomes and regional disparities in care, thereby enhancing the representativeness of our findings. The study's methodological strengths, bolstered by the application of the documentary method, provide a solid framework for analysis. However, we acknowledge certain limitations, such as the challenges in recruiting same-sex couples and the difficulty in reaching individuals from lower socioeconomic backgrounds. Despite these challenges, we will strive to assemble a heterogeneous sample to increase the study's validity and ensure representation across various societal strata.

Theoretical and Practical Implications

The findings of our study are expected to contribute to the theoretical understanding of couple dynamics in the context of chronic illness and rehabilitation. We hypothesize that the variations in coping strategies will not only reflect different communication patterns but will also emerge from the specific characteristics of patients, their relatives, and the types of relationships involved. This differentiation will enhance our understanding of how various relational dynamics influence the rehabilitation process, thereby supporting existing theories while potentially introducing new dimensions to the discussion. By identifying these nuances, we aim to provide a more comprehensive framework for future research and interventions in this field. We assume that our study will support the principles of RDT by indicating that couples oscillate between change and stability, engaging in a dynamic negotiation process as they adapt to evolving relational and emotional landscapes. The theoretical grounding provided by our engagement with these theories (SI and RDT) offers a robust foundation, allowing for connections to be made with established assumptions in the field.

Enabling a deeper understanding of the interactions between professionals, patients, and their family caregivers could ultimately contribute to an increase in the quality of life of patients and their caregivers. This holistic approach has the potential to increase the effectiveness of rehabilitation by making therapy patient- and family-centered. This could create a more positive outcome in life for all those who are involved. Costs for the health care system could be reduced through effective therapy that also takes into account the mental health of relatives. Furthermore, our results could make it easier for health care professionals to provide care and could be used to support the interaction depending on the patient and the relative type as well as the relationship type.

The results will be published in both a scientific journal and a practice-oriented publication in neurological long-term rehabilitation, reaching a broad readership within the health care sector. This includes health care professionals who support affected individuals and their relatives during various phases of rehabilitation, such as doctors, nurses, physiotherapists, occupational therapists, and speech therapists. A brief summary of the results will also be prepared in patient-friendly language, similar to a patient guideline, and sent to participants upon request.

Due to a further increase in chronic diseases in the coming decades, for example, as a result of environmental, climate, and demographic changes, it is necessary to develop interventions on a physical, psychological, and social level to reduce the burden of chronic diseases [30].

Conclusion

The successful completion of the study will provide recommendations for action for practitioners, and, if possible, will facilitate the development of a treatment concept to improve the care of people with neurological disorders and their caring relatives. A deeper understanding of psychosocial processes in connection with chronic illnesses is of great importance for the development of comprehensive, personalized care strategies.

Data Availability

The datasets generated during this study are not publicly available due to confidentiality and ethical considerations but are available from the corresponding author on reasonable request.

Authors' Contributions

AvB was responsible for the conceptualization and research questions, study design, visualization, and writing of the original draft as well as the ethical approval, and is responsible for the analysis of the data material. EJ supported the selection of the study design (methodology), supervised the research work and the preparation of the ethical approval, and will support the analysis. PK supported the conceptualization of the study design against the background of his nursing science perspective and will support the analysis of data.

Conflicts of Interest

None declared.

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Abbreviations

RDT: Relational Dialectics Theory
SI: symbolic interactionism

Edited by A Schwartz; submitted 04.07.24; peer-reviewed by N Weydmann, A Glaessel; comments to author 27.08.24; revised version received 29.08.24; accepted 22.11.24; published 13.01.25.

Please cite as:
von Bosse A, König P, Jansen E
Influence of Partnership Relationships on Long-Term Neurological Rehabilitation in Germany: Protocol for a Qualitative Retrospective Study
JMIR Res Protoc 2025;14:e63949
URL: https://www.researchprotocols.org/2025/1/e63949
doi:10.2196/63949
PMID:39804683

Protocol

In Silico Evaluation of Algorithm-Based Clinical Decision Support Systems: Protocol for a Scoping Review

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Abstract

Background: Integrating algorithm-based clinical decision support (CDS) systems poses significant challenges in evaluating their actual clinical value. Such CDS systems are traditionally assessed via controlled but resource-intensive clinical trials.

Objective: This paper presents a review protocol for preimplementation in silico evaluation methods to enable broadened impact analysis under simulated environments before clinical trials.

Methods: We propose a scoping review protocol that follows an enhanced Arksey and O'Malley framework and PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews) guidelines to investigate the scope and research gaps in the in silico evaluation of algorithm-based CDS models—specifically CDS decision-making end points and objectives, evaluation metrics used, and simulation paradigms used to assess potential impacts. The databases searched are PubMed, Embase, CINAHL, PsycINFO, Cochrane, IEEEXplore, Web of Science, and arXiv. A 2-stage screening process identified pertinent articles. The information extracted from articles was iteratively refined. The review will use thematic, trend, and descriptive analyses to meet scoping aims.

Results: We conducted an automated search of the databases above in May 2023, with most title and abstract screenings completed by November 2023 and full-text screening extended from December 2023 to May 2024. Concurrent charting and full-text analysis were carried out, with the final analysis and manuscript preparation set for completion in July 2024. Publication of the review results is targeted from July 2024 to February 2025. As of April 2024, a total of 21 articles have been selected following a 2-stage screening process; these will proceed to data extraction and analysis.

Conclusions: We refined our data extraction strategy through a collaborative, multidisciplinary approach, planning to analyze results using thematic analyses to identify approaches to in silico evaluation. Anticipated findings aim to contribute to developing a unified in silico evaluation framework adaptable to various clinical workflows, detailing clinical decision-making characteristics, impact measures, and reusability of methods. The study's findings will be published and presented in forums combining artificial intelligence and machine learning, clinical decision-making, and health technology impact analysis. Ultimately, we aim to bridge the development-deployment gap through in silico evaluation-based potential impact assessments.

International Registered Report Identifier (IRRID): DERR1-10.2196/63875

(JMIR Res Protoc 2025;14:e63875) doi:10.2196/63875

KEYWORDS

clinical decision support algorithms; in silico evaluation; clinical workflow simulation; health care modeling; digital twin; quadruple aims; clinical decision; decision-making; decision support; workflow; support system; protocol; scoping review; algorithm-based; screening; thematic analysis; descriptive analysis; clinical decision-making

Introduction

The recent advent of artificial intelligence (AI) in clinical decision support (CDS) systems furthers the intended purpose of such systems to enhance medical decision-making by using clinical knowledge and other health information [1]. Traditionally, such systems rely on either standard of care or knowledge-based models [2]. AI models' statistical learning capability—iteratively identifying and learning patterns from large volumes of data—facilitates including more information to arrive at an optimal decision recommendation [3,4]. Despite the prevalence of AI-based CDS development [5], adoption has been limited [6,7]. A significant barrier to adoption is the high trust and safety requirement of health care applications that demand evidence on implications to the broader system and the clinical workflows across the care value stream [5,8,9].

The current state of reporting traditional statistical analysis and CDS development predominantly focuses on accuracy, sensitivity, specificity, goodness-of-fit, and other discrimination-related measures [3] that do not precisely measure patient-, provider-, process-, and cost-related outcomes. These metrics may not capture the actual clinical improvements or the broader consequences that may arise when implementing CDS within the clinical workflows. For example, such metrics may be limited or require calibration when considering context-specific tradeoffs in predictive accuracies. Preference may be higher sensitivity than specificity in different contexts, such as early screening. Conversely, an oversensitive screen may result in more resources needed for confirmatory testing [10]. Hence, the ability to simulate the impact of model calibration and thresholding decisions for downstream workflows and eventual outcomes may be beneficial, especially when provider and process resources could render any CDS-based recommendation impracticable.

Traditional assessments of the implications of health technologies, such as algorithm-based CDS, focus on generating clinical evidence through randomized controlled trials to balance assessment scope and feasibility [11]. However, such assessments are challenged by the following: (1) the need for continuous evaluation of impact both in the development stage [12,13] and when such systems are deployed [14,15], (2) the need for more robust evidence that accounts for variations among real-world care pathways—characterized by heterogeneous settings and patient populations [5,9,16,17], and (3) the cost of an expanded scope of assessment when considering a broader health care pathway or system [18] such as in the evaluation of bundled payments in health care pathways and value-based health care [19,20].

In silico methods that simulate real-world care pathways present an alternative to evaluate CDS at preimplementation while approximating real-world care pathway events, behaviors, disease states, and resource constraints. These methods enable an iterative analysis of different clinical workflow scenarios, addressing the need for continuous impact evaluation without significant resource demands and disruptions to ongoing usual care practice [11,21,22]. In addition, such methods allow for the integral consideration of practical constraints [11,23], such as when at-risk patients are correctly identified by a CDS but cannot receive the appropriate downstream interventions due to resource constraints [24,25]. The value of clinical workflow simulations as an alternative is put forward by the recent inclusion of preclinical evaluation of CDS in guidelines for academic research reporting. Specific to AI-based CDS, the development and exploratory clinical investigations of decision support systems driven by AI reporting guidelines strongly endorse the concept of preclinical or in silico evaluation—that is, via computer simulations before the first clinical trial [18]. Vasey et al [21] cite the development of other guidelines, for example, transparent reporting of a multivariable prediction model for individual prognosis or diagnosis–artificial intelligence [26,27] and standards for reporting of diagnostic accuracy study–artificial intelligence [28], that tackle the reporting of AI-based CDS evaluation at the preclinical stage. In addition, in silico modeling has been previously argued to be beneficial in drug discovery [29], surgical systems innovation [30], and biomedical product regulation [10], as it can address the trade-off between scope and resource demands existing in traditional impact assessments.

Evaluating CDS under uncertainty can leverage mathematical models that consider the inherent stochasticity of clinical workflows and systems, such as simulation models [22]. As decisions are often time-sensitive [31], simulations should also be dynamic. Discrete events simulation (DES) and agent-based models (ABM) are stochastic dynamic models frequently used [32]. These simulation models allow context-specific domain nuances to be captured in the model logic as discrete states, actions, and transitions, thereby capturing the unique characteristics and uncertainties that define clinical workflows across care settings and sites. Queueing, Markov, and other stochastic process models [22,33,34] are closely associated with these models. System-level workflow simulations such as those using DES [22] and ABM [35] can model intricate health care dynamics and are commonly applied to model clinical workflows in health service delivery. These methods facilitate comprehensive analyses encompassing patient journey, resource use, and stakeholder interactions, providing insights into operational efficiencies, bottlenecks, and unintended consequences of implementing automated decision-support

interventions. It offers a flexible method to capture the dynamic workflows in which the entities (ie, patients and providers) interact and are exposed to important clinical/process events (ie, admission and clinical decision) while consuming and releasing resources (ie, number of nurses in a hospital ward at a given time interval) [36]. By adjusting the decision thresholds, we can evaluate the CDS' impact using a variety of decision-analytic measures, for example, decision curve analysis [37] to determine the most clinically helpful prediction model.

Given the significance of such in silico evaluation via simulation models, a consolidated knowledge base will help to guide their use in evaluating CDS systems. Current research needs to be more cohesive, with disparate methodologies focusing on narrow facets of health care delivery [38,39]. To support the advancement of workflow-sensitive evaluation methodologies for CDS systems, we propose a scoping review protocol that investigates the following components of in silico evaluation: (1) the use of more pragmatic measures of impact that are relevant to the quadruple aims of health care [40,41], and (2) the simulation modeling paradigm used. Specifically, we propose a review protocol that (1) maps out the state-of-art development and application of in silico clinical workflows to evaluate algorithm-based CDS—both traditional statistical analysis- and AI-based—models and (2) identifies relevant research gaps. To our knowledge, this is the first scoping review on in silico evaluation strategies for AI applications in CDS using workflow simulation methods.

Methods

Overview

We followed the stages in a scoping review proposed in the Arksey and O'Malley framework [42] while considering more recent enhancements [43-45] for each stage. Specifically, we followed the steps of (1) identifying the research question, (2) searching and identifying relevant studies, (3) study selection, (4) data extraction, (5) collection, summarizing, and reporting of findings, and (6) consultation with stakeholders. These are detailed in the succeeding sections.

Stage 1: Identifying the Research Question

This scoping review endeavors to synthesize existing knowledge on the in silico evaluation of algorithm-based CDS systems via clinical workflow simulation methods. High-fidelity workflow simulations offer a pragmatic solution by allowing in silico replication of clinical processes, predicting the behavior of systems, and assessing the potential impacts of new models without risking patient safety or disrupting existing services [46]. To identify the scope of the review, we first conducted a rapid scan [45] of existing academic articles that discuss the evaluation of algorithm-based CDS. This review includes those using standards of care, knowledge bases, or AI to support a clinical decision recommendation [2]. In succeeding sections, these are generically referred to as CDS.

Regular team discussions were conducted to summarize findings and shortlist authors who publish peer-reviewed journal articles in our field of interest. Our study team comprises researchers with collective experience in machine learning model development, conducting systematic review studies, systems optimization research, and medical research and practice. The authors of this protocol—a senior clinician (QZ), a senior data scientist (SSWL), a junior data scientist (MD), and a junior pharmacoepidemiology researcher (YLC)—serve as the initial review team. After several initial iterations, we agreed on the research questions in Textbox 1. Further, we identified a list of concepts and accompanying keywords relevant to our main research question. These are presented in Table 1. Our focus lies in the exploration of simulation methods, particularly their application to clinical decision-making tasks. We aim to examine how these simulation models are developed, implemented, and evaluated. Additionally, we seek to identify gaps within the existing body of literature, specifically concerning the design and assessment of simulation-based approaches in health care.

Textbox 1. Main and specific research questions.

Main research question (RQ):

- What are the proposed in silico potential impact evaluation strategies for clinical decision support (CDS) systems?

Specific RQs:

- RQ1: What are the reported clinical decision tasks and domains that report the use of CDS?
- RQ2: What metrics are reportedly used for evaluating potential impact?
- RQ3: What simulation modeling paradigms are used?
- RQ4: What are the intended objectives of the simulation modeling frameworks used?
- RQ5: What are the gaps in existing literature of in silico CDS evaluation?

Table 1. Concept framework used in searching relevant articles.

Key concepts	Keywords
Clinical decision support models, algorithms, and systems	Machine learning, deep learning, artificial intelligence, reinforcement learning, supervised machine learning, unsupervised machine learning, semisupervised machine learning, self-supervised machine learning, expert system
Objective of the CDS[a] model	Clinical decision support, clinical decision-making, prognosis, diagnosis, screening, triage
Evaluation objective	Validation, potential impact, impact assessment, decision analysis, decision analytics measure, model calibration, model tuning, credibility, cost-benefit analysis
Evaluation strategy	In silico, computer simulation, digital twin, simulation, preimplementation, predeployment, computational simulation

[a]CDS: clinical decision support.

Stage 2: Identifying Relevant Studies

In identifying relevant studies, we first conducted an automated search dated May 2023 of medical (PubMed, Embase, CINAHL, PsycINFO, and Cochrane), open-domain (Web of Science), engineering (IEEEXplore), and preprint (arXiv) academic articles databases using keywords from Table 1 generated during stage 1. Including preprint and engineering databases allows the search to extend to perspectives outside of the medical domain. The arXiv preprint archive was searched to account for more recent articles currently unavailable in peer-reviewed publication databases [47]. Duplicated articles and articles found in the preprint archives that were published will be removed from the pool of potential studies.

We undertook a pilot review on a manageable sample of the more relevant studies to refine the search strategy. The pilot review process allows us to refine our inclusion and exclusion criteria further. The pilot review team comprises at least one senior clinician and a senior data scientist with relevant health care domain experience to guide the construction of search strings—these were refined in a series of team discussions in consultation with a medical librarian. Multimedia Appendix 1 provides details of the source database-specific search strings used for each concept, as shown in Table 1. Differences in search strings are due to discrepancies on what databases can accommodate in a search (eg, wildcard characters may be adapted in some but not in others, and databases may vary in the type of subject heading indexing used). Two junior researchers (MD and YLC) collated the pool of articles identified from these search strings.

Stage 3: Study Selection

A 2-step screening procedure was adopted here—a title-abstract screening followed by a full-text screening was conducted for the articles identified from stage 2. Two reviewers independently screened the articles using the criteria presented in the succeeding paragraphs. The articles' titles and abstracts (ie, step 1 screening) and the full text (ie, step 2) were the basis for screening. The criteria for study selection are continuously revised through regular meetings. The reviewers arrange meetings to resolve any disagreements. The senior reviewers in the study team are consulted to reach a consensus when screening conflicts arise. According to the proposed guidelines for scoping reviews [48,49], we report the article search and screening results in a PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews) [50] flow chart shown in the results section.

Our review included the following studies: (1) studies that directly support clinical decision-making specifically for diagnostic, triage, screening, prognostic, and prescriptive purposes; (2) studies that use AI, computer-executed algorithms, machine learning, and traditional statistical multivariate techniques; (3) risk prediction models for a disease condition or a future health outcome; (4) studies that assess CDS models in predeployment stage for its potential impact; (5) studies that propose the use of simulation-based optimization during model development; (6) human studies; (7) experimental or observational studies—including prospective, retrospective, and ambispective studies, clinical trials, pragmatic clinical trials, and validation studies; (8) studies that are published in journal articles, conference proceedings, and preprint archives; (9) studies written in English with no constraints on the year of publication; and (10) risk prediction models for a disease condition or a future health outcome.

We excluded the following studies: (1) studies that do not involve clinical domains as prediction outcomes; (2) studies that focused on the use of AI as therapy (eg, treatment monitoring and glucose control systems); (3) studies that use machine learning, pattern recognition, AI for descriptive analysis; (4) pathological specimen and sensing device signals accuracy-related studies; (5) image segmentation/registration only without classification/prediction with clinical end points; (6) studies that deal with purely system/population level outcomes that are irrelevant to patient-provider interactions; (7) pure qualitative evaluation for clinical usefulness; (8) purely methodological papers on medical data processing (eg, image processing and noise filtering) without specific application domain; (9) studies that use purely ex silico evaluation typically require either a partial or complete deployment of the developed CDS system (eg, randomized controlled trials for actual impact assessment); (10) studies that only use traditional metrics—for example, area under the receiver operating characteristic curve, area under the precision-recall curve, mean squared error, accuracy, sensitivity, specificity, goodness-of-fit, and other discrimination-related measures only—to validate CDS models, systems, and tools, that is, those studies that do not consider broader systems-level usefulness; (11) studies that do not report model development process (eg, proprietary CDS tools or systems) as these do not disclose sufficient information about

underlying technology and algorithms; and (12) studies which report reviews (eg, scoping reviews, systematic reviews, and rapid reviews).

As our primary aim is to exhaustively review the published potential impact evaluation strategies done in silico for CDS, literature or scoping review studies were excluded. No other articles were excluded based on the year of publication. Deduplication was done using Zotero [51].

Stage 4: Data Charting

Overview

Data charting will collect critical information to answer the research question for the articles extracted from stage 3 after the 2-step screening process. An a priori list of coding variables corresponding to this study's concept framework and research questions has been developed (Table 2). Reporting [52,53] and data extraction [54] guidelines related to the concept framework guided the selection of coding variables to be extracted from the screened article database. As studies may or may not conform to these guidelines, and new categories and subcategories may be derived from the literature, the a priori coding variables may change. The emergent categories and subcategories will be checked for co-occurrences (overlapping concepts) and redundancies. Codes with the same concepts will be aggregated and refined to maximize mutual exclusivity and exhaustiveness. Aside from these structured coding variables, we shall also extract general information about the articles as guided by related published review protocols [55-57].

The data charting form will be developed in a shared collaborative Notion.so [58] database with the structure in Multimedia Appendix 1. The form was designed and maintained by an arbiter who ensures it is comprehensive and flexible. The charting process will be initially blinded. As with the article screening, we conducted a pilot charting trial to validate the encoding items. Each researcher can only see their respective chart to facilitate independent charting. An initial charting form is presented in Table 2. Team discussions were held as the team progressed in the charting process to consider other items to extract. At least 2 reviewers will be assigned to each article for validation. Any discrepancies will be resolved together with the entire team for the final determination of the charted codes. After the pilot trial, all articles included from stage 3 will undergo charting, resulting in an encoding database for this review.

Table 2. Data extraction items.

Data extraction broad concepts	Specific items extracted
Characteristics of the studies included	• Publication year • Research location (ie, country) • Data source • Data collection design • Collection period • Patient cohort description
Decision-making objectives and end points	• Objective of the CDS[a] model (ie, triage, diagnostic, prognostic, and prescriptive) • Specific decision-making tasks assisted by CDS • Clinical domains
In silico[b] evaluation metrics	• Specific evaluation metrics • General themes of the metrics (ie, patient, process, provider, and cost-effectiveness outcomes)
In silico evaluation frameworks	• Simulation modeling paradigm • Simulation modeling objective • Simulation parameters (parameters and parameter groups) • Reported reusability • Access to codes and tools used to conduct the simulation

[a]CDS: clinical decision support.

[b]Evaluations via computer simulations of clinical workflows during preimplementation.

Characteristics of the Studies

We include any study that reports the development of an expert system, a computer-aided clinical decision-making tool, or CDS with an underlying rule base or machine learning—including supervised, self-supervised, and unsupervised methods; deep learning; and reinforcement learning. We also include the more traditional multivariate analysis-based CDS such as linear, logistic, and Cox regression approaches to clinical scoring systems and prediction rules [38]. We encode the type of methods or algorithms used, their reported advantages (ie, aside from empirical performance reported), the disadvantages of the method, and their dependencies on data and the population from which the data was collected, as reported by the study authors. We also collected information about where the research was conducted and the year of publication.

Decision-Making Objectives and End Points

Since CDS model outcomes are directly related to its intended task and use, it is necessary to understand the scope of the desired outcomes from the predictions for an objective potential impact assessment. The development and use of clinical rules predate AI-based CDS. The outcomes of these clinical rules are broadly classified into diagnostic, prognostic, and prescriptive

outcomes [52,54,59]. We adopt this same classification for AI-based CDS. Diagnostic outcomes generally predict the risk for a particular condition or disease (based on existing health data) to support early intervention or screening decisions. Prognostic outcomes indicate the future course of an illness or disease, including the likelihood of recovery, quality of life, complications, or mortality. Some CDS studies may prescribe treatment beyond diagnosis or prognosis end points [1,59]. Guidelines for reporting [52,53] and appraisal [54] prediction models mention a comparable taxonomy of CDS outcomes. Another reporting checklist for studies that use AI in medical imaging CDS differentiates the intended use (eg, diagnosis, screening, and staging) with the tools' proposed role (eg, triage, replacement, or add-on) [60]. We shall consider these classifications in our analysis.

In Silico Evaluation Metrics

We explore methods to evaluate CDS' potential impact in silico on clinical workflow operations, patient outcomes, and economic outcomes [5]. Our aims take inspiration from the renewed focus of health care towards the Quadruple Aims, which adds the well-being of care providers as a fourth dimension, in addition to the traditional aims of improved patient experience, better health of populations, and cost reduction [41,61]. This underscores the need to devise workflow-sensitive evaluation methods, for example, considering how CDS sustains service providers' productivity (eg, referral rates as a process metric) within a resource-constrained care pathway. Further, we consider how reported studies propose the measurement of potential impact on patient health beyond the traditional accuracy-related measures [38], such as net benefit [62], realized [24] net benefit, and length of stay [63]. Some studies examine how implementing CDS systems impacts hospital budgets, with related metrics including costs and the incremental cost-effectiveness ratio [64]. More broadly, these metrics may be used to validate potential impact across different periods and study sites; this allows the monitoring of CDS performance consistency and the prompt triggering of model updates when necessary [15].

In Silico Evaluation Frameworks

Simulation modeling is a powerful tool for analyzing complex systems by creating representations that mimic the real world. It allows researchers or decision-makers to study how the system will behave over time prior to the actual deployment. Different simulation methods can be characterized by specific attributes, such as discrete or continuous, static or dynamic, and stochastic or deterministic [32]. A discrete simulation models the state of the system at distinct time points. For example, the number of patients in the waiting room only changes when a patient arrives. In contrast, a continuous simulation models the parameter that changes over time regardless of any triggers that change the state of the parameter. A static simulation models the system only at a specific time point, while a dynamic simulation studies the system's evolution over time. Last, a stochastic simulation involves randomness where simulation parameters can be probabilistic. For example, the patient arrival times may follow a specific distribution. However, a deterministic simulation encompasses parameters that have specific values. For instance, if the simulation sets the number of patients per time interval to 10, the value of such a parameter will stay at 10 throughout the simulation.

Our study focuses on existing research that reports using workflow simulation methods to assess the potential impact before embarking on often challenging and costly actual impact assessment. In silico evaluation can provide a more robust basis for successful implementation trials. As such, we consider studies that evaluate AI tools through an in silico approach without the need for actual deployment. Strategies may use reinforcement learning that optimizes a policy for multiple stages of decision-making (ie, such as machine learning–assisted treatment selection) [65]. Another approach may model a clinical care pathway as a discrete set of states and transitions [25], namely, DES, a popular method in health care workflow simulation to study resource allocation as it incorporates how resources change according to triggering events [36]. Another method, ABM, is particularly useful for modeling the interactions between various entities (ie, health care workers) in a clinical workflow [11]. Studies may also use a retrospective evaluation using cross-validation and decision curve analysis [24,62,66] to measure a decision-analytic score. As data extraction proceeds, we shall consider the more precise taxonomy of the simulation modeling [32] while broadly accounting for other in silico approaches, such as the examples. Other paradigms used will be encoded and reported as they arise.

We further consider the intended purpose of simulation, that is, the simulation modeling objective, which may fall under 1 of the three initial categories: (1) to conduct a straightforward measurement of clinical usefulness metrics, (2) to analyze the sensitivity of outcomes to various workflow parameters and scenarios, and (3) to optimize decision-making capability of CDS via a care pathway simulation.

Last, we consider the parameters used to construct the in silico clinical workflow. Specifically, we shall evaluate how patient, provider, process, and cost considerations are represented as simulation parameters. These clinical workflow factors describe the real-world care pathway, including patient condition states, treatment or intervention events, resource availability, duration of events, and many other factors.

Stage 5: Collection, Summarizing, and Reporting of Results

We will collect the data in a table of values corresponding to each variable (ie, column) and each relevant article (ie, row). An analysis of the values extracted will be done to identify sparse- and well-studied themes within and across critical concepts. Frequency and thematic analysis will be used for this analysis [44,67]. Themes combined with the extracted textual information will allow for the study of trends. Univariate and multivariate statistics will be reported as deemed relevant for each type of analysis. Descriptive statistics and charts will be used to describe the characteristics of the included study across the variables listed in Table 2. When appropriate, ANOVA, Kruskal-Wallis, and Pearson chi-square tests will compare trends across different categories. The association of variables based on co-occurrence will also be investigated. Further, the

reusability of any software artifacts or code repositories associated with included studies will be reported according to the claims of the articles' respective authors. The reporting of results will follow the PRISMA-ScR guidelines [50].

Stage 6: Dissemination and Stakeholder Consultation

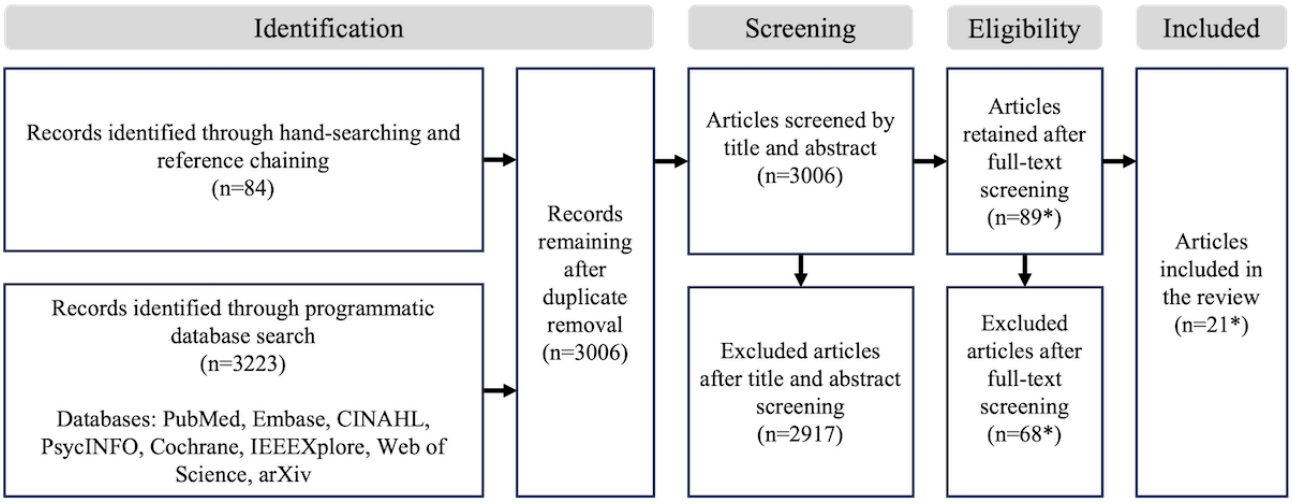
Beyond summarizing the results and findings, we will consider the overall implications of the findings for the in silico potential impact assessment of algorithm-based CDS systems, models, and tools. This scoping review will support the development of a draft framework that will guide clinical workflow simulation modeling for impact assessment, with specific considerations on the model purpose, evaluation scope, objectives, and strategy. This framework will further support the in silico evaluation of proposed CDS studies collected through discussion with potential stakeholders—implementation scientists, modelers, and clinicians conducting. This will also allow stakeholders to provide a higher level of interpretation, domain expertise, and perspective to validate the findings further and support effective knowledge transfer and uptake of evidence to ensure the usefulness of the scoping studies for AI developers and clinical researchers [43].

Results

Our review began with an automated search of selected databases in May 2023. The resulting articles were managed using Zotero [51] and Notion.so [58] for automated article metadata collection and note-taking, respectively. Most of the title and abstract screening were finished by November 2023. However, the review team allows for flexibility as the screening criteria are refined throughout the review. Full-text screening proceeded from December 2023 to May 2024, including hand-searching and reference chaining. Charting was concurrently done with the full-text screening. Analysis and writing of the full scoping review results will be finalized in July 2024. The reporting of this scoping review protocol and results as published literature will be from July 2024 to February 2025.

The current stage of our scoping review yielded the results shown in Figure 1. At the first screening stage, most articles were excluded based on titles and abstracts that did not fulfill the inclusion criteria. Moreover, we also excluded at this stage studies that suggest the development of CDS tools but only perform an evaluation using the area under the precision-recall and receiver operating characteristic curves, accuracy, precision, recall, F_1-score, and other traditional confusion matrix-based scores; further, these were studies that do not attempt to evaluate potential impact and usefulness to its intended clinical care pathway placement [38]. Additional studies were also excluded due to the focus on algorithmic developments in processing medical data (ie, image, text, and structured data). On the contrary, articles that mention usefulness and impact evaluation without providing further details in the title and abstracts were included in the full-text screening.

Figure 1. PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews) flowchart. Asterisk (*) indicates data as of April 2024.



In the second stage of the detailed full-text screening (ie, using the full text as the basis), more articles were excluded due to the lack of potential impact and usefulness evaluation. Other articles were excluded as duplicates not detected in the initial automated deduplication based on article metadata. A few articles were also excluded due to unavailable full text, as only extended abstracts were published. As this stage is ongoing and considering that reference chaining may still be conducted based on the screened articles, the final number of relevant articles will be reported along with the scoping review results. As of April 2024, 21 articles are included in the review.

Discussion

Principal Findings

The proliferation of AI models in health care encourages researchers, patients, and providers to use these technologies to optimize the care delivery processes. Yet, only some models are being translated into clinical practice [6]. The ability of data-driven machine learning methods to generalize to different temporal and geographical patient cohorts is challenged by often changing real-world medical data [17]. This demands more robust and adaptive approaches to encourage user acceptance and trust [12,13,16]. Traditional impact assessments based on

pilot implementation for health technology assessment can be resource-intensive with the rapid proliferation of new models [68,69]. The in silico evaluation of algorithm-based CDS provides a resource-efficient framework for estimating novel CDS' potential clinical impact to facilitate the seamless integration of a model into the workflow. Moreover, computer simulations require much fewer resources and have less direct implications for ongoing patient care, allowing for regular and repetitive use throughout the CDS development and maintenance lifecycle. Our review aims to analyze and report the scope of using in silico CDS evaluation in published academic literature. We expect that the results will uncover the clinical decision-making domains where such evaluations are used or, otherwise, underused, how clinical workflows are simulated, the potential impact metrics used to illustrate the usefulness of CDS, and areas where more research is necessary.

Several US Food and Drug Administration–accepted patient simulators [70,71] and other approaches [30,68] that simulate patient characteristics enable an in silico evaluation of patient-level impact and have been proposed to be used at a preclinical stage. These simulators allow the assessment of the response to different treatments by the same patient—which is unlikely in real-world treatment scenarios due to dynamic patient conditions. Comparably, clinical workflow enables simultaneous evaluation of various scenarios using the same patient cohort characteristics, sharing the same validation capabilities and objectives [72,73]. However, clinical workflow simulations encompass a broader perspective, considering the efficiency and effectiveness of treatments and interventions, such as CDS, across the entire care pathway.

In a preliminary collection of included articles, the broader perspective was demonstrated by the accounting for process-related factors. For example, time intervals (ie, door-to-doctor time) between workflow events were considered by Alenany and Cadi [63] as an evaluation metric. Misic et al [23] and Rodriguez et al [74] focused on patient volume and referral rates to evaluate workflow throughput. In addition, other studies simultaneously assess patient outcomes with cost-related outcomes, such as length-of-stay and costs per visit [75], early-stage cancer detection rate and cost savings [76], and intensive care unit length-of-stay and corresponding costs [77]. Yin et al [5] highlighted that in the real-life evaluation of AI applications, the outcomes considered can be grouped into patient, cost-effectiveness, and clinician outcomes. We consider this in our review and propose distinguishing between provider, that is, clinician outcomes and process outcomes [22], expanding the outcome themes into 4 categories.

Furthermore, similar themes can also be applied to categorize clinical workflow factors, that is, parameters, used in the design of an in silico care pathway. Lee et al [35] considered time intervals between events as simulation parameters. Other studies [23,25] used provider-related parameters such as provider effectiveness and carrying capacity. Other studies simultaneously consider patient-, cost-, and process-related outcomes—such as in [35,77]. These parameters are typically based on historically observed data distributions, expert judgment, cited from published literature, or determined from prospective time-motion studies. We will report such a basis for parameter initialization accordingly.

The interplay of multiple outcomes and drivers and the expansion of health care also aim to consider provider well-being, which adds to the complexity of impact evaluation. Different simulation modeling paradigms are proposed to handle such complexity—such as in the DES frameworks used by [25], the ABM done by [35], and state-transition models shown in the microsimulation by Rodriguez et al [74], and in the Markov-based transition model used in [78] evaluating wait time–saving effectiveness of an AI-based CDS. Moreover, dynamic treatment regime optimization is proposed to capture staged treatment scenarios and optimize outcomes [65]. Last, considering cost-effectiveness approaches, decision trees can also be used to capture costs and benefits attributed to a hierarchical decision-making scenario; this is demonstrated by Tsai et al [77] to evaluate an extubation failure prediction CDS.

While extensive literature on the usefulness of simulation modeling and knowledge of the simulation of clinical care pathways as avenues for CDS in silico evaluation still lack consolidation [79], possibly due to the significant context dependencies across different health systems. When translated into a quantitative modeling framework for rigorous, objective evaluation, the diversity, human-centricity, and complexity of clinical workflows pose unique challenges [18]. Addressing these challenges requires interdisciplinary groups familiar with hospital management, clinical context, process nuances, and the availability of necessary modeling capabilities. Despite the prevalence in the reported development and advancements of CDS models, accelerated by the surge in AI methods—studies that reported the extent of clinical and workflow impact through in silico evaluation are still relatively sparse [5,6]. A critical need remains to reassess the current model simulation practices to advance this field. We believe this will expedite the integration of novel CDS system development. To the best of our knowledge, this is the first review that aims to understand CDS system in silico evaluation methods beyond traditional accuracy metrics.

Conclusion

This scoping review follows the framework proposed by Arksey and O'Malley [42] and other recent enhancements [43-45]. We searched 8 medical-focused and general academic domain databases to gather articles from an interdisciplinary perspective. An automated search followed by a 2-step screening process was done to implement the scope of the review. Unlike previous reviews, we will specifically include CDS related to traditional multivariate models and machine learning. In addition, we designed a data charting table based on discussions with the multidisciplinary review team and previous reviews on related topics. This table will guide the data extraction phase, and the items will be flexibly revised along with further study of the included articles. Finally, we plan to summarize our results using descriptive and co-occurrence analyses. For example, the distribution of race and ethnicity of collected patient information—as reported by the included articles—will show how fairness is represented in current AI research in health care. Similarly, an analysis of co-occurring themes (ie, in statistical

analysis methods, CDS decision-making tasks, evaluation metrics, and simulation paradigms) may surface clinical domain-specific and domain-agnostic approaches to in silico potential impact evaluation.

We anticipate our results will be informative about the state-of-the-art in silico evaluation method based on workflow simulation models and the associated outcome metrics and targets. More specifically, our results will describe the characteristics of the clinical decision-making domains being modeled, the relevant measures of impact that are simulated, and how such are captured in clinical workflow simulation. As we also aim to report the reusability of methods cited, our work will serve as a springboard for the reader to find suitable in silico evaluation frameworks, software artifacts, and code repositories. Ultimately, our work is a starting point in developing a unified in silico evaluation framework adaptable to various clinical workflow scenarios.

Limitations

There are several limitations to our approach. First, while some guidelines for reporting may exist, they may need to be revised to cover the variety of studies in our criteria. For example, a transparent reporting of machine learning models developed for diagnosis, prognosis, or prescriptive analytical support is still being developed [27], and conformance to these guidelines may influence the extent and precision of our data charting. Second, a critical appraisal of articles will not be done as we primarily aim to provide an overview of the scope by which in silico evaluation methods have been used. Third, we also included reports from e-Print archives (arXiv), trading off a more exhaustive scope versus the inclusion of non–peer-reviewed articles; an accounting of such articles will be provided in the reporting results. Last, we included only English articles; thus, we cannot extrapolate our findings to publications in different languages. Our findings will add to the knowledge of applications of statistical learning and simulation methods in health care.

Acknowledgments

We want to acknowledge He Yan for her valuable comments on the data charting forms and thank Ginny Chen Zhenzhi for taking on the project management required to move this research forward.

Data Availability

All data generated or analyzed during this study are included in this published article and its Multimedia Appendix files.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Supplementary material showing the keywords used and other details of the literature search, including a sample encoding sheet that uses Notion.so.
[DOCX File , 611 KB - resprot_v14i1e63875_app1.docx]

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Abbreviations

ABM: agent-based models
AI: artificial intelligence
CDS: clinical decision support
DES: discrete events simulation
PRISMA-ScR: Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews

Edited by A Schwartz; submitted 04.07.24; peer-reviewed by YLE Thompson, M Popovic; comments to author 06.09.24; revised version received 30.09.24; accepted 09.10.24; published 16.01.25.

Please cite as:
Dorosan M, Chen YL, Zhuang Q, Lam SWS
In Silico Evaluation of Algorithm-Based Clinical Decision Support Systems: Protocol for a Scoping Review
JMIR Res Protoc 2025;14:e63875
URL: https://www.researchprotocols.org/2025/1/e63875
doi:10.2196/63875
PMID:

Protocol

Digital Teaching and Learning Media for Nursing and Health Care Courses in Germany: Protocol for a Scoping Review

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Abstract

Background: In Germany, digital transformation and legal regulations are leading to the need to integrate digital technologies into the nursing profession. In addition, to nursing practice, they are also being incorporated into nursing training. Despite comprehensive regulations regarding the use of digital teaching and learning media in nursing education, their specific applicability and implementation vary.

Objective: This study aims to map evidence and identify the main concepts, theories, sources, and knowledge gaps in the use of digital teaching and learning formats in nursing and health care education in Germany.

Methods: The study is planned as a scoping review. The reporting of the study is based on the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) 2020 guidelines. The sources of information for the review include six bibliographic databases (MEDLINE via PubMed, Cochrane Library, Web of Science Core Collection, ERIC, PROSPERO, and APA PsycInfo). The search results will be presented in accordance with the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews) checklist. The eligibility of studies is based on the population, concept, and context criteria: (1) learners of nursing and health care professions, (2) digital teaching and learning formats, and (3) forms of implementation in Germany since 2007.

Results: The literature search is planned for January 2025. The selection of titles, the coding of the data, and the data analysis are expected to be completed by March 2025.

Conclusions: In Germany, there is a growing interest in integrating digital teaching and learning formats into nursing and health care education. Our scoping review will map applications of digital teaching and learning media in the education of nursing and health care professions in Germany. In this way, the scoping review provides relevant impulses for fields of application and design aspects of digital teaching or learning media for nursing and health care education.

International Registered Report Identifier (IRRID): PRR1-10.2196/60427

(JMIR Res Protoc 2025;14:e60427) doi:10.2196/60427

KEYWORDS

digital education; digital learning; digital teaching; e-learning; nursing; health care; digital transformation; digital technology; online learning; distance learning; health care education

Introduction

Background

The idea of learning with machines is not new. Back in the 1920s, Sidney L Pressey developed a machine that asked a question and offered four possible answers, like the multiple-choice method [1]. Nowadays, digital technologies are used to create and provide learning materials and to support and control the learning process [2]. In this context, the term “e-learning” describes all forms of learning with electronic or

digital media [3]. The introduction of the iPhone in 2007 has been an international milestone in the development of e-learning [3,4]. Mobile devices create the conditions for innovative pedagogical approaches such as flipped classrooms or blended learning, by using modern technologies and various teaching methods to make learning more effective and personalized. In corresponding teaching and learning approaches, the time, place, pace, and scope of learning can be freely chosen [2], giving learners more autonomy and control over their individual learning process. A major advantage of mobile devices is that learners often already possess the necessary technical equipment [5]. The digitalization of nursing and health care education is considered to have particular potential due to the complexity of professional requirements and the constant further development of subject-specific knowledge [6,7]. In addition to the relevance of digital teaching and learning formats in nursing and health care education, there is also a need in Germany to incorporate digitalization into health care professional education. This arises from legal regulations such as § 8 Abs. 8 SGB XI or the E-Health Act, which are intended to promote the digitalization of professional practice and require corresponding skills on the part of nursing professionals. The digitalization of health care professional practice is intended to improve the quality of care and effectively prepare professionals for highly complex care situations, which should ultimately lead to better care outcomes for patients [8-10]. In addition, the topic of digitalization can be found in the new legal foundations of the Act on the Nursing Professions (Pflegeberufegesetz, PflBG), the Training and Examination Regulations for the Nursing Professions (Ausbildungs- und Prüfungsverordnung für die Pflegeberufe, PflAPrV) and the framework curricula and framework training plans. These foundations list forms of digital support for various parts of the nursing process.In this regard, there is a need to develop and integrate digital teaching and learning formats for nursing and health care education [6,11].

Objectives

In Germany, there are increasing efforts to integrate digital teaching and learning formats into nursing and health care education. This fact leads to the question, for which educational content and didactic concepts digital teaching and learning formats are used in nursing and health care education in Germany? Furthermore, which scientific findings are present about the use of digital teaching and learning formats in nursing and health care education in Germany? Thus, our main objectives are (1) digital teaching and learning formats and (2) forms of implementation in the context of learners in the nursing and health care professions.

Methods

Study Design

We conduct a scoping review [12,13] in consideration of published primary sources and reviews. All study designs with the exception of opinion studies, commentaries, editorials, letters to the editor, and pure case reports are considered in order to gain a broad overview of the research field. We operationalize the research question by using the population, concept, and context (PCC) scheme [14]. The population includes learners in the nursing and health care professions, the concept focuses on digital teaching and learning formats, and the context refers to forms of implementation in Germany since 2007. Study reporting is based on the PRISMA-ScR (Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews) [15]. The PRISMA-ScR checklist will be available once the review is complete.

Patient and Public Involvement

Patients and the public are not involved in the design of this protocol. Thus, ethics approval is not required for the scoping review.

Eligibility Criteria

The eligibility of studies is based on the PCC criteria: (1) learners of nursing and health care professions, (2) digital teaching and learning formats, and (3) forms of implementation in Germany since 2007. The scoping review aims to map evidence and identify the main concepts, theories, sources, and knowledge gaps in the use of digital teaching or learning formats in nursing and health care education in Germany. The electronic search is conducted in German and English. Only titles, which are published since 2007 will be included because the iPhone was released for the first time in 2007, which enables new forms of learning and represents an international milestone in the development of e-learning [3,4]. Since this introduction, research into e-learning using mobile devices has increased.

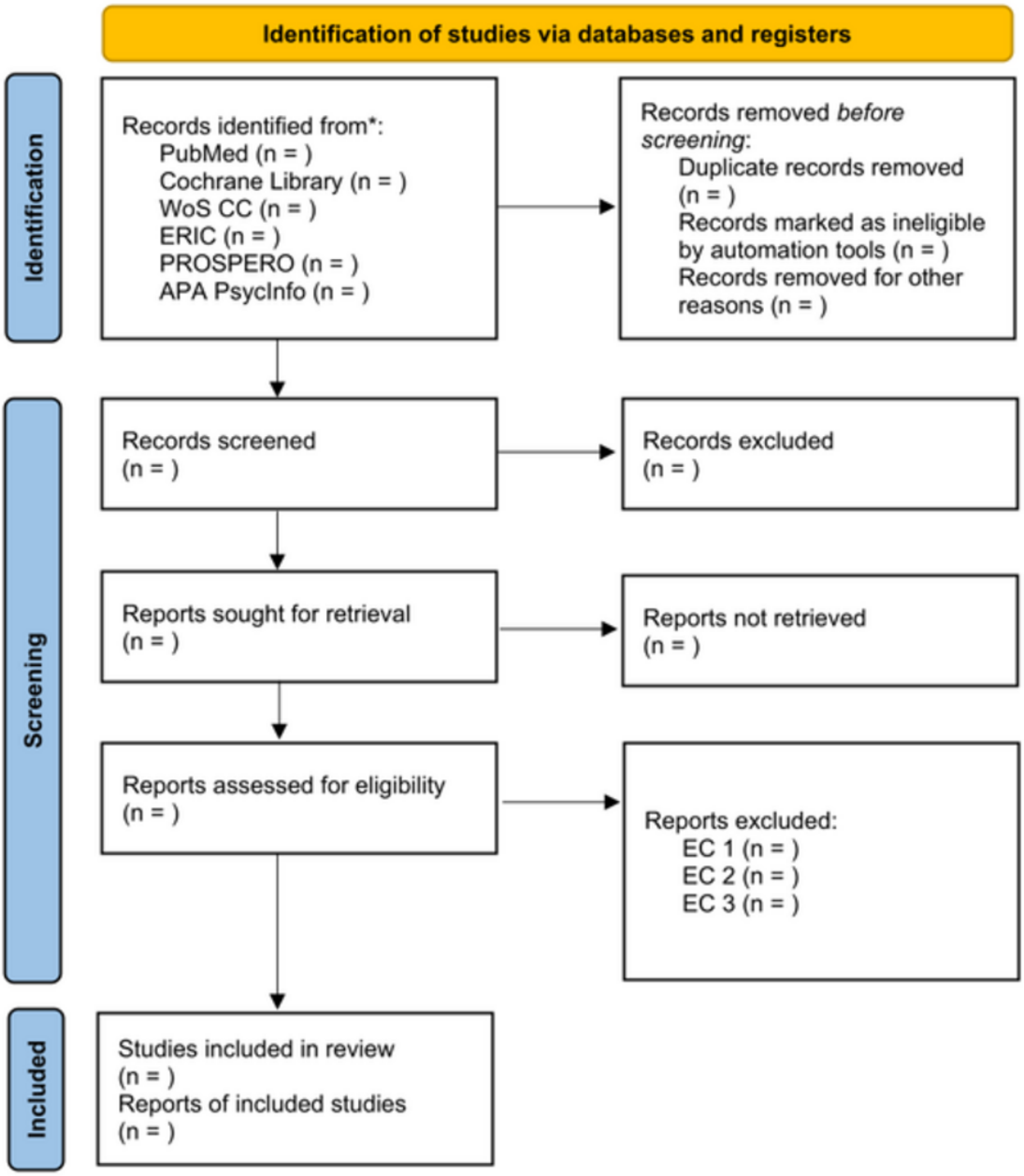
Information Sources

The information sources for the scoping review will include six bibliographic databases (MEDLINE, Cochrane Library, Web of Science Core Collection, Education Resources Information Center [ERIC], PROSPERO, and APA PsycInfo). The starting point will be the search in MEDLINE via PubMed as the central database for scientific studies in the health professions. The PubMed search supports the generation of suitable mesh terms for the research question and is adapted to the databases Cochrane Library, Web of Science Core Collection, ERIC, PROSPERO, and APA PsycInfo [16]. The Cochrane Library provides access to up-to-date and reliable research, which is further complemented by the PROSPERO database as a repository of systematic reviews. ERIC covers the educational discourse on the question and Web of Science Core Collection bundles the vocational education and health care focal points of the question in a database. These focal points are further supplemented and completed by research via APA PsycInfo, which contains peer-reviewed journals, studies, books, and dissertations on learning and teaching methods in health care, including nursing didactics.

Search Strategy

The electronic search strategy will be developed iteratively by the team. The search was based on the PRISMA 2020 statement (Figure 1) [17,18]. The search terms and corresponding MeSH (Medical Subject Headings) terms will be derived to address the two main search topics of the scoping review: (1) digital teaching and learning formats and (2) forms of implementation in the context of learners in the nursing and health care professions.

Figure 1. PRISMA-ScR 2020 flow diagram (source: own illustration, adapted from Page et al [17], licensed under CC BY 4.0 [18]). EC: exclusion criteria; EC 1: lack of reference to nursing and health care education; EC 2: no reference to digital teaching and learning formats; EC 3: no reference to the research question. ERIC: Education Resources Information Center; PRISMA-ScR: Preferred Reporting Items for Systematic Reviews extension for Scoping Reviews; PROSPERO: International Prospective Register of Systematic Reviews; WoS CC: Web of Science Core Collection.



Selection of Sources of Evidence

Two researchers will search in mentioned databases independently of each other using the search strings and will check all studies for relevance and suitability. After screening, two researchers will compare the search results. Any contradictions or inconsistencies in the study assessment will be clarified through discussion. Studies that met the inclusion criteria will be used for the full-text evaluation. This will also be carried out by two researchers. If necessary, we will contact the authors to obtain further information. The study selection will be concluded with a consensus meeting. Afterward, the data for each included study will be extracted by using a self-developed form in Excel (Microsoft Corp). The results of the literature search will be reported in full once the scoping review is complete. A list of included and excluded studies following full-text screening and individual reasons for exclusion will be reported once the review is complete.

Data Charting

We will develop an Excel form for coding and recording all data. Two authors code all data independently of each other. The agreement between the codings is calculated using Cohen κ. If necessary, authors will be contacted to obtain further information. A consensus meeting is supposed to conclude the study selection.

Synthesis of Results

We plan to use qualitative content analysis to form categories in an inductive-deductive alternation [19]. In inductive category

formation, categories are derived directly from the material [20]. Deductive category formation defines the categories before the data analysis [20] and refers to the used PCC scheme. This is categorized into setting, digital teaching, and learning format, as well as application formats. The coded data will be summarized in a table and then synthesized using descriptive statistics (relative frequencies).

Results

The literature search is scheduled for January 2025. We expect to select the relevant studies, code the data, and appraise the studies until March 2025.

Discussion

Principal Findings

Preliminary literature searches have shown that various digital technologies are used in nursing and health care education in Germany, including learning programs, learning platforms [6], and virtual reality technologies [21]. Our scoping review will include a detailed list of such applications once the studies have been selected. We will assess the outcomes of such digital technologies in the context of nursing and health care education in Germany. The most interesting aspect of our review will be application areas and requirements, as well as trends in digital nursing and health care education in Germany.

Comparison to Prior Work

Various digital learning methods have been widely implemented in nursing and health care education. Kimura et al [22] identified interactive online modules and videos as the most frequently used technology-enhanced tools in nursing education. The application period of digital learning formats in nursing and health care training varies [23,24]. Despite the positive associations, the potential of digital teaching and learning is by no means undisputed or proven. For example, the review by Bajpai et al [25] describes a lack of evidence regarding the effectiveness of digital interventions for the training of health care professions. Furthermore, Arkorful and Abaidoo [26] noted potential drawbacks, including reduced interactivity in e-learning environments. Other studies indicated that the achievement of intended learning outcomes through digital teaching or learning media for nursing and health care professions is influenced by variables such as age, training time, and experience of the participants [27,28]. While these findings are valuable, their direct applicability to the German education system is limited, underscoring the importance of examining country-specific implementations of digital education. In this regard, the literature indicates that there are gaps in the implementation of digital media in nursing education [6,29-31]. Our scoping review contributes to this gap by mapping applications of digital teaching and learning media in the education of nursing and health care professions in Germany.

Strengths and Limitations

This protocol has been rigorously developed and the electronic search syntax was iteratively tested and revised by the authors. Scoping reviews, like this study, contain potential biases in the selection of criteria, the search methodology, and the data analysis. Just German and English-language publications in selected databases will be included. The inclusion of other languages, databases, and additional search terms could lead to an increase in literature sources. Especially regarding the background of the heterogeneous study situation, the methodology of the scoping review is relevant to gain a broad perspective of the use of digital teaching and learning media in nursing and health education in Germany. Nevertheless, the possibility of inaccuracies in a combined interpretation exists.

Implications for Practice and Dissemination Plan

Findings from the scoping review could be of interest to various stakeholders, including educational institutions, researchers, health professionals, policy makers, and companies developing digital teaching and learning media. Therefore, the results of the review should be published in a peer-reviewed journal.

Conclusions

Our scoping review maps areas of application of digital teaching and learning methods in nursing and health education in Germany. In addition to the topic areas, the technical implementation methods and the didactic design should also be shown. The findings could be used to establish and expand digital teaching and learning methods in nursing and health care professional educational institutions, especially in Germany.

Acknowledgments

This review was part of the study “Digital Training of Nursing and Health Management” (DigiCare, ESF/14-BM-A55-0021/19). We acknowledge support for the Article Processing Charge from the German Research Foundation (Deutsche Forschungsgemeinschaft [DFG], 491232355) and the Open Access Publication Fund of the Neubrandenburg University of Applied Sciences (Hochschule Neubrandenburg).

Data Availability

This scoping review will be based on previously published data. The datasets generated during or analyzed during this study are available from the corresponding author upon reasonable request.

Conflicts of Interest

None declared.

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Abbreviations

APA PsycInfo: American Psychological Association PsycInfo
ERIC: Education Resources Information Center
MeSH: Medical Subject Headings
PCC: population, concept, and context
PRISMA-ScR: Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews

Edited by T Leung; submitted 10.05.24; peer-reviewed by GRM La Rosa; comments to author 22.07.24; revised version received 30.08.24; accepted 27.11.24; published 17.01.25.

Please cite as:
Vogel JN, Letzin J, Schmidt S
Digital Teaching and Learning Media for Nursing and Health Care Courses in Germany: Protocol for a Scoping Review
JMIR Res Protoc 2025;14:e60427
URL: https://www.researchprotocols.org/2025/1/e60427
doi:10.2196/60427
PMID:

Protocol

Applicability of Retrospective and Prospective Gender Scores for Clinical and Health Data: Protocol for a Scoping Review

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Abstract

Background: Gender is known to have a strong influence on human health and disease. Despite its relevance to treatment and outcome, gender is insufficiently considered in current health research. One hindering factor is the poor representation of gender information in clinical and health (meta) data.

Objective: We aim to conduct a scoping review of the literature describing gender scores. The review will provide insights into the current application of gender scores in clinical and health settings. The protocol describes how relevant literature will be identified and how gender scores will be evaluated concerning applicability and usability in scientific investigations.

Methods: Our scoping review follows the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews) guidelines. A title and abstract screening was conducted on PubMed, followed by a full-text screening. The inclusion and exclusion criteria were discussed by a team of 5 domain experts, and a data-charting form was developed. The charted data will be categorized, summarized, and analyzed based on the research questions during the scoping review.

Results: We will report our research results according to the PRISMA-ScR guidelines. The literature retrieval was carried out on June 13, 2024, and resulted in 1202 matches. As of July 2024, the scoping review is in the data extraction phase and we expect to complete and publish the results in the first quarter of 2025.

Conclusions: The scoping review lays the foundation for a retrospective gender assessment by identifying scores that can be applied to existing large-scale datasets. Moreover, it will help to formulate recommendations for standardized gender scores in future investigations.

International Registered Report Identifier (IRRID): DERR1-10.2196/57669

(JMIR Res Protoc 2025;14:e57669) doi:10.2196/57669

KEYWORDS

gender score; gender medicine; medical informatics; data integration; gender health gap

Introduction

The interaction of sex and gender plays an important role in the symptoms, diagnosis, therapy, outcome, life expectancy, and generally in the health and illness of men and women [1-3]. Gender includes awareness of diverse sexual orientations and identities and their relevance to daily life, including LGBTQ+ (lesbian, gay, bisexual, transgender, queer, and numerous other gender identities and sexual orientations) individuals. Neglecting

or inadequately considering gender aspects in medical research and practice can have serious consequences for diagnosis, treatment, or risk prediction.

The German Ethics Council defines biological sex by genetic, hormonal, and anatomical conditions or markers, more precisely, by chromosomes, hormones, and internal and external sex organs. Gender, on the other hand, is defined by social attributes, an interaction of biological and psychosocial factors, an individual's social biography, and is shaped by someone's role in society. Psychological attributes determine the individual's self-perception and sexual identity. The sexual identity may differ from someone's physical appearance or biological sex [4]

Despite the known importance of gender in health, such as diagnostic and therapeutic responses, clinical manifestations, and disease progression, gender is currently not sufficiently represented in the health sciences, and sex and gender effects cannot yet be distinguished for most diseases [5]. The work of Vader et al [6], for instance, highlights the importance of gender and shows that gender can be seen as a mediator of sex differences. This particularly concerns chronic diseases with a higher prevalence in women (arthritis, chronic pain, and migraine). The authors even claim, that in these diseases, sex differences would not exist if there was no gender.

To improve the validity and reliability of medical research, it is necessary to encode gender information, in addition to biological sex information. We argue that a systematic gender assessment should be mandatory in future scientific investigations and in particular in clinical and health studies. Adding gender to existing data requires a retrospectively applicable score, ideally suitable for a wide range of applications. Moreover, future health research requires reliable and valid gender scores capable of predicting gender with high accuracy. The scoping review will provide an initial overview of existing gender scores and how they are currently being used in the health sciences. The objectives of this review are (1) to identify and characterize existing gender scores reported in the literature in the health sciences and (2) to systematically assess their applicability to clinical and health research (restricted to selected use cases).

Methods

Design

The scoping review method, as defined by Grant and Booth [7], was selected to provide an overview of the topic and to map the existing literature on the problem. It is well suited because our study deals with heterogeneous methods—covering prospective and retrospective scores, developed using strongly differing approaches—and includes a broad selection of research domains, as all subdomains of health research (eg, psychology and epidemiology) are considered. Furthermore, our review will inform future investigations on the topic [8]. In general, we followed the stepwise approach for scoping reviews described by Mak and Thomas [9] and adapted as many characteristics of the systematic review method as possible [10]. In particular, the review follows the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews) guidelines [8], and the following steps were carried out: (1) identification of research questions; (2) identification of relevant studies; (3) study selection; (4) data extraction and charting; and (5) collating, summarizing, and reporting the results.

Due to limited resources, the coding of articles was conducted by a single reviewer and based on the database PubMed. It was selected as it is widely used as a standard database for biomedical literature research and is recommended as one of the most important databases for comprehensive systematic reviews [11].

Stage 1: Identification of Research Questions

As outlined in the Introduction section, gender is currently inadequately reflected in most scientific studies. The research questions therefore arose from an initiative to standardize gender encoding in large-scale data collections maintained by the Medical Informatics Initiative Germany (MII; *Medizininformatik-Initiative*) [12] and the Study of Health in Pomerania (SHIP) [13], and to establish recommendations for standardized gender encodings in routine data provided by the Data Integration Center (*Datenintegrationszentrum*) at the University Medicine Greifswald, Germany [14].

The research questions themselves were formulated by 5 domain experts, 3 with a primary background in medicine, 1 with a background in medical informatics, and 1 with a background in medical documentation. The identified and agreed upon research questions for the scoping review are the following: (1) What gender scores exist in medicine? (2) What gender scores are applicable to the SHIP and MII data? (3) How are gender scores currently applied, or are they purely theoretical constructs?

Stage 2: Identification of Relevant Studies

For the first assessment of the topic, a small number of relevant papers [15-17], identified through an initial manual search, were examined to identify keywords and important phrases. Furthermore, literature regarding gender awareness in the medical context [18-20] was examined to identify commonly used scientific terminology regarding gender. While this work defines a gender score as a method for assessing gender, the initial analysis showed that different terminology, such as gender measure or gender index, is used to refer to gender scores in the literature. Therefore, we included these terms in our query and added further terms as synonyms to achieve broad coverage. English language and status as a peer-reviewed article were additional inclusion criteria for our review. Furthermore, we only considered scores applied to adults and excluded scores targeting children.

Based on the extracted keywords, a query was designed to capture the key elements that identify these studies. The query was optimized for recall regarding the initial literature while considering the amount of results. Specifically, the query was designed using Boolean operators, wildcards, proximity search, and a timeline. The time limit was introduced to identify more recent literature and to exclude obsolete research, such as the well-known Bem Sex-Role Inventory [21] which was shown

to be outdated by Donnelly and Twenge [22]. The timeline was determined based on the distribution of articles, which showed that most research on the topic was published in the last 5 years. Throughout the entire review process, secondary literature relevant to our topic was collected. This particularly concerns older scores, which allows for the identification of earlier published literature that is still applied or cited in more recent publications. Although excluded by our initial time limit, we decided to consider them as secondary literature to evaluate if they are still reasonable to apply or obsolete. The final query was executed on June 13, 2024, and is illustrated in Figure 1.

Figure 1. PubMed query. The query consists of three parts: (1) terminology expressed for gender score, (2) word expressing that the score was developed, (3) timeline restriction (see stage 2 for further explanation); (ot) matches keywords; (tiab) matches title and abstract; (*) wildcards match different word endings; (~1) this proximity search with distance 1 allows another word between the searched terms (different word endings are automatically included).

```
("gender score*"[ot] OR "gender measure*"[ot] OR
 "gender index"[ot]  OR "gender indices"[ot] OR
 "gender model*"[ot] OR "gender classifier*"[ot] OR
 "gender score"[tiab:~1] OR "gender measure"[tiab:~1] OR
 "gender index"[tiab:~1] OR "gender indices"[tiab:~1] OR
 "gender model"[tiab:~1] OR "gender classifier"[tiab:~1])
AND
(create*[tiab] OR establish*[tiab] OR develop*[tiab] OR
 implement*[tiab] OR use[tiab] OR used[tiab])
AND
("2018"[Date - Create] : "3000"[Date - Create])
```

Stage 3: Study Selection

The obtained results were screened by title and abstract to exclude studies that do not relate to gender scores. Articles that could not be clearly excluded based on title or abstract alone were retained for further examination. The final relevance decision for the remaining articles was based on an examination of the full-text document.

Stage 4: Data Extraction and Charting

We developed a data-charting form that was used to determine eligible data extraction points. The form was based on Gierend et al [23] and then adjusted together with the domain experts involved in this study (see stage 2). It was iteratively optimized and continuously updated throughout the process. The charting form is organized into 4 main sections corresponding to an overview and the 3 research questions. The final data-charting form is illustrated and explained in Table 1. Based on the data extraction points, 1 author critically examined the papers and extracted the relevant data. Initially, more than 30% (7/22) of the publications were randomly double-checked by a second domain expert to ensure high data extraction quality. The 2 reviewers were in full agreement on all reviewed articles. Therefore, the remaining articles are reviewed by a single reviewer throughout the remainder of the review process. Irrelevant papers are removed from the charting form.

Table 1. Summary of data charting.

Section	Description
Section 1: Overview	Summary of the basic publication information
Article metadata	Title, Digital Object Identifier, year of publication (YYYY), keywords
Corresponding author information	Name, research discipline, institute, Research Organization Registry (registry of open persistent identifiers for research organizations)
Publication type	Peer-reviewed or preprint
Study type	Gender score development, use case, or recommendation
Continent	Continents where the study took place or focused on
Funding source	Public, industry, none, or missing
Citation count	Citation count as reported by PubMed and Google Scholar
Objective	Aim or objective of the publication
Methods	The procedures or techniques used to identify, select, process, and analyze information
Summary results	Short description of results
Conclusion	Short description of the conclusion
Section 2: Research questions	Includes the research questions and the required data
What gender scores exist in medicine?	• Necessary variables for the developed gender score • Retrospective or prospective application • Clinical or epidemiological study • Size of cohort • Target variables (feminine, masculine, binary, or continuously) • Model type (statistical model or questionnaire)
What gender scores are applicable to the SHIP[a] and MII[b] data?	• Existence of tool support or executable model • Availability of raw data or code • Reproducibility • Validation • Limitations (eg, restricted scope) • Variable coverage
How are gender scores currently applied, or are they purely theoretical constructs?	• Applicability in other research domains • Practical example of usage • Name and number of used records or databases • Expert evaluation

[a]SHIP: Study of Health in Pomerania.

[b]MII: *Medizininformatik-Initiative* (Medical Informatics Initiative Germany).

Stage 5: Collating, Summarizing, and Reporting the Results

This scoping review aims to summarize recently developed gender scores in health research. The extent of the review is limited to PubMed, the most relevant database for medical research outcomes. We assume that most relevant publications related to health sciences are contained in the resulting dataset. The commonly applied tools for the analytical interpretation of literature such as summary statistics, charts, and figures will be applied to discuss the collected relevant data [24]. We will follow the PRISMA-ScR guidelines [8] and discuss the general interpretation of the results compared to other evidence, the overall aim of the study, effects on practice, and future research, limitations, and recommendations.

Results

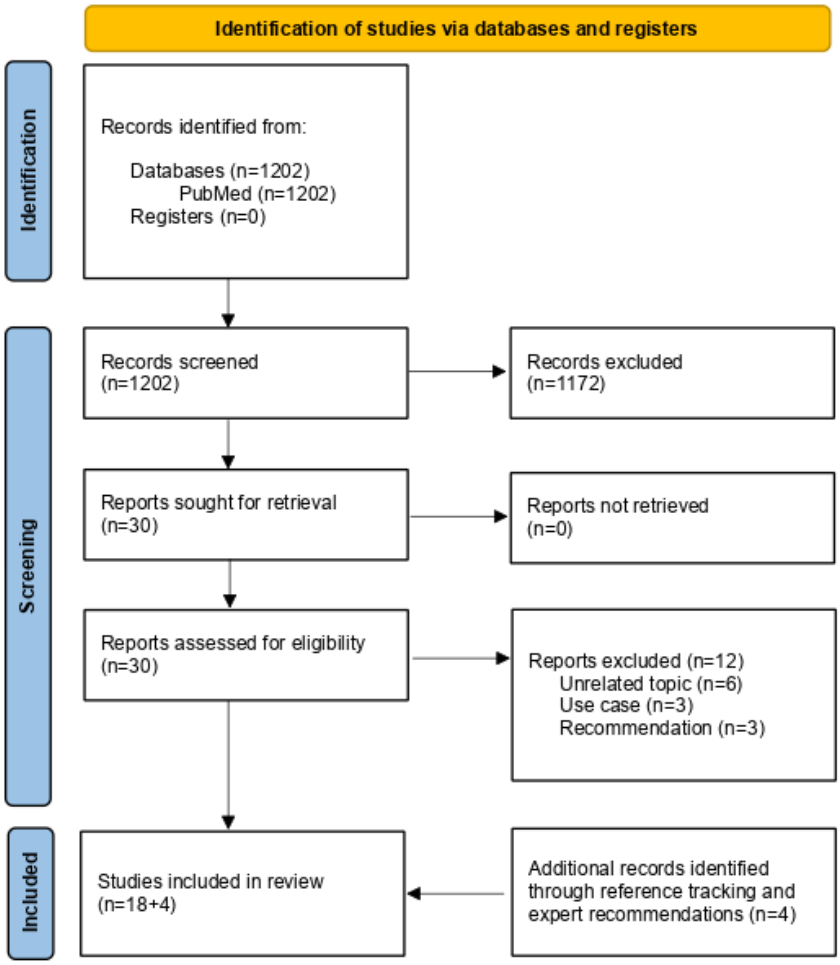
In preparation for the scoping review, a search of the database PubMed on June 13, 2024, resulted in 1202 matches. The title-abstract screening step reduced the set to 82 and 30 potentially relevant publications, respectively. It reduced the set of considered papers more than expected. Specifically, our review identified a large number of articles not directly related to the development of gender scores. On the one hand, this is due to the positive trend that gender receives increasing attention in current research. Many articles explicitly consider gender in the form of variables or by applying existing gender scores [25-27]. These articles were matched, as we designed the query to be as inclusive as possible in order not to miss any existing scores or potential extensions of existing scores (including the terms “use” and “used” in our query). On the other hand, in the examined papers the term gender is often used to refer to binary sex categories, for example, girl or boy, female or male, or

woman or man [28-32]. These papers were excluded from our review.

Full-text screening resulted in a final set of 18 papers identified in the scoping review. An additional 4 articles were identified as secondary literature, which were not covered in the timeline of the query but are still relevant in the current literature, as described earlier. A total of 22 studies were included in the review. The described process is further illustrated by the PRISMA-ScR flow diagram [8] in Figure 2. The results will be included into data charting.

We finalized the data extraction process in the third quarter of 2024 and the review will subsequently be concluded by summarizing and analyzing the results in the first quarter of 2025. The scoping review will provide an overview of recently developed gender scores in the literature. The research questions will allow us to select suited gender scores based on quality criteria and underlying research fields. The charting process will further provide information about their quality and retrospective applicability. This will serve as a basis for selecting eligible gender scores for retrospective application to existing data. Furthermore, the identified prospective scores will allow us to formulate recommendations for the inclusion of gender-dependent variables in future investigations, particularly, to incorporate standardized gender scores in investigations performed in the scope of the MII. The review will also reveal potential gaps and limitations of current gender scores, for example, regarding restrictions in underlying cohorts or research fields.

Figure 2. PRISMA-ScR flow diagram. The diagram illustrates the applied steps for the selection of relevant publications. PRISMA-ScR: Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews.



Discussion

Our review investigates the current development and usage of gender scores in health research and aims to assess the applicability of these scores. On the one hand, the insights can help to model gender information in existing data. On the other hand, we anticipate that our data charting will help to identify gender scores that are sufficiently generic and efficient to be implemented on a large scale in future research. Furthermore, our review will provide the basis for future works on the design and development of standardized prospective approaches to gender assessments.

Our review is also a valuable addition to existing scoping reviews that address gender topics. For instance, in 2020 Horstmann et al [33] focused on recently used instruments for the operationalization of sex and gender in health research. Our review identifies gender scores that were recently developed but have not necessarily been implemented yet. We aimed to identify the latest innovations in a very active research field, so we deliberately limited our search to the last 5 years. Indeed,

13 of the 18 articles in our primary result set were published after 2020. Miani et al [34] published an overview of epidemiological aspects of gender scores. Our work, in contrast, includes gender scores from all areas of health research, such as psychology, cardiology, or neurology. Similarly to Horstmann et al [33] and Miani et al [34], we included publications until 2021.

Limitations of this work are that a single reviewer screened titles and abstracts and that our search was limited to PubMed, as explained in the Design section. However, we believe that a major strength of our review protocol is that it addresses all methods of gender assessment and that our data charting covers a wide range of information.

Appropriate consideration of gender aspects in clinical and health studies remains a fundamental issue, and we believe that further work is required to establish the standardized use of gender scores in medical data recording. While our study will provide an overview of existing gender scores, a general, broader awareness of the topic remains of high importance, and solutions need to be found to systematically apply gender scores to clinical and health studies in the future. Therefore, further effort is required to make this topic more present in the scientific community.

Acknowledgments

This work was funded by the German Federal Ministry of Education and Research as part of the projects InkE (01FP23G10A)—Excellence through Inclusiveness in Medicine—and the Network of Data Integration Centers of the University Medicine (D352210009).

Data Availability

We plan to release the generated data persistently on Zenodo.

Authors' Contributions

LS did the conceptualization, data curation, investigation, methodology, visualization, writing of the original draft, and review and editing of the writing. HB and SR handled the data curation, validation, and review and editing of the writing. EK conducted the conceptualization, validation, methodology, supervision, and review and editing of the writing. SS and DW carried out the conceptualization, funding acquisition, methodology, supervision, writing of the original draft, and review and editing of the writing.

Conflicts of Interest

None declared.

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Abbreviations

MII: Medizininformatik-Initiative (Medical Informatics Initiative Germany)
PRISMA-ScR: Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews
SHIP: Study of Health in Pomerania

Edited by A Mavragani; submitted 23.02.24; peer-reviewed by MN Shalaby, F Krueger; comments to author 03.06.24; revised version received 01.08.24; accepted 18.09.24; published 20.01.25.

Please cite as:
Schindler L, Beelich H, Röll S, Katsari E, Stracke S, Waltemath D
Applicability of Retrospective and Prospective Gender Scores for Clinical and Health Data: Protocol for a Scoping Review
JMIR Res Protoc 2025;14:e57669
URL: https://www.researchprotocols.org/2025/1/e57669
doi:10.2196/57669
PMID:

Protocol

Occupational Infections Among Workers in Europe: Protocol for a Scoping Review

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Abstract

Background: Workers may be exposed to different infectious agents, putting them at risk of developing occupational diseases. This can occur in many ways, through deliberate use of specific microorganisms or through potential exposure from close contact with biological material. Infection prevention and control measures against biohazards can reduce the risk of infection among workers. During the last few decades, an increasing proportion of workers in Europe have been exposed to infectious biological agents in their workplace. Knowledge gaps on this topic in Europe have limited our understanding of the overall phenomenon in occupational settings.

Objective: This study aims to understand the extent and type of evidence on the epidemiology of occupational or work-related infections caused by bacterial, viral, fungal, and parasitical agents in European countries, the factors affecting their occurrence among workers, and the burden of disease among workers due to occupational risk.

Methods: The review will be conducted following the Joanna Briggs Institute methodology for scoping reviews and the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews) guidelines. This review will consider studies that include data on the epidemiology of occupational infections, risk factors and determinants, and burden of disease among workers employed in specific occupational sectors in European countries in the period 2010-2023. The search will include MEDLINE, Web of Science, and Scopus databases. Independent reviewers (including GD, SC, AR, PD, and SM) will screen the titles, abstracts, and full texts of the selected studies. Data extraction will be performed using a tool developed by the researchers. The data will be mapped and analyzed according to the type of extracted data.

Results: The literature search through different scientific databases started in April 2024 and is expected to be completed by December 2024. The findings will be extracted using an ad hoc data extraction tool, and relevant results will be presented in narrative and tabular form.

Conclusions: This scoping review aims to provide rigorous evidence to fill the knowledge gap in the epidemiology of occupational or work-related infections in European countries, the factors affecting their occurrence, and the burden of disease in different professional settings. Such findings could improve the understanding of this complex occupational phenomenon in the European context, enabling more accurate and up-to-date surveillance of infections incurred in the workplace.

International Registered Report Identifier (IRRID): PRR1-10.2196/59606

(JMIR Res Protoc 2025;14:e59606) doi:10.2196/59606

KEYWORDS

infection; work-related; biological hazard; narrative synthesis; Europe; occupational infection; worker; scoping review; infectious; prevention and control; occupational health; epidemiology; burden of disease; phenomenon

Introduction

Biological agents include a variety of microorganisms, toxins, and allergens that may harm human health. In particular, microorganisms capable of causing infections, such as bacteria, viruses, and fungi, can be pathogenic or can produce diseases that can be transmitted to individuals through various modes of transmission, determining acute or chronic health conditions [1].

In the occupational setting at the European level, prevention and management of all hazards and risks present in the workplace are required to safeguard occupational health and safety for all workers [2]. From this perspective, infection prevention and control measures implemented in the workplace against biological hazards can reduce the risk of infection among workers.

Indeed, employees in different professional sectors may be exposed to a variety of infectious agents, putting them at risk of disease. This exposure can occur in many ways, either through "deliberate use" of specific microorganisms (eg, laboratories and biotechnological industries), through "potential exposure" from processes of activities that require close contact with biological material (composting, recycling, and wastewater recycling), through animal contact (agriculture and food processing), or through contact with humans (health care and education). Globally, the overall annual mortality attributable to occupational infections is estimated at approximately 320,000 deaths, 5000 of which occur in the European Union [3]. However, morbidity from work-related infections could be largely underreported in national and international surveillance systems, possibly because of the lack of distinctive characteristics of work-related infectious diseases compared with infections acquired in nonoccupational settings, thereby making it difficult to establish a causal link between work and disease. Nonetheless, work-related infections may result in significant harm to workers' health, potentially resulting in a high disease burden on the working population. Indeed, experiences in tracking occupational diseases from biological agents are rather different [4], facilitating underestimation of the phenomenon. Indeed, there is often vast heterogeneity between countries in the definition of occupational or work-related diseases or injuries caused by biological agents. The case of SARS-CoV-2 infection among workers is paradigmatic: despite the large literature published on the subject, few countries notify this disease as an occupational accident or injury (eg, China and Italy), while the majority of countries have labeled this event as an occupational disease [5]. In fact, according to the Italian legislation on workers' compensation, cases of infectious and parasitic diseases are included in the category of accidents at work "because the virulent cause is equated to the violent one," which is a required characteristic to identify a work-related injury [6,7].

In particular, during the last few decades, increasing proportions of workers in Europe have been reported to be exposed to infectious biological agents in the workplace [8]. This has increased the need to provide more insight into the appropriate study and assessment of biological risks present in European countries, as well as their potential health effects among the workforce, especially in light of the impact of the COVID-19 pandemic on occupational health. Recent reports from the European Agency for Safety and Health at Work have identified several high-risk occupations for occupational infections (eg, animal-related occupations, waste and wastewater management, health care setting, farming, and traveling for work) and have provided recommendations on the implementation of specific preventive and protective measures in these settings. However, due to limited knowledge caused by the lack of up-to-date information on the ecology of pathogens and epidemiology of associated diseases in the European Union, particularly due to data gaps in monitoring systems for occupational diseases in member countries, it has not yet been possible to reach a comprehensive understanding of the overall phenomenon in all occupational settings [9]. Indeed, in many countries, biological agents are often not considered an Occupational Safety and Health priority, resulting in a reactive rather than a proactive approach to recognizing occupational biohazards and managing the risks to the safety and health of workers.

To understand the available knowledge on this topic, a scoping review will be performed to map the existing literature on infectious diseases in the occupational setting, enabling us to gather evidence on both traditional and emerging occupational biological agents and provide useful insights into their determinants and health impact. The scoping review was chosen as the most appropriate type of review as our aim is to achieve breadth rather than depth in our analysis. Therefore, other types of reviews are not deemed methodologically effective [10].

This scoping review is expected to provide the first rigorous analytical and updated synthesis of research data on the epidemiology of injury or disease due to infectious biological hazards, as well as information on the occupational burden. Stratifying infections according to the type of infectious disease and work task involved could add meaningful information and increase our understanding of the risk factors and corresponding determinants. Indeed, filling knowledge gaps and acquiring high-quality evidence concerning the epidemiology of occupational infections in European countries could be used as the scientific basis for developing and implementing effective preventive programs as well as for informing the activities of Occupational Health Services. This would contribute significantly not only to employers, employees, researchers, and occupational health professionals but also to overall public health.

A preliminary search of MEDLINE, the Cochrane Database of Systematic Reviews, and Joanna Briggs Institute (JBI) Evidence Synthesis was conducted, and 2 published systematic reviews

on the topic were identified [11,12]. However, these 2 systematic reviews did not specifically report data on the prevalence and incidence of occupational infections, definition of risk factors and determinants, as well as direct and indirect burden of disease (eg, economic impact and days absent from work due to ill health). In addition, the most recent systematic review was limited to non–health care workers and covered the period 2009-2020 [12]. Hence, we decided to perform a new review to gather updated evidence on all occupational categories, including health care settings. Furthermore, we decided to restrict the focus of our review to studies performed in European countries, in consideration of sufficiently comparable economic development and diversification, good standards of health care services, including occupational safety and health requirements provisions, as well as similar microorganism ecology, in order to better grasp the updated scientific evidence and possibly reduce confounders and heterogeneity in the subsequent synthesis.

The objectives of this scoping review are (1) to provide a comprehensive and up-to-date synthesis of all studies concerning occupational or work-related infections in European countries; (2) to identify the factors that impact the occurrence of infections among workers; and (3) to quantify the burden of infection among workers in terms of related disabilities, residual working capability, absence from work, and direct and indirect costs generated.

Methods

The proposed scoping review will be conducted in accordance with the JBI methodology for scoping reviews [13] and in line with the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews) guidelines [14].

Review Questions

The review questions of our planned study are as follows:

1. What is the incidence or prevalence rate of infections among workers in European countries?
2. What are the determinants of infection among workers in European countries?
3. What is the burden imposed by infections among European workers in terms of related disabilities, residual working capability, absence from work, and direct and indirect costs?

Eligibility Criteria

Eligibility criteria, defined according to Population, Concept, and Context criteria, are listed in Textbox 1.

Textbox 1. Eligibility criteria defined according to Population, Concept, and Context criteria.

Participants

- Workers employed in specific occupational sectors.

Concept

- Epidemiology of occupational infections, associated risk factors and determinants, burden of impact on health in terms of related disabilities, residual working capability, absence from work, and direct or indirect costs.

Context

- Studies published since 2010, performed in European countries with a common geographical definition of Europe [15].

Types of Sources

- This scoping review will consider all publications that meet the inclusion criteria. This includes, but is not limited to, quantitative, qualitative, and mixed methods studies. Systematic reviews that meet the inclusion criteria will also be considered depending on the research question. If the same data are reported in more than one publication, the primary article or article with the most complete data will be used.
- Analytical observational studies, including prospective and retrospective cohort, case-control, and analytical cross-sectional studies, will be considered for inclusion. Studies not matching the defined Population, Concept, Context criteria, review articles, modeling studies, case series, and individual case reports will be excluded from the review.

Search Strategy

A 3-step search strategy will be followed, as described in the JBI Manual for Evidence Synthesis [13].

An initial limited search of MEDLINE was undertaken to identify articles on the topic of interest. Text words contained in the titles and abstracts of relevant articles and the index terms used to describe the articles were used to develop a full search strategy for MEDLINE (Multimedia Appendix 1). To improve the specificity of the search strategy for injuries and diseases caused by occupational exposure, we adapted the specific filter developed by Mattioli et al [16] to retrieve potentially pertinent citations. The search strategy, including all identified keywords and index terms, will be adapted for each included database and information source. The databases to be searched will include MEDLINE, Web of Science, and Scopus. The reference lists of all included reports will be screened for additional studies. If the full text of a report cannot be accessed, the authors will be contacted. Studies published in English, Italian, French, and Spanish since 2010 will be included.

The second step will consist of a second search of all included databases using the fields, index, and MeSH terms, and all keywords identified during step 1. The databases to be searched will include MEDLINE, Web of Science, and Scopus. An example of the search strategy, including the index and MeSH

terms and keywords and Boolean logic (AND/OR and truncations), is provided in Multimedia Appendix 1.

The third step will consist of screening the reference lists of all the included articles for additional sources. The search strategy will be adapted for each included database and information source.

Study or Source of Evidence Selection

The source of evidence selection will be completed in the following steps. First, all citations identified through the full search of all included databases will be uploaded into Mendeley Reference Manager 2.91.0, and duplicates removed. Second, titles and abstracts will be screened by 4 independent reviewers to assess the inclusion criteria for the review. Finally, the same 4 independent reviewers will evaluate in detail the full text of the selected articles to verify if inclusion criteria are met. Reasons for exclusion of articles that do not satisfy the inclusion criteria will be reported in the scoping review. Disagreements between the reviewers will be resolved by the fifth reviewer or through discussion to reach a consensus. The complete study inclusion process will be reported in the scoping review and presented in a PRISMA-ScR flow diagram [14].

Data Extraction

Data will be extracted from the included studies by 4 independent reviewers by means of a data extraction tool developed by the Authors (Multimedia Appendix 2). The extracted data will include details on the participants, concept, context, study methodology, as well as key findings.

Data Analysis and Presentation

Data analysis and presentation will depend on the data extraction process and potential modification of the data extraction tool; therefore, it will be subject to changes. All changes will be documented in the review. The data will be manually entered into a Microsoft Excel spreadsheet. The data will also include specific details regarding the participants, study methodology, and most relevant findings. If necessary, the draft data extraction tool will be revised during the extraction process, with details on the modifications presented in the scoping review. Relevant results will be presented in tabular form and with a narrative synthesis. Disagreements between the reviewers will be resolved by an additional reviewer or through discussion. All relevant findings will be assessed and discussed by a national collaborative group of researchers from different Italian Universities, Hospitals, and Local Health Authorities.

Results

The literature search through different scientific databases started in April 2024 and is expected to be completed by December 2024. The review will be submitted for publication in 2025.

Discussion

The findings of this review will demonstrate an up-to-date epidemiological picture of occupational or work-related infections in European countries, the factors affecting their occurrence, as well as the burden of disease among different professional settings. Recently published data have shown several professional groups at risk of infection, such as the military, livestock farm workers, dairy producers, abattoir workers, and forestry workers, with the majority of these occupational groups being exposed to respiratory pathogens [12]. This review will add to the currently available evidence, by involving studies performed on all working categories, including health care workers. Such findings could improve the understanding of this complex occupational phenomenon in the European context, enabling a more accurate and up-to-date surveillance of infections caused by occupational exposure. This study is strengthened by the comprehensive and rigorous methodological approach adopted in the search strategy. Moreover, the composition of a national collaborative group, gathering expertise from researchers from different Italian Universities, practitioners, and professionals from reference Polyclinic Hospitals, and Local Health Authorities from different Regions of Italy, provides the unique possibility for multifaceted discussions of the findings, offering multiple perspectives from the different actors implicated in Occupational Health. However, the scoping review will be limited by a reduced resolution on the specific types of infections and work categories, as well as by the lack of a quantitative synthesis. To improve both limitations, further targeted systematic reviews and meta-analyses will be necessary. Nonetheless, this scoping review may serve as a foundational resource to inform policymakers with updated evidence, which can be used to improve the definition of occupational diseases and injuries caused by infectious agents in Italy, but also in different European countries. Furthermore, this updated evidence could provide useful practical insights for Occupational Health professionals, as well as guide future research goals by highlighting understudied professional categories and pathogens, with the aim of reducing possible knowledge gaps.

Acknowledgments

This study is partially supported by the Italian Workers' Compensation Authority (INAIL) in the framework of BRIC 2022: "*Metodologie innovative per la raccolta di informazioni sui casi di tecnopatie da agenti biologici e per l'individuazione dei relativi fattori causali*" (Bando BRIC 2022_ID 22).

Data Availability

The datasets generated during and/or analyzed during this study are available from the corresponding author on reasonable request.

Authors' Contributions

All the authors were writing original drafts, reviews, and editing. Conceptualization was performed by GD, SC, AR, PD, and SM. Methodology was handled by GD, SC, and AR. Funding acquisition and supervision were conducted by PD and SM.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Tentative search strategy.
[DOCX File , 18 KB - resprot_v14i1e59606_app1.docx]

Multimedia Appendix 2
Data extraction tool.
[DOCX File , 14 KB - resprot_v14i1e59606_app2.docx]

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Abbreviations

JBI: Joanna Briggs Institute
PRISMA-ScR: Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews

Edited by T Leung; submitted 17.04.24; peer-reviewed by UG Adamu; comments to author 29.07.24; revised version received 05.08.24; accepted 08.08.24; published 24.01.25.

Please cite as:
Dini G, Curti S, Rahmani A, Durando P, Mattioli S
Occupational Infections Among Workers in Europe: Protocol for a Scoping Review
JMIR Res Protoc 2025;14:e59606
URL: https://www.researchprotocols.org/2025/1/e59606
doi:10.2196/59606
PMID:

Protocol

Exploring the Credibility of Large Language Models for Mental Health Support: Protocol for a Scoping Review

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Abstract

Background: The rapid evolution of large language models (LLMs), such as Bidirectional Encoder Representations from Transformers (BERT; Google) and GPT (OpenAI), has introduced significant advancements in natural language processing. These models are increasingly integrated into various applications, including mental health support. However, the credibility of LLMs in providing reliable and explainable mental health information and support remains underexplored.

Objective: This scoping review systematically maps the factors influencing the credibility of LLMs in mental health support, including reliability, explainability, and ethical considerations. The review is expected to offer critical insights for practitioners, researchers, and policy makers, guiding future research and policy development. These findings will contribute to the responsible integration of LLMs into mental health care, with a focus on maintaining ethical standards and user trust.

Methods: This review follows PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews) guidelines and the Joanna Briggs Institute (JBI) methodology. Eligibility criteria include studies that apply transformer-based generative language models in mental health support, such as BERT and GPT. Sources include PsycINFO, MEDLINE via PubMed, Web of Science, IEEE Xplore, and ACM Digital Library. A systematic search of studies from 2019 onward will be conducted and updated until October 2024. Data will be synthesized qualitatively. The Population, Concept, and Context framework will guide the inclusion criteria. Two independent reviewers will screen and extract data, resolving discrepancies through discussion. Data will be synthesized and presented descriptively.

Results: As of September 2024, this study is currently in progress, with the systematic search completed and the screening phase ongoing. We expect to complete data extraction by early November 2024 and synthesis by late November 2024.

Conclusions: This scoping review will map the current evidence on the credibility of LLMs in mental health support. It will identify factors influencing the reliability, explainability, and ethical considerations of these models, providing insights for practitioners, researchers, policy makers, and users. These findings will fill a critical gap in the literature and inform future research, practice, and policy development, ensuring the responsible integration of LLMs in mental health services.

International Registered Report Identifier (IRRID): DERR1-10.2196/62865

(JMIR Res Protoc 2025;14:e62865) doi:10.2196/62865

KEYWORDS

large language model; LLM; mental health; explainability; credibility; mobile phone

Introduction

Background

The emergence of generative artificial intelligence (AI) and the rapid evolution of large language models (LLMs) are introducing new complexities and accelerating technological advancements. Our understanding of the inner workings of these systems remains limited. However, there is a widespread rush across all sectors to adopt these technologies, often overlooking the ethical considerations and potential threats to data privacy and confidentiality [1]. The use of LLMs, such as Bidirectional Encoder Representations from Transformers (BERT; Google) and GPT (OpenAI), in mental health research and health care is growing. However, their ability to provide reliable and empathetic mental health support remains underexplored. LLMs have been shown to excel in tasks such as text generation and summarization, but their application in sensitive fields such as mental health requires careful consideration of factors such as ethical concerns, privacy, and model explainability.

As generative AI becomes increasingly integrated into various tools and applications, its presence in our everyday lives grows. The deployment of AI in smartphones, social media, and platforms such as OpenAI's ChatGPT, Google's Gemini, Anthropic's Claude, and Meta's Llama is a testament to this trend. These technological advancements are becoming a staple in our personal and professional spheres, a presence set to expand further. Their influence on our choices is significant and will only intensify in the coming years, potentially impacting our mental health and overall well-being [2].

A recent research study published on the alignment of outcomes of LLMs to human intentions [3] concluded that, based on publicly available users' opinions about their use of LLMs, in general, users tend to trust those LLMs more that demonstrate higher alignment to human intentions. In *Harvard Business Review* [4], the authors of the review "AI can be both accurate and transparent," which was a study to examine the trade-off between accuracy and explainability, tested a wide array of AI models on nearly 100 representative datasets and found that 70% of the time, a more explainable model could be used without compromising accuracy. This suggests that a reliable LLM can be developed and aligned with transparency and social norms. Another study [5] suggested that ethics-based auditing can be a governance mechanism for building and deploying LLMs and potentially bridge the gap between principles and practice in AI ethics. It argues that ethics-based auditing will improve the quality of decision-making, users' satisfaction with privacy and confidentiality at the center, influence laws and policies that govern these systems and minimize human harm.

Given that this technology is still nascent and research into its effects on society is scarce, evaluating its implications and integration into the medical and health care sectors, particularly in mental health support, is essential. It is imperative to recognize and scrutinize this progression, understand its benefits [6] and associated risks, and identify potential measures to prevent and reduce the adverse effects of these technologies on human lives. The ethical dilemmas surrounding the use of these systems, the safeguarding of user privacy and confidentiality, and the accountability of developers remain largely uncharted territories [7]. It can be said that a lot of the published literature and journals either provide general solutions or look into a specific domain, such as applicability or accuracy.

This exploration seeks to shed light on the current state of LLMs, focusing on their reliability and explainability, especially in providing support for mental health. It will try to add more consistent factors that can account for the credibility of LLMs. There is now a growing body of research on using LLMs for mental health care provision [8]. However, it is worth noting that there are very few to almost no studies on the credibility of LLMs, particularly in medicine [9,10] and mental health support. This review intends to address this gap.

Objectives and Research Questions

The study's overall objective is to explore the current state of evidence on the credibility of LLMs by comprehensively reviewing research on credibility factors such as reliability and explainability. A secondary objective is to derive insights into ethical implications for the responsible use of LLMs in mental health support.

To this end, the following research questions will be pursued in the scoping review:

1. How credible are LLMs in providing mental health information and support?
   - What factors influence the reliability of LLMs for mental health support?
   - How credible are LLMs providing mental health information and support?
2. What are the users' perceptions of using LLMs as reliable and explainable sources of mental health support?
3. What ethical implications should be considered for the responsible use of LLMs in mental health support?
   - How can we ensure privacy and confidentiality when users interact with LLMs for sensitive mental health issues?
   - How can we ensure that the shared sensitive information by the user is secure and private?

Methods

Study Design

The PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews) [11] will be used as a basic tool, and the Joanna Briggs Institute's (JBI) approach to scoping reviews will be followed [12-14].

Research Strategy and Terms

Information Sources

The selected databases cover a wide range of disciplines relevant to the scope of our review. PsycINFO and MEDLINE focus on psychology and medical research, providing comprehensive coverage of mental health studies. Web of Science ensures multidisciplinary coverage, while IEEE Xplore and ACM Digital Library focus on technological advancements and AI research,

critical for studies on LLMs. These databases together provide a robust and well-rounded search strategy for this scoping review.

Search Strategy

The search strategy will be continuously updated to capture newly published studies during the review period (Multimedia Appendix 1). Monthly alerts will be set up in key databases, and any relevant new papers will be incorporated into the review until the final synthesis phase. An iterative approach will be followed to develop the search strategy. First, search terms used in previous studies and reviews related to the credibility of LLMs in mental health support will be identified. Second, an initial search in MEDLINE via PubMed and ACM Digital Library will be conducted after analyzing text words (title and abstract) and indexed terms, according to JBI methodology. The initial search strategy for MEDLINE via PubMed is given in Multimedia Appendix 1. This approach will use all received search terms in all databases. Finally, the references for all included contributions will be checked. The terms will be adapted to the essential search particulars such as wildcards (*), truncations, and Boolean operators in each electronic database.

For a more precise explanation of the inclusion criteria, the Population, Concept, and Context (PCC) framework will be followed. Textbox 1 shows the most important criteria based on the PCC framework.

The kinds of literature and papers that provide information on at least one research question from the *Objectives and Research Questions* section will be included. Detailed inclusion and exclusion criteria are mentioned below for each review.

Textbox 1. Population, Concept, and Context scheme.

Population

- Mental health practitioners, researchers, educators, students, and adults (age group: 18-65 years)

Concept

- Nonparticipatory, exploratory, cocreation, and co-design

Context

- Exploration of credibility (reliability and explainability) of large language models for mental health support

Types of sources

- Secondary sources, electronic databases, studies published in the last 5 years (2019-2024), studies published in English or that have an English translation available, and full-text papers

Eligibility Criteria

Papers to be included must meet the criteria mentioned in Textbox 2.

Textbox 2. Eligibility criteria.

Study design

- The study must be empirical, exploring the application of transformer-based generative language models in mental health support.

Model type

- The study should involve transformer-based models such as Bidirectional Encoder Representations from Transformers (BERT), GPT-2, or later models designed for generative tasks.

Mental health focus

- The study should address mental health support, encompassing therapy, counseling, or other relevant interventions.

Credibility assessment

- The study should evaluate credibility factors, including accuracy, reliability, explainability, or user satisfaction.

Publication date

- Studies published from 2019 onward are included. We chose 2019 as the starting year for including studies because this marks the beginning of a transformative phase in large language model (LLM) development. In late 2018, BERT was introduced, followed by GPT-2 in 2019, setting the stage for subsequent advancements that significantly impacted the field.

Language

- The study must be published in English or have an English translation to maintain data extraction and analysis consistency.

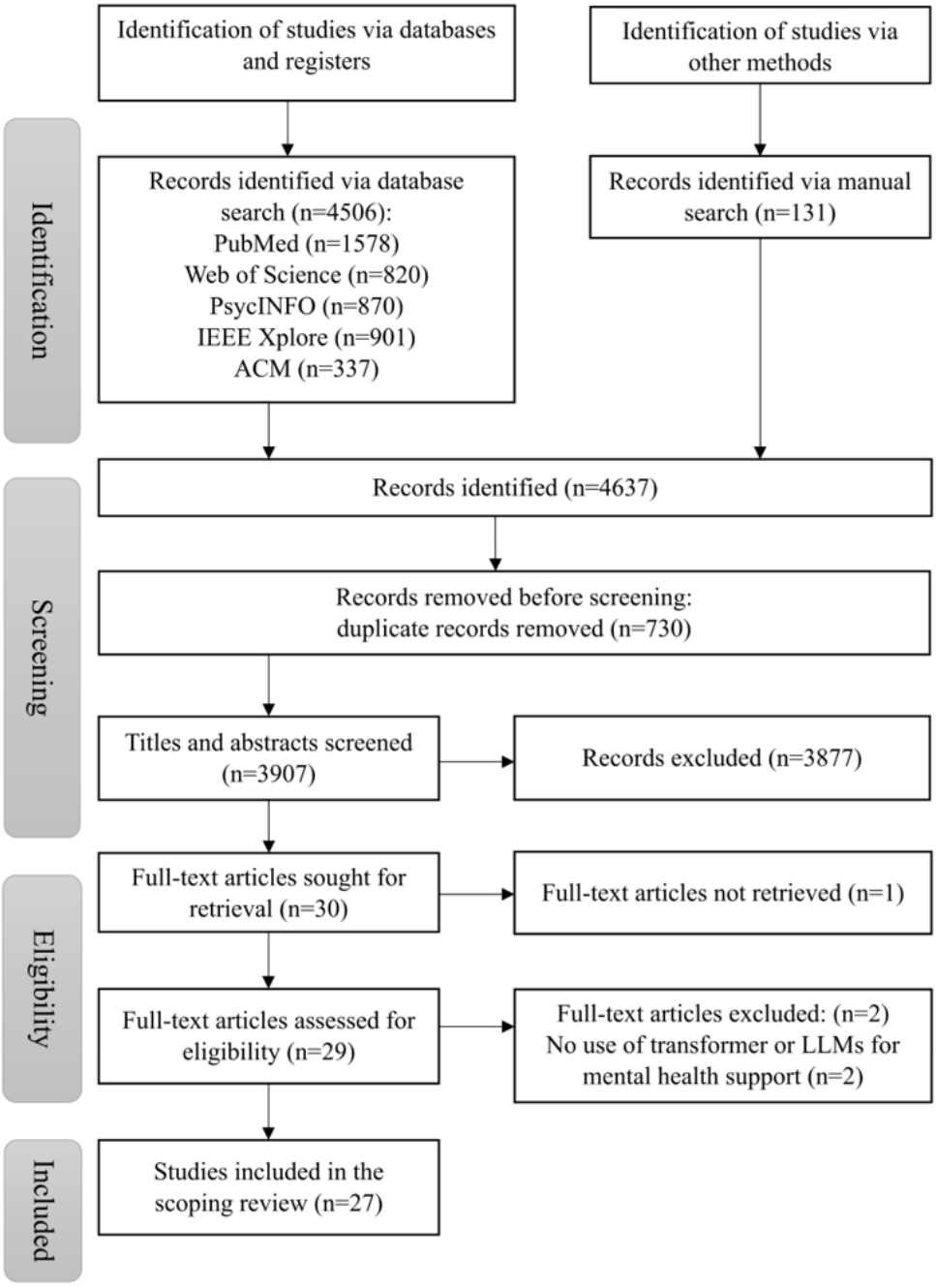
Peer-review or preprint status

- We will prioritize peer-reviewed studies; however, to capture the rapid advancements in this field, we will also include preprint papers from ArXiv and peer-reviewed book chapters. Information from these sources will be presented in a separate table, and interpretations based on these sources will be limited and contextualized regarding the publication status.

Study Selection

The saved papers will be checked for duplicates. The open-source app Zotero (Corporation for Digital Scholarship) [15] will be used as a bibliographic tool. Paper screening will be done using the open-access tool Rayyan.ai (Rayyan Systems Inc) [16]. Two independent reviewers will screen all titles and abstracts separately for inclusion or exclusion. Any discrepancies will be resolved through discussions between the 2 reviewers during the screening and data extraction phases. If consensus cannot be reached, a third reviewer will be consulted. This process will ensure reliability and minimize bias by incorporating multiple perspectives and systematic resolution of disagreements. The search results and the study inclusion or exclusion process will be transparently reported in full in the final scoping review, which will be presented in a PRISMA flowchart (Figure 1).

Figure 1. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flowchart. LLM: large language model.



Data Extraction

We will use the literature review matrix method [17] to organize and chart the data extracted from the included research papers. Two reviewers will chart the data independently, continually update the matrix in an iterative process, and discuss the results while all the changes are detailed in the scoping review. After independent extraction, the 2 reviewers will compare their extracted data. Any discrepancies or disagreements will be discussed and resolved through consensus. A third reviewer will be consulted to decide if a consensus cannot be reached. Data extracted will include metrics such as accuracy, reliability, model explainability (eg, explainable AI methods used), user satisfaction scores, and ethical considerations such as privacy and data security measures. Data will be synthesized to address the research questions systematically. The data extraction form will be continually updated in an iterative process as new insights are gained and new studies are reviewed. Reviewers will keep detailed records of any changes to the extraction process and document the rationale. The extracted data will be managed and stored using Zotero for reference management and Rayyan.ai for screening and collaboration. A literature review matrix is given in Multimedia Appendix 2.

Data Analysis and Presentation

To assess the quality of the included studies, we will apply the JBI Critical Appraisal Checklist for Qualitative Research [18]. This tool will evaluate the methodological quality of each study by examining factors such as the clarity of research questions, the appropriateness of the study design, the rigor of data collection, and the credibility of the results. The results of this appraisal will be presented descriptively, helping to

contextualize the findings of the review and ensuring a nuanced understanding of the evidence base. Given the expected heterogeneity in study designs, methodologies, and outcomes, this scoping review will focus on qualitative synthesis rather than meta-analysis. Descriptive synthesis is more appropriate for mapping the broad and varied landscape of LLM applications in mental health support. This will involve evaluating methodological rigor, reporting clarity, and the findings' relevance to the research questions. The results of this appraisal will be presented descriptively, helping to contextualize the findings of the review. The findings will be presented according to the PRISMA-P (Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols) checklist (Multimedia Appendix 3). The extracted data will be presented logically and descriptively, including diagrams and tables based on the objectives and research questions of the scoping review. Data synthesis and presentation will follow an inductive approach. A summary description and discussion of the findings according to the research questions, the flowchart, and the entire research process will be provided in text form and described narratively.

Ethical Considerations

Since the data used in the review are collected from secondary sources and primary data are not collected, formal ethical approval is not required.

Dissemination Plan

The findings of this scoping review will be disseminated through various channels, including a peer-reviewed journal publication and presentations at key conferences in the fields of AI and mental health. We also plan to engage with policy makers and health care stakeholders to help inform the development of guidelines and frameworks that promote the responsible use of LLMs in mental health care. This dissemination strategy aims to ensure that the results reach both academic and clinical audiences, as well as those involved in ethical oversight.

Results

As of September 2024, we have completed the initial search, yielding 1578 studies. Out of these, 244 studies were included for title and abstract screening. Full-text screening is underway for 76 studies. Figure 1 shows the PRISMA flowchart, and the PRISMA-P checklist documenting this process is given in Multimedia Appendix 3. The target date for submitting the scoping review is November 30, 2024.

Discussion

Overview

The anticipated findings of this scoping review will focus on identifying and mapping the factors that influence the credibility of LLMs in mental health support. We expect to find evidence related to the reliability and explainability of these models, particularly in the areas of user trust, data privacy, and ethical considerations. These insights are expected to inform future research, policy development, and clinical practice in integrating LLMs for mental health services.

Principal Findings

This scoping review aims to map factors such as model reliability, explainability, and ethical concerns in the context of LLMs for mental health support. These findings will offer a deeper understanding of how LLMs are evaluated for their potential role in sensitive areas such as mental health. We anticipate uncovering gaps in transparency and user trust as key components influencing the integration of LLMs into clinical settings.

Comparison to Previous Work

This review builds on previous work in AI ethics and health care applications, with a particular focus on LLM credibility. Our findings are expected to align with previous studies that emphasize the need for explainability and user trust, but they will also highlight the specific challenges that arise when these models are applied in mental health contexts. Unlike past research that has focused on broader AI applications, this review narrows its scope to LLMs in therapeutic settings, addressing concerns such as misdiagnosis and misinformation.

Strengths and Limitations

The comprehensive nature of this scoping review, using the PRISMA-ScR framework, allows for a systematic exploration of diverse studies across various domains. However, limitations include the exclusion of non-English studies, which may lead to the omission of important research from non–English-speaking regions. In addition, the rapid development of LLM technologies means some newly published studies may be missed, and publication bias could skew the results toward studies reporting positive findings.

Future Directions

This review will highlight the need for further research, particularly in the user-centered evaluation of LLMs within clinical mental health settings. We expect to identify several gaps in the literature, such as the underrepresentation of studies focusing on the impact of LLMs on vulnerable populations. Future work should explore ways to improve model transparency, explainability, and user trust while addressing ethical concerns surrounding the use of LLMs in mental health.

Conclusions

This scoping review addresses a critical gap in the current literature by systematically evaluating the credibility of LLMs in mental health support. By mapping factors such as reliability, explainability, and ethical considerations, this review will provide a comprehensive understanding of how these models can be responsibly integrated into mental health services. The findings will offer valuable insights for mental health practitioners, researchers, and policy makers, helping to shape future studies and ethical guidelines. In particular, the results will inform decisions about the use of LLMs in clinical practice, guiding the development of policies to safeguard user trust and data privacy. Furthermore, the review will serve as a foundation for further research on improving the reliability and transparency of LLMs in sensitive areas such as mental health.

Acknowledgments

This scoping review is conducted as part of the master's thesis of author Dipak Gautam under the supervision of Prof Dr med Philipp Kellmeyer. Data and Web Science Group, School of Business Informatics and Mathematics, University of Mannheim, Germany.

Data Availability

Data sharing is not applicable to this article as no datasets were generated or analyzed during this study.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Search strategy.
[DOCX File , 17 KB - resprot_v14i1e62865_app1.docx]

Multimedia Appendix 2
Literature review matrix.
[DOCX File , 18 KB - resprot_v14i1e62865_app2.docx]

Multimedia Appendix 3
PRISMA-P (Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols) checklist.
[DOCX File , 16 KB - resprot_v14i1e62865_app3.docx]

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Abbreviations

AI: artificial intelligence
BERT: Bidirectional Encoder Representations from Transformers
JBI: Joanna Briggs Institute
LLM: large language model
PCC: Population, Concept, and Context
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRISMA-P: Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols
PRISMA-ScR: Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews

Edited by A Schwartz; submitted 03.06.24; peer-reviewed by CN Hang, S Mao; comments to author 31.07.24; revised version received 25.08.24; accepted 12.11.24; published 29.01.25.

Please cite as:
Gautam D, Kellmeyer P
Exploring the Credibility of Large Language Models for Mental Health Support: Protocol for a Scoping Review
JMIR Res Protoc 2025;14:e62865
URL: https://www.researchprotocols.org/2025/1/e62865
doi:10.2196/62865
PMID:

Protocol

Migration of Health Workers and Its Impacts on the Nigerian Health Care Sector: Protocol for a Scoping Review

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Abstract

Background: Health worker migration from Nigeria poses significant challenges to the Nigerian health care sector and has far-reaching implications for health care systems globally. Understanding the factors driving migration, its effects on health care delivery, and potential policy interventions is critical for addressing this complex issue.

Objective: This study aims to comprehensively examine the factors encouraging the emigration of Nigerian health workers, map out the effects of health worker migration on the Nigerian health system, document the loss of investment in health training and education resulting from migration, identify relevant policy initiatives addressing migration, determine the effects of Nigerian health worker migration on destination countries, and identify the benefits and demerits to Nigeria of health worker migration.

Methods: This study will follow the Joanna Briggs Institute methodology. A search strategy will retrieve published studies from MEDLINE, CINAHL, Embase, Global Health, Academic Search Premiere, and Web of Science. Unpublished studies will be sourced from dissertations and theses. A comprehensive search will involve keyword scans and citation searches. Exclusion criteria will filter out irrelevant studies, such as studies unrelated to the international migration of health workers and non-English language studies. A total of 2 independent reviewers will screen the titles and abstracts and then review the full text. Data will be extracted from the included studies using a data extraction tool developed for this study. The study selection process will be shown using a PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews) flowchart. While the traditional risk of bias assessments is not applied to scoping reviews, the quality of included studies will be evaluated based on methodological transparency.

Results: The process of selecting studies will be shown using a PRISMA ScR flowchart, and information gathering will be done through a charting table that has been prepared in advance. We plan to collect data from January 2025 to March 2025 and present the results to examine publication patterns and study details. The final summary is expected to be released by the summer of 2025. It will provide an in-depth look at how health worker migration impacts the health care sector in Nigeria.

Conclusions: This study holds immense potential to contribute to understanding health worker migration from Nigeria and inform policy and practice interventions to address its challenges. By synthesizing existing evidence, the scoping review will guide future research and policy efforts to mitigate the adverse effects of migration on health care systems and workforce sustainability. Furthermore, the results will aid in recognizing deficiencies in the existing literature; this will offer a defined path for specific policy measures and methods to retain health care workers effectively and thus support the sustainability of health care systems.

International Registered Report Identifier (IRRID): PRR1-10.2196/62726

(JMIR Res Protoc 2025;14:e62726) doi:10.2196/62726

KEYWORDS

training and education; health policy; healthcare workforce; policy interventions; socio-political factors; political instability; workforce capacity

Introduction

Overview

Nigeria is the most populous country in Africa and has one of the largest supplies of health workers on the continent; however, the country has been particularly affected by the migration issue [1]. It is estimated that 20,000 of the 72,000 Nigerian physicians educated in Nigeria were practicing abroad in 2008 [2]. This number represents 28% of the physician workforce trained in Nigeria and is significantly higher than the proportion for any other African country [3]. As a result, Nigeria has a fragile health system that is unable to effectively deliver quality health services to its populace. This includes increased workload for the remaining health workers, decreased access to health care services, and compromised quality of care [4-6]. Furthermore, Nigeria invests substantial resources in training its health workforce, yet many of these trained professionals ultimately migrate to seek better opportunities abroad. Documenting the loss of investment in health training and education due to health worker migration is essential for assessing the economic and human resource implications for Nigeria's health care system [7].

The global crisis in human resources for health has been described as one of the most pressing issues facing the health sector and is now widely acknowledged as a global priority [8]. Addressing the shortage and maldistribution of health workers, including policy dialogue and coordinated action in the area of international migration of health workers, is deemed necessary to avert a long-term global health workforce crisis, which would be detrimental to the attainment of the health-related Sustainable Development Goals and Universal Health Coverage, and ultimately to global health [9]. Policy initiatives have been proposed to address health worker migration in Nigeria, including retention schemes such as offering competitive salaries and benefits, incentive programs like providing opportunities for professional development, and bilateral agreements to regulate the recruitment of Nigerian health workers by foreign countries. Evaluating the effectiveness and impact of these policies is critical for policy makers and stakeholders to develop evidence-based strategies to mitigate the adverse effects of health worker migration [10]. In addition, understanding the effects of Nigerian health worker migration on destination countries is vital for promoting ethical recruitment practices and fostering global health workforce planning. While migration poses challenges for the Nigerian health care system, it also generates remittances, fosters knowledge exchange, and promotes international engagement in health care development initiatives [11].

The migration of highly skilled health workers from developing to developed countries has been cited as contributing to shortages of qualified health workers in many African and Southeast Asian countries. In relation to the Nigerian context, there is evidence that Nigeria has experienced high levels of emigration of health professionals, where the United Kingdom, United States, and Canada are among the leading destination countries [12]. It is important to understand the journeys, distribution, and characteristics of migrant health workers, with the aim of identifying specific policy measures to enhance positive impacts and mitigate negative impacts of migration on health systems in source and destination countries [9,13,14]. In summary, this scoping review protocol seeks to provide a comprehensive overview of health worker migration and its impacts on the Nigerian health care sector. By addressing these issues, the review will inform evidence-based policies and interventions to optimize the management of health worker migration and strengthen the resilience of Nigeria's health care system.

A preliminary search of Campbell's systematic reviews, the Cochrane Database of Systematic Reviews, PROSPERO (International Prospective Register of Systematic Reviews), and Joanna Briggs Institute (JBI) evidence synthesis was conducted. Interestingly, no current or underway systematic reviews or scoping reviews on the topic were identified, highlighting the unique contribution of this study.

Aim and Review Questions

The primary purpose of this study is to establish a better understanding of how migration affects individual developing nations. This understanding will pave the way for new policies that can better manage the recruitment and retention of health professionals, thereby minimizing any negative effects caused by migration. Importantly, this study also holds the potential for positive outcomes, such as increased skill and knowledge within the sector, which can significantly benefit the health care system.

This review will seek to identify the breadth and depth of the available literature, including studies on the causes and consequences of health worker migration, the effectiveness of policy interventions, and the experiences of health workers and their families. This will provide an opportunity to identify research gaps and inform future research and policy decisions. At this preliminary stage in conducting the scoping review, the authors have also found that this type of review is best suited to the resources and time available. Specifically, the review questions are as follows: (1) What factors contribute to the emigration of Nigerian health workers? (2) How does health worker migration impact the Nigerian health system, including its strengths and weaknesses? (3) What effective strategies should be used to promote the retention of skilled health workers within the Nigerian health care system?

Methods

Overview

Following the JBI methodology [15], the study will conduct a comprehensive search across multiple databases to find relevant studies. Data from these studies will be systematically extracted, organized, and analyzed, ensuring a reliable and comprehensive review, with findings presented in a clear and descriptive format.

Search Strategy

The scoping protocol, a detailed plan outlining the methods and search strategy for the scoping review, will initiate with an initial limited search of databases, focusing on analyzing text words in titles, abstracts, and index terms. This will be followed by a comprehensive 2-way search strategy across multiple databases, including MEDLINE, CINAHL (EBSCO), Embase, Global Health, Academic Search Premiere, and Web of Science (Table 1). Unpublished studies will be sourced from dissertations and theses. The search will involve specified keywords (eg, emigration, immigration, and health workers) and free keywords (eg, brain drain and migration). Additional strategies, such as citation and chain searches, will be used to enhance search completeness. Exclusion criteria will filter out studies unrelated to the international migration of health workers or not centered on the Nigerian health care sector. Only English-language studies from an appropriate date range will be considered, aligning with the review's scope and context. Finally, hand-searching of reference lists from relevant primary studies or review articles will be conducted. To address potential publication bias, the review will include measures such as searching for gray literature, unpublished studies, and reports that may contain negative or nonsignificant findings. This approach will help ensure a more comprehensive and balanced understanding of the topic. The scoping protocol plays a crucial role in ensuring the systematic and rigorous conduct of the scoping review, and its adherence will be reported in the final scoping review.

Table 1. Search strategy on databases.

Participant, context, and concept scheme	Number	Search string	MEDLINE (March 28)	CINAHL	Web of Science	Embase	Global Health	Academic Search Premier
International migration AND its impacts on the Nigerian healthcare sector	1	emigration OR immigration OR health workers OR skilled healthcare workers OR health professionals OR healthcare professionals OR healthcare personnel	339,025	119,968	349,710	22,039	12,876	3789
International migration AND its impacts on the Nigerian healthcare sector	2	brain drain OR migration OR healthcare workers	387,827	43,054	851,446	9098	456	1789
	3	#1 AND #2	19,789	11,006		2004	55	2908
Migration AND its impacts on the Nigerian healthcare sector	4	Nigeria OR Nigerian	41,946	7366	4540	455	34	45
Combined	5	#3 AND #4	292	113		23	12	9
Filters	6	English, from 2001 to date (excluding Magazine and book chapters)	33	112		34	33	54

Eligibility Criteria

This scoping review will incorporate the PCC (Population, Concept, Context) framework as a guide, ensuring a comprehensive and inclusive approach. We will thoroughly describe the characteristics of participants, concepts, and contexts alongside our search strategies, data extraction methods, analysis techniques, and result presentation formats. The eligibility criteria, designed to be comprehensive and inclusive, are detailed in Textbox 1. In addition, this review will involve iterative consultations with experts and stakeholders to refine the research questions and inclusion criteria.

Textbox 1. Inclusion and exclusion criteria.

Inclusion criteria:

- Health workers migration from Nigeria.
- English.
- Studies from 2001 to 2024.
- Conference papers.
- Quantitative and qualitative evidence.
- Gray literature.
- Studies identifying policy initiatives aimed at addressing health worker migration in Nigeria.
- Research mapping out the impacts of health worker migration on the Nigerian health system.

Exclusion criteria:

- Meeting abstracts.
- Editorial materials.
- Book chapters.
- All other languages.
- Studies from 2001 and earlier.
- Studies not related to health worker migration from Nigeria.
- Literature not focused on the effects of health worker migration on the Nigerian health system.
- Articles lacking information on factors encouraging health worker emigration from Nigeria.
- Publications not discussing policy initiatives addressing health worker migration in Nigeria.

Participants

This scoping review will include studies involving health workers who have migrated from Nigeria to other countries. The focus will be on health care professionals, including but not limited to doctors, nurses, midwives, pharmacists, radiographers, and laboratory scientists. In addition, individuals receiving health care services in Nigeria impacted by the migration of health workers will also be considered participants in this review.

Concept

The primary concept under investigation is the migration of health workers and its impacts on the Nigerian health care sector. This includes examining factors contributing to health worker migration, such as motivating factors, as well as the consequences of migration on health care delivery, workforce dynamics, health care access, quality of care, and health outcomes in Nigeria.

Context

The review will consider studies conducted regarding the Nigerian health care sector, including public and private health care facilities, hospitals, clinics, primary health care centers, and community health centers. Equally important, studies focusing on the health care systems of destination countries where Nigerian health workers have migrated will also be included to provide a comprehensive understanding of the context.

Types of Sources

This scoping review will consider a variety of sources, including empirical research studies, policy documents, reports, and gray literature. Gray literature, which refers to nontraditional sources of information that are not published in commercial publications, can include conference papers, theses, government documents, and unpublished research. Specifically, quantitative studies such as surveys, cohort studies, and quantitative analyses of secondary data will be included. Qualitative research using methods such as interviews, focus groups, and case studies will also be considered. In addition, policy documents, government reports, organizational reports, and academic publications addressing the migration of health workers and its impacts on the Nigerian health care sector will be included in the review. For instance, a government report on the brain drain of health workers from Nigeria would be a relevant source for this review.

Study or Source of Evidence Selection

Following the search, all identified citations will be collated and uploaded into EndNote (version 20; Clarivate Analytics), and duplicates will be removed. Following a pilot test, titles, and abstracts will then be screened by 2 or more independent reviewers for assessment against the inclusion criteria for the review. Potentially relevant sources will be retrieved in full, and their citation details will be imported into the JBI System for the Unified Management, Assessment, and Review of Information [16]. Two or more independent reviewers will thoroughly assess the full text of selected citations against the inclusion criteria. Reasons for the exclusion of sources of evidence in full text that do not meet the inclusion criteria will

be recorded and reported in the scoping review. Any disagreements that arise between the reviewers at each stage of the selection process will be resolved through discussion or with an additional reviewer or reviewers. The results of the search and the study inclusion process will be reported in full in the final scoping review and presented in a PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews) flow diagram [17]. This process ensures the transparency and rigor of the study selection process.

Data Extraction

To ensure the reliability and consistency of the data, 2 independent reviewers will meticulously extract data from each included study using a standardized data extraction form. The data extracted will include specific details about the participants, concept, context, study methods, and key findings relevant to the review questions. This thorough process guarantees the accuracy of our findings. A draft charting table will be developed as a data extraction tool. This charting table will also serve as the basis for data synthesis, and it will be modified and revised as necessary during the process of extracting data from each included evidence source. The purpose of this table is to provide a structured format for recording the extracted data, ensuring consistency and facilitating the analysis process. The synthesis will follow a narrative, descriptive approach, with identified patterns, gaps, and emerging themes categorized for further analysis. Modifications to the charting table will be detailed in the scoping review. Any disagreements that arise between the reviewers will be resolved through discussion or with an additional reviewer or reviewers. If appropriate, authors of papers will be contacted to request missing or additional data, where required.

Results

The findings of this scoping review will be shared once we finish extracting the data as planned. Our goal is to finalize the data mapping and synthesis by March 2025. The review results will be organized to showcase a thorough overview of the data based on the main themes recognized during the review process. The table for charting will contain information like the publication year and country of the study as well as its objectives and methodology, along with details on the population studied and sample size considered in the research analysis process, including outcomes assessed and intervention duration when relevant. The final summary of results, which will detail the impact of health worker migration on Nigeria's health care system, is anticipated to be released by the summer of 2025. The analysis will be finalized and submitted for publication in the autumn of 2025.

Discussion

Principal Findings

This scoping study will uncover insights into how health workers from Nigeria migrate and how it affects the country's health care system. The results should highlight patterns in what drives their migration, such as reasons and job prospects along with working conditions, while also pointing out the difficulties caused by this shortage of health care workers in delivering services and ensuring access to health care. Furthermore, the review seeks to pinpoint areas where existing research lacks information, which can serve as a basis for studies and policy making decisions to address the consequences of health worker migration.

Dealing with health worker migration challenges is crucial to improving health care delivery. Like countries facing an aging population, Nigeria is also tackling both an aging populace and a scarcity of health care workers, which is straining the health care system [10]. Projections suggest a severe shortage in the health care workforce by 2038, underscoring the urgent need to address health worker emigration as a top priority [13]. This urgency should resonate with policy makers, health care administrators, researchers, and professionals involved in health care workforce management and policy development in Nigeria.

Recent studies on health worker migration in Nigeria shed light on the factors contributing to the departure of professionals from the country. For instance, some studies pointed out that sociopolitical factors such as political instability and insecurity, as well as professional factors like low wages and poor working conditions, are driving health worker emigration [9,14]. The findings underscore the potential of focused interventions to address issues and motivate health workers to remain in Nigeria, instilling a sense of optimism for the future of Nigeria's health care system.

The consequences of health worker migration go beyond workforce shortages; they also impact the quality and accessibility of health care services in Nigeria. For instance, some research studies emphasized how health care delivery is strained and how health inequalities worsen due to the departure of professionals [12,18]. This should underline the gravity of the situation for policy makers, health care administrators, researchers, and professionals involved in Nigeria's health care workforce management and policy development. Moreover, the issue of health workers leaving the country poses challenges to the health care systems' long-term stability and ability to withstand pressures, highlighting the need for measures to retain and develop capacity [7].

Efforts to address these obstacles and encourage health professionals to stay within Nigeria's health care system have been gaining traction. Research conducted by Ossai et al [19] Falase et al [3] emphasized the significance of overcoming hurdles and offering incentives to retain health workers in the country. Furthermore, the World Health Organization's Global Code of Practice on International Recruitment of Health Personnel serves as a guideline for collaboration in tackling health worker migration and bolstering health care systems [20].

In summary, this review aims to focus on the reasons and effects of health care worker migration from Nigeria and sheds light on the challenges faced by the workforce and health care disparities in the country. Drawing comparisons with research will help put the findings into perspective by highlighting trends and new insights discovered. The study's strengths lie in its methodology and thorough analysis of data; however, it may have limitations due to gaps in less-known sources. Moving

forward, efforts should be made towards creating targeted policy recommendations and implementing strategies to mitigate the impacts of migration on the health care system. An effective dissemination strategy guarantees that the research outcomes are communicated to policy makers and experts in the field so they can contribute to solutions.

Strengths and Limitations of the Study

The scoping review is designed to identify the gaps in the literature and recommend strategies for further research in this area. The methods used will provide us with an idea of how much research already exists in this domain and examine how research has been conducted on this topic [21]. In addition, the research team, with its extensive experience in different types of systematic reviews, brings a wealth of knowledge and expertise in this specific field, making it well-equipped to tackle the complexities of this research [21-24].

This review has a few limitations that have been considered when considering the findings. A significant limitation of this review is that the studies identified and included provided very little detail on the health worker's experiences abroad and the impact of migration on the health sector (if they were mentioned). It will, therefore, be difficult to provide a comprehensive account of the health worker migration situation and its impacts on the health sector in Nigeria. Given the limited information available in the literature, it may be necessary to consider broadening the scope of the review in the future. This could involve incorporating nonacademic literature and reports, a step that could potentially provide a more comprehensive understanding of the situation. Another potential limitation is the exclusion of any language other than English, such as French language studies. This is due to the reviewers' lack of proficiency in French, making the use of French language studies a time-consuming process. This may have introduced a language bias.

Given the broad scope of the review, it has been a challenge to frame precise research questions and define specific inclusion criteria. This complexity has made it difficult to assess the relevance of the retrieved studies. Moreover, there was significant variation in the concepts and definitions of health professional and "brain drain" among these studies, a factor that will likely influence the findings once the data is extracted and synthesis is carried out.

Conclusion

This analysis sheds light on the studied topic of health care staff migration and the limited data regarding its extent and effects, despite public worry and ample unofficial publications on the matter. The absence of supporting data has resulted in differing opinions; some term it a "crisis" while others raise concerns. Our scoping review approach has mapped the key concepts and sources, provided an understanding of the existing evidence, and paved the way for a comprehensive follow-up review.

Acknowledgments

The authors thank the librarians from the University of Bradford for their guidance and assistance in this research. This study is being undertaken without external funding. However, a publishing grant from Linnaeus University has been received as part of the University Library's research support. No generative AI was used in any portion of the manuscript writing.

Data Availability

All supporting data will be reported in the manuscript. Any raw data sets supporting the results will be available and presented in the main manuscript or additional supporting files when submitting the systematic review article.

Authors' Contributions

DO contributed to conceptualization, methodology, data curation, writing, original draft, and visualization. EA managed formal analysis, investigation, and visualization. MC handled resources, writing, review, and editing. MSRJ performed supervision, validation, review and editing.

Conflicts of Interest

None declared.

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Abbreviations

JBI: Joanna Briggs Institute
PCC: Population, Concept, Context

PRISMA-ScR: Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews
PROSPERO: International prospective register of systematic reviews

Edited by T Leung; submitted 29.05.24; peer-reviewed by RS Gomaa Mahmoud, U Sinha; comments to author 29.07.24; revised version received 06.08.24; accepted 22.11.24; published 30.01.25.

Please cite as:
Omiyi D, Arubuola E, Chilaka M, Rahman Jabin MS
Migration of Health Workers and Its Impacts on the Nigerian Health Care Sector: Protocol for a Scoping Review
JMIR Res Protoc 2025;14:e62726
URL: https://www.researchprotocols.org/2025/1/e62726
doi:10.2196/62726
PMID:

Protocol

Challenges and Strategies Adopted for Remote Teaching of Biochemistry During the COVID-19 Pandemic: Protocol for a Scoping Review

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Abstract

Background: In March 2020, the global landscape witnessed widespread upheavals in both socioeconomic and educational spheres due to the onset of the COVID-19 pandemic. With measures imposed to control the virus's spread, educational institutions around the world embraced digital learning, introducing challenges in the adaptation to virtual education. This shift proved especially daunting in resource-limited nations with limited digital infrastructure.

Objective: This scoping review aims to explore the experiences of biochemistry educators during the COVID-19 pandemic, focusing on successful pedagogical strategies used to overcome challenges in remote teaching. The goal is to compile valuable information applicable to health-related undergraduate and postgraduate courses.

Methods: This review considers studies and experiences related to the transition to remote biochemistry education during the pandemic. It encompasses a variety of pedagogical approaches, including online teaching tools, interactive methods, and alternatives to practical laboratory classes. The search spans databases such as MEDLINE, the Cochrane Database of Systematic Reviews, and Joanna Briggs Institute (JBI) Evidence Synthesis, with a focus on identifying systematic or scoping reviews; however, none were identified in the preliminary search.

Results: Starting in February 2022, the scoping review protocol was scheduled for completion by July 2024. From an initial pool of 1171 results, 85 articles were selected, with duplicate verification pending for the subsequent phase of the project. The findings from this review on biochemistry teaching strategies will be communicated using a combination of descriptive narrative, graphical, and tabular formats, emphasizing diverse pedagogical approaches pertinent to the subject. Dissemination will occur through regional and national scientific conference presentations, alongside publication in a peer-reviewed journal.

Conclusions: This review aims to generate innovative pedagogical approaches and pinpoint learning activities, materials, and tools that support social and collaborative learning across various subjects, including biochemistry. Moreover, it will offer perspectives from students and educators on the implemented activities, with the intention of integrating them as supplementary methods to boost student participation, and thereby, improve learning outcomes and skill development.

Trial Registration: Open Science Framework VZSA7; https://osf.io/VZSA7/

International Registered Report Identifier (IRRID): DERR1-10.2196/59552

(JMIR Res Protoc 2025;14:e59552) doi:10.2196/59552

KEYWORDS

COVID-19; biochemistry; education, distance; teaching; educational technology; review; digital learning; virtual education; teaching tools; remote learning; social support; distance learning; remote teaching

Introduction

The COVID-19 pandemic, declared by the World Health Organization (WHO) in March 2020, caused significant impacts on both socioeconomic and educational fronts, disrupting the routine of in-person education worldwide [1]. Due to restrictions on people's movement to prevent the spread of the coronavirus, schools and universities shifted to digital learning, which helped prevent 2% to 4% of COVID-19 deaths [2]. Consequently, educators and students were compelled to use digital platforms as universities faced the dilemma of either suspending activities indefinitely or restructuring through online education, with the latter prevailing [3,4]. This transition from traditional to virtual education posed challenges, requiring students and educators to adapt to digital platforms and teachers to develop some level of computer proficiency. In resource-limited countries, the limited digital infrastructure hindered online access, rendering online education less effective [3].

While online teaching tools were already used by various institutions, the widespread shift to this mode of education was abrupt for educators across all levels, from basic to postgraduate courses [4,5]. Therefore, pedagogical strategies had to be rapidly developed to achieve desired competencies through virtual learning without significant learning setbacks [4]. In addition, the need to identify optimal communication tools arose early on to facilitate practical aspects, such as ease of use, compatibility with teachers' and students' computer systems, and avoidance of additional costs for students [5]. This led to the adoption of online meeting programs, such as Microsoft Teams, Cisco Webex, GoToMeeting, Jitsi, and Zoom, on all available electronic devices and required changes in the education system to facilitate the development of students' learning habits and critical thinking; this demanded quick adaptability and creativity from teachers in transitioning from a structured teaching method to an innovative one, especially in medical education [5]. Conventional methods of distance learning often involve prerecorded video lectures and theoretical materials, which may be insufficient to engage students and promote learning [6]. Furthermore, the unavailability of teachers to clarify doubts during and after the class may impede communication and content comprehension, a limitation recognized for several years and accentuated by the COVID-19 pandemic [6,7]. As an alternative to maintaining quality education and direct teacher-student contact, interactive pedagogical tools were used to promote active learning through student participation in online classes [8].

The rapid shift to distance learning during the pandemic presented significant global challenges, as evidenced by Lassoued et al [9], which identified pedagogical, technical, and financial obstacles affecting the quality of education in Arab universities, and by Jalali et al [10], who highlighted similar issues in Iran, where prosthetics and orthotics students faced unreliable internet and a lack of digital competence among both students and faculty, severely impacting the quality of online education. Similarly, Anwar et al [11] in Pakistan and Baticulon et al [12] in the Philippines identified several barriers to effective online learning, including low digital literacy, lack of institutional support, financial difficulties, unreliable internet access, the need for students to manage household responsibilities, and mental health challenges exacerbated by the pandemic, all of which hindered students' ability to engage effectively with online education.

In the field of biochemistry education, specific examples of innovative approaches include the work of Botasini et al [13], who assessed the learning objectives of each practical biochemistry class at the University of Montevideo, distinguishing between those developing skills suitable for remote learning and those primarily requiring hands-on laboratory skills. Gasparello et al [14] replaced applied biochemistry practical classes with a remote activity simulating the use of different techniques for diagnosing SARS-CoV-2, the infectious agent responsible for the COVID-19 pandemic. They suggested continuing this strategy in person, with small groups of students to maintain social distancing. Similarly, Vasiliadou [15] proposed adopting virtual laboratories where practical classes were simulated, allowing students to perform them at their own pace, familiarizing them with health and safety regulations, and providing instant feedback. These virtual experiments could be conducted in groups, promoting social interaction and collaboration among students, crucial in a socially distant situation to facilitate communication and reduce feelings of isolation and loneliness.

Singh and Arya [1] reported the development of new approaches tested on various online platforms with a class of 200 biochemistry students. After using 4 different teaching strategies and analyzing student feedback, they combined these approaches with the flipped classroom method. This involved providing slides, quizzes, and support material links at least 24 hours before delivering a video lecture on a carbohydrate metabolism topic. Students' questions were available to tutors before the online class, and the interactive phase of this hybrid strategy was recorded for students with poor connectivity to answer a related questionnaire later.

Challenges continued to emerge as the need to fulfill educational objectives clashed with the physical distance of students [8,16]. Practical laboratory classes, integral to health professionals' training, posed a particular challenge. Teachers in these disciplines had to address how to teach practical content and skills remotely, leading to the implementation of various alternatives based on available digital tools [16].

As some researchers shared their experiences, such as Thibaut and Schroeder's [17] guide for creating short cases for virtual case-based learning, the value of virtual learning as a complementary tool for the future became evident. In this regard, this scoping review aims to explore different experiences of biochemistry educators during the COVID-19 pandemic, identifying successful pedagogical strategies that engaged students in overcoming challenges posed by this conceptual and abstract discipline. This information can be compiled and used by educators in health-related undergraduate and postgraduate courses. Understanding complex molecular structures, intricate metabolic pathways, and subtle chemical interactions provides profound knowledge of the molecular basis of organism function and, consequently, the development, diagnosis, and treatment of diseases. A preliminary search of MEDLINE, the Cochrane Database of Systematic Reviews, and Joanna Briggs Institute (JBI) Evidence Synthesis did not identify any current or ongoing systematic reviews or scoping reviews on the topic.

Methods

Overview

The research methodology will involve the utilization of the Arksey and O'Malley [18] approach for scoping reviews, comprising the following steps: (1) identify the research question; (2) identify relevant studies; (3) perform study selection; (4) extract and chart the data; and (5) collate, summarize, and report the results. The scoping review methodology will be guided by this framework, and the protocol will follow the relevant PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews) guidelines [19]. The review protocol was registered in the Open Science Framework [20].

Identify the Research Question

As per Levac et al [21], the research question intended for exploration in this review has been clearly articulated and focused. The question being investigated in this exploratory literature review is "What were the challenges and strategies adopted for remote biochemistry teaching during the COVID-19 pandemic?"

Participants, Concept, and Context Framework for Eligibility Criteria

The inclusion of eligible studies in this scoping review will be guided by the Participants, Concept, and Context framework [22].

Participants

This scoping review will include studies that involve students who participated in biochemistry courses at undergraduate or postgraduate levels, delivered remotely.

Concept

The focus of the study is to analyze the challenges and strategies adopted for remote biochemistry teaching, covering both theoretical and practical approaches, during the COVID-19 pandemic. Studies discussing pedagogical methods, online teaching tools, adaptation of laboratory practices, and other approaches to maintaining the quality of distance education will be considered.

Context

Only studies conducted during the COVID-19 pandemic will be included, as the objective is to explore how biochemistry teaching was adapted and the challenges faced during this specific period. Studies published in any language will be considered.

Exclusion

Duplicate articles, editorials, reviews, conference proceedings, theses, dissertations, and monographs will be excluded.

Identify Relevant Studies

The literature search will be performed from January 2020 to December 2023, during the time period when articles related to tools used for remote teaching during the COVID-19 pandemic were published, in collaboration with a specialized librarian, using an iterative approach. Following the formulation of the question, keywords will be identified ("Teaching"; "Biochemistry"; "Distance Education"; and "COVID-19") that managed to capture articles related to the topic, namely "translational medical research" (Medical Subject Headings terms) and "knowledge translation."

The following databases will be consulted: National Library of Medicine (PubMed), MEDLINE, Scopus, Directory of Open Access Scholarly Resources, Education Resources Information Center, Directory of Open Access Journals, and Google Scholar, through descriptors and their synonyms, according to the Health Sciences Descriptors and Medical Subject Headings, for each item of the strategy (Tables 1 and 2). For the combination of descriptors, the Boolean terms AND, OR, and NOT will be considered.

Table 1. Search keywords and key terms used for this study.

Subjects	Subject and synonyms in Portuguese (DeCS[a])	Subject and synonyms in English (MeSH[b])
1	"Ensino" OR "Atividade de Treinamento" OR "Atividades Formativas" OR "Atividades de Capacitação" OR "Atividades de Formação" OR "Atividades de Treinamento" OR "Atividades de Treino" OR "Capacitação Acadêmica" OR "Didática" OR "Docência" OR "Formação Acadêmica" OR "Método de Ensino" OR "Métodos Pedagógicos" OR "Métodos de Ensino" OR "Pedagogia" OR "Treinamento Acadêmica" OR "Treino Acadêmico" OR "Técnica de Treinamento" OR "Técnicas Educacionais" OR "Técnicas Educativas" OR "Técnicas de Ensino" OR "Técnicas de Formação" OR "Técnicas de Treinamento" OR "Técnicas de Treino"	"Teaching" OR "Training Technique" OR "Training Technique" OR "Technique, Training" OR "Techniques, Training" OR "Training Technic" OR "Technic, Training" OR "Technics, Training" OR "Training Technic" OR "Pedagogy" "Pedagogies" OR "Teaching Method" OR "Teaching Method" OR "Method, Teaching" OR "Methods, Teaching" OR "Academic Training" OR "Training, Academic" OR "Training Activities" OR "Training Activity" OR "Activities, Training" OR "Activity, Training" OR "Techniques, Educational" OR "Educational Techniques" OR 'Educational Technique" OR "Technique, Educational" OR "Educational Technics" OR "Educational Technic" OR "Technic, Educational" OR "Technics, Educational"
2	"Bioquímica"	"Biochemistry"
3	"Educação a Distancia" OR "Aprendizado Online" OR "Aprendizado a Distância" OR "Aprendizagem Online" OR "Aprendizagem a Distância" OR "Ciberaprendizagem" OR "Cursos por Correspondência" OR "Educação Online" OR "Ensino a Distância" OR "Formação à Distância" OR "Formação à Distância através das TIC" OR "Formação à Distância através das Tecnologias da Informação e das Comunicações" OR "Tele-Educação" OR "Tele-Educação Interativa" OR "Teleducação" OR "Teleducação Interativa" OR "Teleformação" OR "eLearning"	"Education, Distance" OR "Distance Education" OR "Distance Learning" OR "Learning, Distance" OR "Online Learning" OR "Learning, Online" OR "Online Education" OR "Education, Online" OR "Online Educations" OR "Correspondence Courses" OR "Correspondence Course" OR "Course, Correspondence"
4	"Covid-19" OR "COVID19" OR "Doença Viral COVID-19" OR "Doença pelo Novo Coronavírus (2019-nCoV)" OR "Doença por 2019-nCoV" OR "Doença por Coronavírus 2019" OR "Doença por Coronavírus 2019-nCoV" OR "Doença por Coronavírus-19" OR "Doença por Novo Coronavírus (2019-nCoV)" OR "Doença por Novo Coronavírus de 2019" OR" Doença por Vírus COVID-19" OR "Epidemia de Pneumonia por Coronavírus de Wuhan" OR "Epidemia de Pneumonia por Coronavírus de Wuhan de 2019-2020" OR "Epidemia de Pneumonia por Coronavírus em Wuhan" OR "Epidemia de Pneumonia por Coronavírus em Wuhan de 2019-2020" OR "Epidemia de Pneumonia por Novo Coronavírus de 2019-2020" OR "Epidemia pelo Coronavírus de Wuhan" OR "Epidemia pelo Coronavírus em Wuhan" OR "Epidemia pelo Novo Coronavírus (2019-nCoV)" OR "Epidemia pelo Novo Coronavírus 2019" OR "Epidemia por 2019-nCoV" OR "Epidemia por Coronavírus de Wuhan" OR "Epidemia por Coronavírus em Wuhan" OR "Epidemia por Novo Coronavírus (2019-nCoV)" OR "Epidemia por Novo Coronavírus 2019" OR "Febre de Pneumonia por Coronavírus de Wuhan" OR "Infecção Viral COVID-19" OR "Infecção pelo Coronavírus 2019-nCoV" OR "Infecção pelo Coronavírus de Wuhan" OR "Infecção pelo SARS-CoV-2" OR "Infecção por 2019-nCoV" OR "Infecção por Coronavírus 2019-nCoV" OR "Infecção por Coronavírus de Wuhan" OR "Infecção por Novo Coronavírus de 2019" OR "Infecção por SARS Coronavirus 2" OR "Infecção por SARS-CoV-2" OR "Infecção por Vírus COVID-19" OR "Infecções por SARS-CoV-2" OR "Pandemia COVID-19" OR "Pandemia por COVID-19" OR "Pandemias por COVID-19" OR "Pneumonia do Mercado de Frutos do Mar de Wuhan" OR "Pneumonia por Coronavírus de Wuhan" OR "Pneumonia por Novo Coronavírus de 2019-2020" OR "Surto de Coronavírus de Wuhan" OR "Surto de Pneumonia da China 2019-2020" OR "Surto de Pneumonia na China 2019-2020" OR "Surto pelo Coronavírus 2019-nCoV" OR "Surto pelo Coronavírus de Wuhan" OR "Surto pelo Coronavírus de Wuhan de 2019-2020" OR "Surto pelo Novo Coronavírus (2019-nCoV)" OR "Surto pelo Novo Coronavírus 2019" OR "Surto por 2019-nCoV" OR "Surto por Coronavírus 2019-nCoV" OR "Surto por Coronavírus de Wuhan" OR "Surto por Coronavírus de Wuhan de 2019-2020" OR "Surto por Novo Coronavírus (2019-nCoV)" OR "Surto por Novo Coronavírus 2019" OR "Virose COVID-19" OR "covid-19"	"COVID19" OR "COVID 19" OR "SARS-CoV-2 Infection" OR "Infection, SARS-CoV-2" OR "SARS CoV-2 Infection" OR "SARS-CoV-2 Infections" OR "2019 Novel Coronavirus Disease" OR "2019 Novel Coronavirus Infection" OR "2019-nCoV Disease" OR "2019-nCoV Disease" OR "2019-nCoV Diseases" OR "Disease, 2019-nCoV" OR "COVID-19 Virus Infection" OR "COVID 19 Virus Infection" OR "COVID-19 Virus Infections" OR "Infection, COVID-19 Virus" OR "Virus Infection, COVID-19" OR "Coronavirus Disease 2019" OR "Disease 2019, Coronavirus" "Coronavirus Disease-19" OR "Coronavirus Disease 19" OR "Severe Acute Respiratory Syndrome Coronavirus 2 Infection" OR "SARS Coronavirus 2 Infection" OR "COVID-19 Virus Disease" OR "COVID 19 Virus Disease" OR "COVID-19 Virus Diseases" OR "Disease, COVID-19 Virus" OR "Virus Disease, COVID-19" OR "2019-nCoV Infection" OR "2019-nCoV Infection" OR "2019-nCoV Infections" OR "Infection, 2019-nCoV" OR "COVID19" "COVID-19 Pandemic" OR "COVID 19 Pandemic" OR "Pandemic, COVID-19" OR "COVID-19 Pandemics"

[a]DeCS: Health Science Descriptors.

[b]MeSH: Medical Subject Headings.

Table 2. Search strategy for databases used for this study.

Databases	Search details
National Library of Medicine (PubMed), MEDLINE, Scopus, Directory of Open Access Scholarly Resources, Education Resources Information Center, and Directory of Open Access Journal	(“Teaching” OR “Training Technique” OR “Training Technique” OR “Technique, Training” OR “Techniques, Training” OR “Training Technic” OR “Technic, Training” OR “Technics, Training” OR “Training Technic” OR “Pedagogy” “Pedagogies” OR “Teaching Method” OR “Teaching Method” OR “Method, Teaching” OR “Methods, Teaching” OR “Academic Training” OR “Training, Academic” OR “Training Activities” OR “Training Activity” OR “Activities, Training” OR “Activity, Training” OR “Techniques, Educational” OR “Educational Techniques” OR ‘Educational Technique” OR “Technique, Educational” OR “Educational Technics” OR “Educational Technic” OR “Technic, Educational” OR “Technics, Educational”) AND (“Biochemistry”) AND (“Education, Distance” OR “Distance Education” OR “Distance Learning” OR “Learning, Distance” OR “Online Learning” OR “Learning, Online” OR “Online Education” OR “Education, Online” OR “Online Educations” OR “Correspondence Courses” OR “Correspondence Course” OR “Course, Correspondence”) AND (“COVID19” OR “COVID 19” OR “SARS-CoV-2 Infection” OR “Infection, SARS-CoV-2” OR “SARS CoV-2 Infection” OR “SARS-CoV-2 Infections” OR “2019 Novel Coronavirus Disease” OR “2019 Novel Coronavirus Infection” OR “2019-nCoV Disease” OR “2019-nCoV Disease” OR “2019-nCoV Diseases” OR “Disease, 2019-nCoV” OR “COVID-19 Virus Infection” OR “COVID 19 Virus Infection” OR “COVID-19 Virus Infections” OR “Infection, COVID-19 Virus” OR “Virus Infection, COVID-19” OR “Coronavirus Disease 2019” OR “Disease 2019, Coronavirus” “Coronavirus Disease-19” OR “Coronavirus Disease 19” OR “Severe Acute Respiratory Syndrome Coronavirus 2 Infection” OR “SARS Coronavirus 2 Infection” OR “COVID-19 Virus Disease” OR “COVID 19 Virus Disease” OR “COVID-19 Virus Diseases” OR “Disease, COVID-19 Virus” OR “Virus Disease, COVID-19” OR “2019-nCoV Infection” OR “2019-nCoV Infection” OR “2019-nCoV Infections” OR “Infection, 2019-nCoV” OR “COVID19” OR “COVID-19 Pandemic” OR “COVID 19 Pandemic” OR “Pandemic, COVID-19” OR “COVID-19 Pandemics”
Google Scholar (in Portuguese)	(“Ensino” OR “Atividade de Treinamento” OR “Atividades Formativas” OR “Atividades de Capacitação” OR “Atividades de Formação” OR “Atividades de Treinamento” OR “Atividades de Treino” OR “Capacitação Acadêmica” OR “Didática” OR “Docência” OR “Formação Acadêmica” OR “Método de Ensino” OR “Métodos Pedagógicos” OR “Métodos de Ensino” OR “Pedagogia” OR “Treinamento Acadêmica” OR “Treino Acadêmico” OR “Técnica de Treinamento” OR “Técnicas Educacionais” OR “Técnicas Educativas” OR “Técnicas de Ensino” OR “Técnicas de Formação” OR “Técnicas de Treinamento” OR “Técnicas de Treino”) AND (“Bioquímica”) AND (“Educação a Distancia” OR “Aprendizado Online” OR “Aprendizado a Distância” OR “Aprendizagem Online” OR “Aprendizagem a Distância” OR “Ciberaprendizagem” OR “Cursos por Correspondência” OR “Educação Online” OR “Ensino a Distância” OR “Formação à Distância” OR “Formação à Distância através das TIC” OR “Formação à Distância através das Tecnologias da Informação e das Comunicações” OR “Tele-Educação” OR “Tele-Educação Interativa” OR “Teleducação” OR “Teleducação Interativa” OR “Teleformação” OR “eLearning”) AND (“Covid-19” OR “COVID19” OR “Doença Viral COVID-19” OR “Doença pelo Novo Coronavírus (2019-nCoV)” OR “Doença por 2019-nCoV” OR “Doença por Coronavírus 2019” OR “Doença por Coronavírus 2019-nCoV” OR “Doença por Coronavírus-19” OR “Doença por Novo Coronavírus (2019-nCoV)” OR “Doença por Novo Coronavírus de 2019” OR “Doença por Vírus COVID-19” OR “Epidemia de Pneumonia por Coronavírus de Wuhan” OR “Epidemia de Pneumonia por Coronavírus de Wuhan de 2019-2020” OR “Epidemia de Pneumonia por Coronavírus em Wuhan” OR “Epidemia de Pneumonia por Coronavírus em Wuhan de 2019-2020” OR “Epidemia de Pneumonia por Novo Coronavírus de 2019-2020” OR “Epidemia pelo Coronavírus de Wuhan” OR “Epidemia pelo Coronavírus em Wuhan” OR “Epidemia pelo Novo Coronavírus (2019-nCoV)” OR “Epidemia pelo Novo Coronavírus 2019” OR “Epidemia por 2019-nCoV” OR “Epidemia por Coronavírus de Wuhan” OR “Epidemia por Coronavírus em Wuhan” OR “Epidemia por Novo Coronavírus (2019-nCoV)” OR “Epidemia por Novo Coronavírus 2019” OR “Febre de Pneumonia por Coronavírus de Wuhan” OR “Infecção Viral COVID-19” OR “Infecção pelo Coronavírus 2019-nCoV” OR “Infecção pelo Coronavírus de Wuhan” OR “Infecção pelo SARS-CoV-2” OR “Infecção por 2019-nCoV” OR “Infecção por Coronavírus 2019-nCoV” OR “Infecção por Coronavírus de Wuhan” OR “Infecção por Novo Coronavírus de 2019” OR “Infecção por SARS Coronavirus 2” OR “Infecção por SARS-CoV-2” OR “Infecção por Vírus COVID-19” OR “Infecções por SARS-CoV-2” OR “Pandemia COVID-19” OR “Pandemia por COVID-19” OR “Pandemias por COVID-19” OR “Pneumonia do Mercado de Frutos do Mar de Wuhan” OR “Pneumonia por Coronavírus de Wuhan” OR “Pneumonia por Novo Coronavírus de 2019-2020” OR “Surto de Coronavírus de Wuhan” OR “Surto de Pneumonia da China 2019-2020” OR “Surto de Pneumonia na China 2019-2020” OR “Surto pelo Coronavírus 2019-nCoV” OR “Surto pelo Coronavírus de Wuhan” OR “Surto pelo Coronavírus de Wuhan de 2019-2020” OR “Surto pelo Novo Coronavírus (2019-nCoV)” OR “Surto pelo Novo Coronavírus 2019” OR “Surto por 2019-nCoV” OR “Surto por Coronavírus 2019-nCoV” OR “Surto por Coronavírus de Wuhan” OR “Surto por Coronavírus de Wuhan de 2019-2020” OR “Surto por Novo Coronavírus (2019-nCoV)” OR “Surto por Novo Coronavírus 2019” OR “Virose COVID-19” OR “covid-19”)

After conducting the search, the following will be included: studies conducted in English and Portuguese languages, with quantitative and qualitative approaches; primary studies, systematic reviews, meta-analyses, and meta-syntheses; and books and guidelines published in indexed sources that address the established question.

Duplicate articles, editorials, reviews, conference proceedings, theses, dissertations, monographs, undergraduate final projects, opinion publications, consensuses, retractions, editorials, websites, and advertisements disseminated will be excluded.

Perform Study Selection

The citations gathered will be transferred to Mendeley Reference Manager for Desktop (version 2.109.0; Elsevier Ltd.) after the search, and the duplicates will be manually removed. Following this, 2 reviewers (TI and JCA) will independently assess titles and abstracts for eligibility using the Participants, Concept, and Context framework. Full texts of potentially relevant articles meeting the eligibility criteria will be retrieved for the 2 reviewers to scrutinize and compare against the inclusion criteria. In case of discrepancies during any phase of article selection between TI and JCA, resolution will be sought through discussion or consultation with ARdAL, the third reviewer. The final scoping review will feature a descriptive account of the search and study selection process alongside a PRISMA-ScR flow diagram [15].

Extract and Chart the Data

The data from all eligible studies will be extracted and processed through data charting. This process involves extracting information from the selected full-text articles. A Microsoft Excel table will be created for this purpose, encompassing sections, such as title, authors, year of publication, geographic area, study objectives, pedagogical approaches, collaborative learning activities, resources adopted, and summary of findings.

Collate, Summarize, and Report the Results

The characteristics of each identified study will be summarized and described (eg, author name, study location, and year of publication), along with the pedagogical approach used in teaching biochemistry; the learning activities, content, and resources used; and any evaluation by students of the strategies used by their professors.

Results

Initiated in February 2022, the protocol for this scoping review was anticipated to wrap up by July 2024. The research process yielded 1171 results, from which 85 articles were selected. Verification of duplicates has not yet been conducted, and this will be carried out in the next stage of the work.

The outcomes of this scoping review on teaching strategies for biochemistry will be conveyed through a blend of descriptive narrative, graphical, and tabular formats. The presentation will be structured to underscore the various pedagogical approaches relevant to the field. These findings will be shared through regional and national scientific conference presentations, as well as publication in a peer-reviewed journal.

Discussion

Expected Findings

During the COVID-19 pandemic, the teaching of undergraduate and graduate courses in the health care field faced significant challenges [9]. The interruption of in-person laboratory activities and the need for quick adaptation to online teaching were some of the main obstacles [11,12]. Furthermore, the lack of access to laboratories and the disruption of clinical practice affected the development of essential practical skills for students [4].

However, some advantages were identified with the strategies adopted by teachers and institutions during the pandemic [8,17]. For instance, the use of online resources such as prerecorded videos and animated slides allowed for greater efficiency in academic work [1,5]. In addition, engaging in vital scientific activities such as reading articles and preparing presentations, coupled with the flexibility provided by remote learning, which enabled greater student participation, contributed to the cognitive development and enhancement of communication and technological skills of the students [1,4,5].

Considering these observations, continuing remote teaching strategies after the pandemic can bring various benefits [8]. The learning flexibility offered by online classes allows students to access content conveniently and effectively, promoting greater inclusion and expanding access to education [5,16]. Moreover, the possibility of continuous material review facilitates understanding and reinforces learning [1].

It should be emphasized that the use of educational technologies helps students develop essential digital skills for the current and future job market [5]. Therefore, blending educational strategies developed during the pandemic with in-person classes could bring additional opportunities for the improvement of teaching and learning not only in biochemistry but also in other disciplines [6,7].

In addition, this scoping review presents limitations. Specifically, there will be no evaluation of the quality of the studies included. There is a possibility of overlooking pertinent data, given that our search is restricted to published studies exclusively. We have chosen multiple sources and formulated meticulous search strategies to enhance the identification of eligible studies.

Conclusions

The results of this review are expected to bring forth ideas for new pedagogical approaches and identify learning activities, content, and resources that facilitate social and collaborative learning processes, both for biochemistry and other disciplines. In addition, insights from students and teachers regarding the activities developed will be provided, aiming to apply them as additional strategies to enhance student engagement, and consequently, learning and the development of various skills.

Acknowledgments

We would like to thank Zélia Cristina Regis at the Faculty of Medicine of São José do Rio Preto (FAMERP) for her contribution to the development of the research process.

Authors' Contributions

TI, HLGC, ARdAL, and JC conceptualized, designed, and interpreted the data and were the main contributors to writing the manuscript. ABGC, NBGC, VMSB, and DRSS analyzed and interpreted the data. TI, ERdS, NAdASRC, FNFJ, AH, and CM have supervised and revised the final draft.

Conflicts of Interest

None declared.

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Abbreviations

JBI: Joanna Briggs Institute
PRISMA-ScR: Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews
WHO: World Health Organization

Edited by T Leung; submitted 15.04.24; peer-reviewed by T Babaee; comments to author 07.08.24; revised version received 15.08.24; accepted 25.11.24; published 31.01.25.

Please cite as:
Iembo T, Cristóvão HLG, Santos ERD, Cristóvão ABG, Cristóvão NBG, Martins CC, Castro NADASR, Facio Júnior FN, Oliani AH, Lima ARDA, Brienze VMS, Souza DRS, André JC
Challenges and Strategies Adopted for Remote Teaching of Biochemistry During the COVID-19 Pandemic: Protocol for a Scoping Review
JMIR Res Protoc 2025;14:e59552
URL: https://www.researchprotocols.org/2025/1/e59552
doi:10.2196/59552
PMID:

Protocol

Access to Health Care and Use of Health Care Services Among Males in Africa: Protocol for a Scoping Review

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Abstract

Background: There is a scarcity of data on males' health-seeking behavior, as well as their access to and use of health care services, in Africa. According to some studies, men are less likely than women to seek medical help for issues such as communicable and noncommunicable diseases, depression, substance abuse, physical disabilities, and stressful life events. The study of males' health-seeking behaviors is important, because it allows us to learn about male health, how masculinity encourages underuse of health care services, how this affects males' overall health and well-being, and how cultural values and backgrounds may impact older men's health-seeking behaviors.

Objective: The objective of this review is to assess evidence on how males access and use health care services and their health knowledge, attitudes, and perceptions to identify gaps for targeted, context-specific strategies to improve males' health and outcomes, particularly in Africa.

Methods: The scoping review process will be guided by the methodology frameworks of the Joanna Briggs Institute and Arksey and O'Malley and will follow the Preferred Reporting Items for Systematic reviews and Meta-analysis Protocols Extension for Scoping Reviews guidelines. The following electronic databases will be systematically searched for evidence published between January 2010 and 2023: PubMed, Scopus, Web of Science, African Journals Online, and Google Scholar. Two reviewers will independently screen full texts and chart the data; a third reviewer will be engaged in the event of disagreement between the 2 independent reviewers. The results of this scoping review will be summarized quantitatively through numerical counts and qualitatively through a narrative synthesis.

Results: The electronic database search was conducted between March and April 2023 and redone in April 2024 to include the most recent articles. A total of 114,737 articles were retrieved and 4258 removed as duplicates. After title screening, 337 results remained, and after abstract selection, 140 results remained. As of December 2024, the scoping review was in the full-text screening phase. We plan to complete data extraction, synthesis, and writing of the entire manuscript of the review in January 2025, and then submit it to a journal for peer review and publication in February 2025.

Conclusions: The scoping review results will advance the current knowledge about health-seeking behavior and access to and uptake of health care services among African males. To our knowledge, this scoping review is the first on this topic, and it will identify vital information on the barriers to and facilitators of African males' health care access and uptake. It will also provide information on successful health care programs for males that may be tailored and adopted across different African contexts.

Trial Registration: OSF Registries https://osf.io/xz6sr

International Registered Report Identifier (IRRID): DERR1-10.2196/52351

(JMIR Res Protoc 2025;14:e52351) doi:10.2196/52351

KEYWORDS

health-seeking behavior; health care; access; uptake; services; men; boys; scoping review; Africa; male; health care services; accessibility; use; noncommunicable disease; depression; substance abuse; overdose; physical disability; stress; older men; men's health; well-being; health literacy; perception; systematic reviews; meta-analysis; electronic database; EHR; electronic health record; narrative synthesis

Introduction

The World Health Organization (WHO) defines health as "a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity" [1]. Sustainable Development Goal 3 complements this definition by pinpointing the need for global commitment to "ensure healthy lives and promote well-being for all at all ages" without exclusion [2]. Admirable and essential as these intentions may be, their success is incumbent upon reaching key populations so that the health care requirements of those populations may be fulfilled. Males the world over are one such key population, and they generally underuse the health care opportunities available to them [3-5]. This is concerning, since it is projected that men's health burden will result in men's lifespans being 7 years less than women by 2030. In South Africa, the male health risk and mortality rates are high due to tuberculosis, as well as noncommunicable diseases like diabetes and cardiovascular diseases, all of which are mostly preventable [6]. There are various reasons for men delaying or avoiding seeking health interventions, with some of the most regularly identified ones being a paucity of male-centered interventions, sociodemographic factors, and attitudes toward health services [7-9]. Nonetheless, there is evidence that a shift in males' attitudes is emerging and that they are becoming increasingly willing to access health care. Consequently, there is a drive to not only provide health care services that cater specifically to men and minimize the barriers to their seeking health care, but also to increase research in this field [8]. Our research will thus add to the body of knowledge that is used to fulfill the aforementioned commitment.

"Men" is a broad term; according to the WHO, there are different terminologies, age ranges, and characteristics used to describe the transition from childhood to adulthood for men. Adolescence has been described as the ages of 10 to 19 years and young adulthood as 10 to 24 years [10]. Guided by these clarifications, the age range in our scoping review included all male-related studies involving individuals aged 13 to 17 years as teenagers and those aged 18 years and older as adults. This age range of minors was included due to the fact that the onset of the teenage years is when young people experience "physiological, psychological, and social changes that lay bare the world of sexual experimentation" [11] and the consequences thereof, which may call for health care. This was deemed significant as it could yield a better understanding of males in this population, specifically with regard to their sexual reproductive health practices. Another population that was deemed significant to our study was transgender males, as their health-seeking behavior is currently underresearched, despite their experience of inordinate health risks and challenges [12].

An examination of health policies of 10 low- and middle-income countries revealed that health care priorities in these countries are largely driven by cost-saving measures and the types of disease that are prevalent. This means that health care priorities can differ significantly across geographical areas. Nonetheless, in most sub-Saharan countries, HIV is prioritized, with lymphatic filariasis, syphilis in pregnant or new mothers, human papilloma virus, tuberculosis, and sexually transmitted diseases being other common conditions [13]. What is striking is that not only are none of these conditions unique to males, but some of them are solely female focused. This is concerning because it conveys the impression that particularly male diseases are not a high priority. For example, the incidence of prostate cancer is escalating in West Africa, and treatment is usually delayed for so long that the health outcomes for men with the condition are dismal. Further, men with prostate cancer symptoms either remain ignorant of the disease or are too poor to seek treatment [14]. Equally dangerous are unhealthy lifestyle choices, like smoking and alcohol abuse, which are more prevalent among men, as well as some chronic diseases like diabetes and cerebrovascular disease, two of the main causes of death in men over the age of 45 years: the South African government has recently acknowledged all of these conditions as worthy of being addressed [4]. It is therefore not unreasonable to conclude that improved health literacy targeted specifically at males could help to mitigate their life-threatening health conditions and choices [15].

Apart from the obvious benefits of disease management, males who are inspired and empowered to take control of their own health can inadvertently improve the lives of their families, as well as society in general. Economically, better health would, in the long run, reduce medical costs that would usually be borne by the family and in some part, the government. Socially, healthy men would more likely be able to lead an active life in which they do not feel compelled to avoid health care to preserve their masculinity, nor fear stigmas associated with, for example, mental health conditions or undergoing antenatal HIV screening with their partners [8,16].

But, within the ambit of our study, we first have to ascertain what strategies have the most reasonable chance of uptake to be able to speculate on the benefits of males engaging in health-seeking practices. What has to be borne in mind is that men's health-seeking behavior, which in Africa is influenced by a particularly patriarchal ethos, limited resources, and faith in traditional medicines and cultural superstitions [8,17], may not necessarily match the behavior of males in countries that do not share similar characteristics.

In essence, this scoping review will seek to describe the variations in health-seeking behaviors among males across the African continent, assess their access to and use of health care services, and identify both challenges and facilitators of health care uptake. Additionally, it will explore males' knowledge, attitudes, perceptions, and beliefs regarding their health care needs and available services. The overall goal is to assess the

current evidence on these factors to guide the development of strategies that enhance males' health and improve outcomes across the region. To this end, the primary objective of this scoping review is to map evidence on males' access to and use of health care services and identify gaps for targeted, context-specific strategies to improve males' health outcomes, particularly in Africa.

Methods

Study Design

We will use a scoping review approach to map out existing evidence on males' health-seeking behavior and access to and uptake of health care services in Africa. This will enable us to identify aspects for tailored intervention to improve males' health-seeking behavior. In conducting this review, we will apply the methodological approach and review process of the Joanna Briggs Institute (JBI) [18]. The JBI framework enables an extensive and less-biased synthesis of studies by using comprehensive and transparent methods [19]. The JBI framework synthesizes existing knowledge rather than creating new knowledge [20]. This yields decisions that reflect on the feasibility, appropriateness, meaningfulness, and effectiveness of health behavior [19,20] The Preferred Reporting Items for Systematic reviews and Meta-analyses extension for Scoping Reviews (PRISMA-ScR) guidelines [21,22] will be adhered to in reporting this scoping review. The PRISMA-ScR guidelines are congruent with the JBI approach for scoping reviews, which emphasizes the importance of methodological precision for scoping reviews. We believe that the PRISMA-ScR will improve the reporting of our scoping review [22]. According to the 5 main steps [18], we discuss our review process in the following sections.

Step 1—Identifying the Research Question

The scoping review questions will be formulated according to the population, concept, and context (PCC) approach recommended by the JBI. The PCC framework is suitable when developing objectives and eligibility criteria for scoping reviews [23]. In our study, the PCC inclusion criteria will be useful to guide how the data should be extracted. There is no need for outcomes or interventions of interest to be identified for a scoping review [24] (Table 1).

Based on the PCC framework mentioned above, the research questions we will explore are outlined below:

1. What are the varying health-seeking behaviors among males across the African continent?
2. What are health services for males and how do males access and use health care services in Africa?
3. What knowledge, attitudes, perceptions, and beliefs exist among males about their health care needs and health care services in Africa?
4. What are the challenges and facilitators of health care uptake by males in Africa?

Table 1. The population, concept, and context (PCC) elements in this review.

Element	Description
Population	Males only
Concept	Health-seeking behavior; health care service access, use, and uptake
Context	Africa

Step 2—Identifying Relevant Studies

We will systematically search PubMed, African Journals Online, Web of Science, Scopus, and Google Scholar. The search will include papers with publication years from 2010 to 2023 to better reflect more recent information and current health-seeking behavior among males across the African continent. In addition, government reports available on the websites of departments and ministries of health and associations will be reviewed with a focus on males' access to health care services, knowledge, perceptions, and attitudes regarding health care services, as well as barriers and facilitators to uptake of health services by males. This will help us to identify reports related to males' health-seeking behavior in Africa.

The search strategy will include titles, abstracts, and combinations of keywords, as presented in Multimedia Appendix 1 and Multimedia Appendix 2.

Step 3—Study Selection

After collection of study data from the aforementioned bibliographic databases, 3 reviewers will conduct the review; 2 will perform data selection and database searching and the third will perform quality checking and resolve inclusion and exclusion disagreements between the 2 primary reviewers. The 2 primary reviewers will independently use the inclusion and exclusion criteria to search the titles and abstracts, and they will document reasons for inclusion and exclusion as outlined below. Any discrepancies will be discussed and resolved between these 2 reviewers, but if no conclusion can be reached, the third reviewer will be included in the discussion. Furthermore, the reviewers will independently source full-text versions of articles found to be eligible during the title and abstract screening phase. They will exclude articles without full-text versions available after a conclusive discussion regarding the excluded articles is reached. The searched articles will include male-related studies and include qualitative, quantitative, and mixed methods interventions for males' health, knowledge, attitudes, and perceptions regarding health services for males, as well as access and challenges to use of health care services. Overall, this scoping review will include material that fulfill the criteria outlined in Tables 1 and 2. The exclusion criteria entail studies not conducted in Africa; not including males' health care service access and uptake or health-seeking behavior; and those conducted prior to 2010.

Table 2. The eligibility criteria.

Criteria for study inclusion	Component details
Setting	Only studies from Africa will be considered for the scoping review.
Language	Only English-language studies will be included.
Date	Only studies from the years 2010 to 2023 will be included.
Publication status	All documented studies will be considered and included in the scoping review. This will include only published peer-reviewed articles.
Method	The study will be designed and reported according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews. Population, concept, and context will be used as the search strategy approach. Qualitative, quantitative, and mixed methods studies will be included.

Step 4—Charting the Data

Data from the identified eligible studies will be collected and charted. Reviewers will record key themes from each eligible article. The themes will include author, journal, publication status, study duration, year, and demographic information (age, ethnicity, marital/relationship status, employment, residential location [rural or urban], income, and education level), geographical information (country and region in which the study was done), research methodology, and findings included in the synthesis (study design, health-seeking behavior, access, uptake, intervention, main results and outcome, limitations, and other important discoveries; Textbox 1). Microsoft Excel, EndNote, and Rayyan will be used in obtaining the data, saving the search, cleaning the data, screening the data, and charting the data for this scoping review.

Textbox 1. Data chart template (to be expanded during actual review).

Details of elements included in the synthesis

- Author
- Journal
- Publication status
- Study duration
- Year

Demographic information on participants in the synthesis

- Age
- Residential location (rural or urban)
- Ethnicity
- Marital/relationship status
- Income
- Employment
- Education level

Geographic information in the synthesis

- Region where the study was done
- Country

Research methodology and summary findings in the synthesis

- Study design
- Health-seeking behavior
- Access
- Uptake
- Intervention
- Main results and outcome
- Limitation
- Other important discoveries

Other comments, if any

Step 5—Collating, Summarizing, and Reporting the Results

A qualitative and quantitative approach will be used to report and summarize the scoping review. The number and type of eligible studies will be reported numerically, and methods, results, health care services, program, and health-seeking behavior information will be described in a narrative form. Tables and charts will be used to map out the screening process and results. Discussion will be guided by developed themes and study objectives and will include definitions of keywords. The risk of bias will not be assessed, as the scoping review is meant to provide an overview of existing literature about health-seeking behavior of African males and not critically analyze or appraise the selected articles; the limitations of the studies will be noted. Secondary analyses will be performed looking at health-seeking behavior and challenges, knowledge, and stigma regarding access to and uptake of health care services among boys and the transgender population. Analyses will also compare males' health-seeking behavior and service access and use across different regions.

Results

The electronic database search was conducted between March and April 2023 and was redone in April 2024 to include the most recent publications. A total of 114,737 results were retrieved, and 4258 were identified as duplicates. The database was first title screened, and this yielded a total of 337 articles for further abstract screening, which resulted in 140 articles remaining for full article screening. We are currently finalizing full-article screening for the synthesis. We intend to complete the synthesis and initial manuscript write-up in January 2025, for submission for peer review and publication in February 2025.

Discussion

Expected Findings

We expect to substantiate that the burden of disease in males compared to females is high for a plethora of reasons, such as availability of context-specific health care services for males, access by males to health care, and the socioeconomic position of households. Moreover, available evidence has shown that male health-seeking behavior is often delayed, and the uptake of health care services is poor due to barriers such as cultural beliefs, perceptions of masculinity, stigma, gaps in health knowledge, and social and economic factors [25,26]. Based on the limited number of published articles on males' access to and uptake of health care services, especially in Africa, and observations on trends in the proportions by sex of outpatients (ie, there are more females than males) seeking care in primary health care centers [27-30], there is a need for male health care to be taken into consideration. Facilitators like community-based interventions, male-targeted programs, and peer support have been shown to improve male engagement with health care [26]. To our knowledge, this scoping review is the first on this topic, and it will identify key themes and gaps regarding the barriers to and facilitators of African males' health care access and uptake. The scoping review will summarize and discuss our findings, including challenges and facilitators of health care service access and uptake and health-seeking behavior among African males. The results may form the basis for future qualitative research on exploring the health-seeking behavior of African males, quantitative research on barriers to and facilitators of access to and uptake of health care services, implementation research on intervention programs to influence African males to access and use health care services voluntarily, or systematic reviews of programs for working African males to access health care and support systems and increase their health care–seeking behavior. The results may also help policy makers to develop programs and interventions specifically tailored for the needs of males through males' input. The literature synthesis will support the development of evidence-based practices that will address challenges related to males' access to health care services, enhance their health care knowledge, and promote intervention programs to improve uptake, which may result in a decreased burden of disease and mortality rate among males. We expect our main findings to provide insights into what geography-specific health services are available across the African region, as well as provide the latest evidence on the extent of access and uptake, including contributing factors. The results of this scoping review will be disseminated through scientific conference proceedings and presentations, stakeholder meetings, and by publication in a peer-reviewed journal. During the dissemination of findings, stakeholders will be invited to discuss gaps and challenges affecting males' health-seeking behavior and the uptake of health care services to develop context-specific strategies that can be implemented to address the identified gaps and challenges. The dissemination report will also include recommendations for future research, review limitations, and discuss the risk of bias.

Potential Limitations to the Scoping Review

Through this scoping review, we intend to provide a range of information about the health-seeking behavior of males, including their access to and use of health services. However, as we will limit our search to include only published works written in English and implemented in Africa, we are likely to inadvertently exclude relevant programs, thereby skewing the comprehensiveness of the review. Constraints related to the publication type, language, and geographic region will restrict the diversity of the included sources, limiting its applicability across various contexts. Our search strategy did not use the built-in search functionalities of the relevant electronic databases, such as Medical Subject Headings terms for PubMed. Our search strategy might have increased the risk of missing literature. To mitigate this, we constructed a wide range of search terms to ensure a wider reach.

Acknowledgments

This publication was supported by the National Heart, Lung, And Blood Institute of the National Institutes of Health (UH3HL156388). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Data Availability

The data sets generated during and/or analyzed during this study are available from the corresponding author on reasonable request.

Authors' Contributions

All authors contributed equally to conceptualization, methodology, and writing of the manuscript. STL-E contributed to funding acquisition.

Conflicts of Interest

None declared.

Multimedia Appendix 1

Search permutations.
[DOCX File , 17 KB - resprot_v14i1e52351_app1.docx]

Multimedia Appendix 2
Search strategy.
[DOCX File , 14 KB - resprot_v14i1e52351_app2.docx]

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Abbreviations

JBI: Joanna Briggs Institute
PCC: population, concept, and context
PRISMA–ScR: Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews
WHO: World Health Organization

Edited by A Schwartz, T Leung; submitted 31.08.23; peer-reviewed by A Yazdanian, A Gangadhara Rao, GRM La Rosa; comments to author 11.03.24; revised version received 29.03.24; accepted 09.12.24; published 31.01.25.

Please cite as:
Mashilo NJ, Oladimeji KE, Gumede S, Lalla-Edward ST
Access to Health Care and Use of Health Care Services Among Males in Africa: Protocol for a Scoping Review
JMIR Res Protoc 2025;14:e52351
URL: https://www.researchprotocols.org/2025/1/e52351
doi:10.2196/52351
PMID:

Protocol

Interdisciplinary Strategies to Reduce Surgical Infectious Risk in the Operating Theater: Protocol for Scoping Review

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Abstract

Background: Surgical site infections (SSIs) represent one of the most prevalent and significant complications associated with surgical procedures, often leading to prolonged hospitalization and delayed patient recovery. While recent international consensus guidelines have proposed evidence-based strategies to mitigate SSIs, they fall short in addressing the efficient and interdisciplinary implementation of these measures within the operating theater. Consequently, further research is required to identify and evaluate optimal interdisciplinary organizational approaches for the prevention of SSIs.

Objective: This study aims to map the scope, diversity, and nature of research on interdisciplinary strategies aimed at reducing SSIs and to analyze the impact of interdisciplinary on the effectiveness of preventive interventions.

Methods: Using the Joanna Briggs Institute (JBI) methodology for scoping reviews, a comprehensive search will be conducted across databases including Embase (encompassing MEDLINE and PubMed-not-MEDLINE), CINAHL, and the Cochrane Library, supplemented by manual searches of reference lists from included papers. This review targets studies published between 2016 and 2024, aligning with the World Health Organization's 2016 SSI prevention guidelines, which introduced significant advancements in practice and remain the global benchmark. Only studies published in English or French will be considered. Around 5 reviewers independently distributed the included papers for detailed reading and data extraction, while the lead author concurrently and independently reviewed all papers. Inclusion criteria follow the Participants, Concept, and Context (PCC) framework, specifying that the eligible population comprises surgical teams. The primary concept of interest is interdisciplinary strategies aimed at preventing infection risk. The context focuses on adult surgical procedures within the operating room during turnover periods. Studies using experimental, quasi-experimental, preexperimental, observational, case-control, or cross-sectional designs will be included.

Results: From the 1679 papers initially identified, 45 were selected for detailed analysis by 5 reviewers, with the selection process completed by November 2024.

Conclusions: Emerging interdisciplinary strategies demonstrate significant potential in reducing the incidence of SSIs. This initiative forms part of a broader global project focused on codeveloping standardized protocols for preoperative preparation within the operating room to mitigate SSI risks. The findings of this scoping review will serve as the foundation for a subsequent

qualitative survey and a pre-post quasi-experimental quantitative study to evaluate the integration and effectiveness of these strategies in clinical practice. The review protocol will be formally registered in the Open Science Framework (OSF) in 2024.

International Registered Report Identifier (IRRID): DERR1-10.2196/67660

(JMIR Res Protoc 2025;14:e67660) doi:10.2196/67660

KEYWORDS

surgical site infection; infection prevention; interdisciplinary strategies; surgical team; operating room; standardized operating procedures

Introduction

Background

The transition to advanced health care technologies is inherently linked to heightened patient safety risks within acute care hospital settings [1]. Operating theaters are environments where multiple risk factors converge, contributing to adverse or severe events. Among these, the risk of infection remains a primary concern and a persistent daily challenge, as infections represent a leading cause of preventable hospital mortality [2]. These infections contribute substantially to morbidity and mortality while also imposing significant additional burdens on health care costs [3]. In Switzerland, surgical site infections (SSIs) are the most prevalent type of health care–associated infection within medical facilities [4].

Adhering to evidence-based practice (EBP) has the potential to significantly reduce infection rates, with the corresponding levels of evidence for SSIs already well-documented in the literature [5]. In the operating theater, the implementation of both standard and procedure-specific precautions is crucial for effective infection prevention [6].

SSIs are nosocomial in nature, occurring after surgical procedures, and primarily influenced by pre-, intra-, and postoperative conditions, host immune response, and surgical cleanliness. Pathogen transmission predominantly occurs through contact, with health care workers' hands serving as a major vector. Effective hand hygiene is paramount in preventing infections, particularly in acute care settings, where it plays a critical role in reducing the incidence of bacteremia, urinary tract infections, SSIs, and ventilator-associated pneumonia [3,7].

Key strategies include maintaining high standards in medical device disinfection, bio cleaning, and surface cleaning to minimize infection risks [8]. Monitoring adherence to disinfection protocols during turnover periods is essential for evaluating interdisciplinary coordination and minimizing contamination risks [9]. Adherence to current guidelines is crucial, given the rapidly evolving nature of EBP, as many practices once deemed acceptable are now considered contraindicated [10,11].

The World Health Organization (WHO) and Society for Healthcare Epidemiology of America (SHEA) recommendations for SSI prevention differ slightly in the level of evidence [2,10]. However, consensus exists regarding key practices, such as appropriate hair removal, surgical hand preparation, the use of alcohol-based skin antiseptics (eg, chlorhexidine gluconate solutions), optimal timing of antibiotic prophylaxis, and effective glycemic control [7,12,13]. Emphasis is also placed on the development of soft skills, the implementation of checklists, adherence to bundled care protocols, SSI monitoring, and providing feedback to operating theater staff members as key strategies for enhancing patient safety [5,12,14,15].

Low compliance with SSI prevention measures persists due to the challenges associated with implementing clinical guidelines effectively. Globally, only 29% of tertiary hospitals across 133 countries have established infection prevention and control (IPC) programs. In Switzerland, according to Swissmedic (2022), 93% of 35 surveyed institutions out of 300 reported deficiencies in critical areas, including procedural adherence, staff training, the presence of hygiene specialists, and cognitive dissonance within operating theater teams.

Operating theaters demand the coordinated efforts of surgeons, anesthetists, technicians, and nurses to deliver high-quality care. Effective IPC depends on robust collaboration, clear communication, cohesive teamwork, and streamlined logistics across various hospital disciplines [16]. The complex and highly technical environment of operating theaters, combined with the diverse professional backgrounds of team members, necessitates effective interprofessional collaboration, particularly in time-sensitive situations [17]. Managing human error in the perioperative period remains a major challenge [18-24].

Interprofessionality emphasizes practical collaboration among skilled professionals, while interdisciplinary focuses on integrating knowledge from diverse academic disciplines to address complex challenges. Both approaches are essential for effective IPC in health care settings.

Although expert guidelines from organizations such as WHO, SHEA, Infectious Diseases Society of America (IDSA), Association for Professionals in Infection Control and Epidemiology (APIC), and American Hospital Association (AHA) provide a strong foundation, they lack sufficient specificity regarding the interdisciplinary applications required for SSI prevention in operating theaters [10]. A preliminary search revealed a lack of recent systematic reviews, underscoring the necessity of investigating and evaluating effective interdisciplinary strategies for reducing SSIs.

Review questions:

1. What are the interdisciplinary strategies to reduce SSIs in the operating theater?

2. What are its characteristics?

3. What improvements have been observed concerning the interventions and their evaluation?

4. Would it be possible to apply a model considering the culture and the local specificities?

Study Aim

This scoping review seeks to map the scope, diversity, and nature of existing research on interdisciplinary strategies for reducing SSIs. The objective is to identify patterns, gaps, and innovations in the literature while evaluating how the integration of diverse disciplinary approaches enhances outcomes in SSI prevention.

Methods

Overview

The proposed scoping review will be conducted according to the Joanna Briggs Institute (JBI) methodology for scoping reviews [25] and the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews) [26].

Search Strategy

A 3-step search strategy will be used for this review. Initially, a preliminary limited search was conducted in MEDLINE (via PubMed) to identify relevant papers on the topic. The text words in the titles and abstracts of these papers, along with the index terms used to describe them, were extracted and cataloged for use as search terms. The second step involves a comprehensive search incorporating all identified keywords and index terms, tailored for each database and information source. Databases to be searched include CINAHL (Multimedia Appendix 1), Embase (Multimedia Appendix 2), MEDLINE (Multimedia Appendix 3), and the Cochrane Library (Multimedia Appendix 4).

The third step comprises a manual search of the reference lists of all included papers to identify additional studies meeting the inclusion criteria. This review focuses on studies published between 2016 and 2024, a period defined by the WHO's designation of SSIs as a global priority and the release of its prevention guidelines. This time frame reflects significant advancements with outdated practices being phased out. Priority was given to studies adhering to these guidelines as no major updates have been introduced since their publication.

Systematic reviews conducted by organizations such as the Centers for Disease Control and Prevention, SHEA, and others broadly align with WHO recommendations, with variations primarily in evidence grading. Additional studies were identified through reference list searches of included papers. Only papers published in English or French were included in the review.

Inclusion Criteria

The Participants, Concept, and Context (PCC) framework was used to guide the identification and selection of studies for inclusion in this review [25].

Participants

The eligible population comprises surgical teams, encompassing all professionals involved in patient preparation within the operating room immediately before surgery. This includes surgeons, anesthetists, anesthetic nurses, registered nurses, scrub nurses, instrument technicians, and nursing assistants. Papers will be included if they address the involvement of at least 3 distinct disciplines [6].

Concept

This review focuses on interdisciplinary strategies for IPC. Interdisciplinary in this context does not merely refer to the diverse characteristics of personnel, such as education or professional roles, but rather to a coordinated framework for joint action, exemplified by standard operating procedures. These interdisciplinary approaches leverage shared mental models and visual triggers to activate synchronization among team members. Such frameworks have been described and validated in other industries, such as task-sharing standard operating procedures used by Airbus in cockpit operations. Papers will be included if they report on at least one interdisciplinary strategy.

Context

The specific context is adult surgical procedures within operating theaters during turnover, defined as the period between the closure of one patient's surgical wound and the incision of the next. This turnover period is critical for infection prevention through measures such as antibiotic prophylaxis and skin preparation. In adult surgeries, turnover often involves high-risk procedures, necessitating robust infection control strategies. Only studies that report interventions during turnover in adult surgical settings will be included; those focusing on pediatric surgery or unrelated contexts will be excluded. A significant body of EBP emphasizes reducing infection risks during this critical transitional phase.

Types of Sources

This scoping review will include experimental and quasi-experimental study designs, such as randomized controlled trials, nonrandomized controlled trials, before-and-after studies, and interrupted time-series studies. In addition, analytical observational studies, including prospective and retrospective cohort studies, case-control studies, and analytical cross-sectional studies, will be considered for inclusion. Publications such as editorials, commentaries, letters, conference proceedings, and gray literature will be excluded as the focus is on identifying effective and validated interdisciplinary models.

Study or Source of Evidence Selection

Following the search, all identified citations will be compiled and uploaded into EndNote 20 (Clarivate), where duplicate entries will be removed. After conducting a pilot test, titles and abstracts will be screened by 2 independent reviewers to determine their alignment with the inclusion criteria. Study selection will involve a dual-review process of titles and abstracts, followed by a thorough analysis of the full text. In cases of discrepancies, a third reviewer will be consulted to reach a consensus. Full-text versions of potentially relevant sources will be retrieved and their citation details will be imported into the JBI System for the Unified Management, Assessment, and Review of Information (JBI) [27]. Around 5 reviewers will independently evaluate the full text of selected citations against the inclusion criteria. Reasons for excluding

sources that do not meet these criteria will be systematically documented and reported in the scoping review. To ensure thoroughness and consistency, all reviewers will collectively read and analyze a subset of the included papers, while the lead author will independently review all included papers to guarantee a comprehensive and unbiased assessment.

Any disagreements among reviewers at any stage of the selection process will be resolved through discussion or, if necessary, with the involvement of additional reviewers. The search results and study inclusion process will be fully documented in the final scoping review and presented using a PRISMA-ScR flow diagram.

Data Extraction

A total of 5 reviewers divided the included papers among themselves for in-depth reading and data extraction, while the lead author independently reviewed all papers in parallel. In cases of confusion or disagreement, the extraction files were compared and discussed with the relevant reviewer to ensure accuracy and consensus. All reviewers used a custom-designed data extraction tool (Data extraction instrument, Multimedia Appendices 5-8; Textbox S1 in Multimedia Appendix 9) to systematically collect data from the studies included in the scoping review.

The data extracted includes detailed information on participants, the concept under investigation, the context, study methodologies, and key findings pertinent to the review question. In addition, general information about each study, as well as its methods, characteristics, and results, will be documented to provide a comprehensive overview. The draft data extraction tool will be adapted and refined as necessary to ensure the accurate extraction of data from each included evidence source. Any modifications made to the tool will be documented in detail within the scoping review. Disagreements among reviewers regarding data extraction will be resolved through discussion or, if required, with the involvement of an additional reviewer. Where appropriate, the authors of the included papers will be contacted to obtain missing or supplementary data.

Results

From the 1679 papers initially identified, 45 were selected for detailed analysis by 5 reviewers, with the selection process completed by November 2024.

The interprofessional perspectives and interdisciplinary interventional components of various strategies aimed at reducing SSIs in the operating theater will be thoroughly detailed. The review will specify whether these interventions were introduced and developed within the framework of a particular implementation model or care concept. In addition, key elements of the triggers synchronization bundle, which facilitate safe organizational practices, proper procedural sequencing, and the delivery of high-quality care, will be highlighted. At the beginning of the year 2025, the identified preventive strategies will be presented through narrative syntheses and summary tables, supplemented by graphs illustrating the distribution of studies and emerging trends related to the scoping review questions. General extraction information will be summarized in a descriptive table (Textbox S1 in Multimedia Appendix 9) and further detailed (Multimedia Appendix 5) for each category. These categories include years of publication, study locations, study designs, sample sizes, and participant demographics. In addition, for the observed interventions, it will be specified whether they fully or partially align with EBP and international recommendations.

Discussion

Overview

We are conducting a comprehensive review of the literature to identify the most effective multidisciplinary models implemented in operating theaters for reducing SSIs. Our objectives are to characterize the key features of these models, evaluate their impact on organizational outcomes, and explore their association with SSI rates. While it is likely that we will identify efficient models, establishing a definitive hierarchy of their effectiveness may be challenging due to the unique characteristics inherent to each surgical specialty. However, several interdisciplinary practices are expected to exert significant influence—either positively or negatively—on the incidence of SSIs.

Our goal is to propose a generalizable model applicable across the majority of surgical specialties, focusing on improving practices and enhancing communication within the operating room to reduce variability. Furthermore, we aim to identify a replicable model suitable for implementation in Switzerland, emphasizing the importance of a collaborative approach adapted to the specific constraints of health care settings.

Evidence-based interdisciplinary strategies have demonstrated effectiveness in reducing SSIs. Research indicates that the successful implementation of care bundles is frequently associated with improvements in process outcomes rather than direct patient outcomes. Nonetheless, patient outcomes consistently show significant reductions in postoperative infection rates when interdisciplinary interventions are rigorously applied [28]. A significant challenge lies in ensuring the consistent engagement of health care professionals, particularly surgeons, in implementing interdisciplinary strategies. The studies reviewed predominantly offer moderate-quality evidence, highlighting the pressing need for standardized approaches and tools to enhance the effectiveness and reproducibility of interventions [29]. However, the concept of interdisciplinary remains underexplored in the existing literature. While support and training programs are frequently emphasized, no singular pivotal factor emerges as decisively shaping the health care system or fostering interdisciplinary collaboration. Notably, critical principles such as decompartmentalization and care synchronization—core components of the cognitive model bundle developed by the Airbus industry to optimize team efficiency—have yet to be systematically identified or applied within this context.

Limitations

This scoping review is restricted to adult patients and the included papers are limited to those published in English and

French, which may result in the exclusion of some relevant evidence. In addition, in several selected studies, the outcome measures are not reported, complicating the evaluation of the interventions' impact on SSI rates. Even when SSI rates are provided, the variability in monitoring methods must be taken into account, as it can influence the interpretation and comparability of results.

Conclusions

Emerging interdisciplinary strategies demonstrate promising potential for the prevention of SSIs and could be effectively replicated in Switzerland through a tailored implementation model. The bundles of care analyzed in this review appear to be robust in structure; however, the quality of interdisciplinary and their implementation in the operating theater remains challenging to evaluate, with adherence to recommended practices consistently falling short of optimal levels. The need for standardization of these bundles is frequently emphasized across studies.

Notably, this review did not reveal significant innovations, underscoring a gap in the literature. It forms part of a global initiative to cocreate a standardized approach to preoperative preparation in the operating room to reduce SSIs. While studies often highlight what should be done, they rarely address how to implement these measures effectively, pointing to an urgent need for innovative and actionable strategies. This presents an opportunity to develop a coconstructed model in collaboration with surgical teams, ensuring its feasibility and effectiveness through evaluation in real-world clinical settings.

Acknowledgments

We thank Dr Rita Nugem for her careful proofreading and valuable advice and the Nurse Directorate of HUG for its support. Open Access funding for this research was provided by the research fund of the Care Directorate at HUG. The doctoral studies for DJ are partially funded by the Geneva University Hospitals.

Authors' Contributions

DJ and SB contributed to conceptualization. DJ, SB, AR, and CD assisted with methodology. SK, CB, AH, AW, SB, and DJ performed data curation. DJ was involved in writing–original draft. SB and AR were involved in writing–review and editing. CD and AR performed supervision.

Conflicts of Interest

None declared.

Multimedia Appendix 1
CINAHL Search strategy from Dec 2016 to May 2024.
[DOCX File , 15 KB - resprot_v14i1e67660_app1.docx]

Multimedia Appendix 2
Embase Search strategy from Dec 2016 to May 2024.
[DOCX File , 15 KB - resprot_v14i1e67660_app2.docx]

Multimedia Appendix 3
MEDLINE Search strategy from Dec 2016 to May 2024.
[DOCX File , 15 KB - resprot_v14i1e67660_app3.docx]

Multimedia Appendix 4
Cochrane Library Search strategy from Dec 2016 to May 2024.
[DOCX File , 14 KB - resprot_v14i1e67660_app4.docx]

Multimedia Appendix 5
Data extraction instrument.
[DOCX File , 14 KB - resprot_v14i1e67660_app5.docx]

Multimedia Appendix 6
Data extraction instrument Characteristics 1.
[DOCX File , 14 KB - resprot_v14i1e67660_app6.docx]

Multimedia Appendix 7
Data extraction instrument Characteristics 2.

[DOCX File , 14 KB - resprot_v14i1e67660_app7.docx]

Multimedia Appendix 8
Data extraction instrument Characteristics 3.
[DOCX File , 13 KB - resprot_v14i1e67660_app8.docx]

Multimedia Appendix 9
Data extracted from studies.
[DOCX File , 14 KB - resprot_v14i1e67660_app9.docx]

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Abbreviations

AHA: American Hospital Association
APIC: Association for Professionals in Infection Control and Epidemiology
EBP: evidence-based practice
IDSA: Infectious Diseases Society of America
IPC: infection prevention and control
JBI: Joanna Briggs Institute
OSF: Open Science Framework
PCC: Participants, Concept, and Context
PRISMA-ScR: Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews
SHEA: Society for Healthcare Epidemiology of America
SSI: surgical site infection
WHO: World Health Organization

Edited by T Leung; submitted 17.10.24; peer-reviewed by I Uçkay, YY Kristian, C Oko; comments to author 27.11.24; revised version received 14.12.24; accepted 26.12.24; published 12.02.25.

Please cite as:
Joubert D, Boloré S, Baroni C, Hans AS, Wasser A, Kivrak S, Murat-Ringot A, Dussart C
Interdisciplinary Strategies to Reduce Surgical Infectious Risk in the Operating Theater: Protocol for Scoping Review
JMIR Res Protoc 2025;14:e67660
URL: https://www.researchprotocols.org/2025/1/e67660
doi:10.2196/67660
PMID:

Protocol

Understanding the Psychosocial Impact of Assistive Technologies for People With Visual Impairments: Protocol for a Scoping Review

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Abstract

Background: There has been a rapid growth in the literature on the design and evaluation of assistive technologies for people with visual impairments; yet, there is a lack of a comprehensive analysis of the existing literature on the classification of immediate-, short-, medium-, and long-term psychosocial impact of assistive technologies on the quality of life of people with visual impairments.

Objective: This protocol outlines the methodology for a scoping review aimed at identifying and synthesizing the existing literature on the psychosocial impact of assistive technologies on the quality of life of people with visual impairments.

Methods: The review will include primary research studies published in English between 2019 and 2024 that focus on the psychosocial outcomes of assistive technologies for people with visual impairments. Eligible studies will involve participants with visual impairments, of all ages and across various settings, examining psychological (eg, emotional well-being and self-esteem) and social outcomes (eg, social participation and support). Searches will be conducted across 7 electronic research databases: CINAHL (EBSCO), PsycINFO (EBSCO), ACM Digital Library, IEEE Xplore, Scopus, Web of Science, and Google Scholar (first 100 records). Studies will undergo screening and selection based on predefined eligibility criteria, with data extraction focusing on publication details, study design, population characteristics, type of assistive technology, and psychosocial impacts. Results will be summarized using descriptive statistics, charts, and narrative synthesis.

Results: The database search, conducted in July 2024, identified 1145 records, which will be screened and analyzed in subsequent stages of the review process. This protocol outlines the planned approach for identifying, categorizing, and synthesizing evidence. The study findings are anticipated to be finalized and submitted for publication in a peer-reviewed journal by February 2025.

Conclusions: This study will synthesize the recent body of work on the psychosocial impact of assistive technologies for people with visual impairments and recommendations for researchers and designers interested in this research area.

Trial Registration: Open Science Framework 10.17605/OSF.IO/SK7N8; https://osf.io/4gc5t

International Registered Report Identifier (IRRID): DERR1-10.2196/65056

(JMIR Res Protoc 2025;14:e65056) doi:10.2196/65056

KEYWORDS

assistive technology; psychosocial impact; quality of life; visual impairment; scoping review protocol; mobile phone

Introduction

Background

Globally, visual impairment affects approximately 1 billion people [1]. Visual impairment significantly impacts people's quality of life, affecting activities of daily living, education, employment, and social interactions [2-4]. The most prominent effects of vision loss are loss of independence and social isolation, leading to anxiety, depression, and other mental health conditions [4]. Due to this, many people with visual impairments

experience low self-esteem and self-efficacy in their mobility and social interaction [5]. Furthermore, the participation of people with visual impairments in leisure activities is low. Where they do, people with visual impairments participate in passive leisure activities (eg, watching television and listening to the radio) rather than actively participating in physical activities, social interaction, and sports in outdoor places [6]. Research shows that people with visual impairments have low mental health outcomes and overall quality of life compared to sighted people [4,7,8].

The World Health Organization [9] defines assistive technology (AT) as an umbrella term for assistive products, systems, and services designed to maintain or improve one's functioning related to cognition, communication, hearing, mobility, self-care, and vision, therefore promoting health, well-being, inclusion, and participation. The European Parliament research report on AT for people with disabilities [10] distinguishes among five types of ATs for blindness and visual impairment: (1) haptic aids (eg, the white cane, the traditional Braille system, embossed pictures, advanced Braille apps, advanced canes, haptic aids for computer use, and matrices of point stimuli), (2) traveling aids (eg, low-technology haptic aids, obstacle and object location detectors, electronic travel devices, assistive apps in mobile phone technology, embedded technologies, and mixed systems), (3) AT for accessible information and communication, (4) AT for daily living (eg, labeling systems, talking readers, tactile and vibrating clocks and alarms, talking kitchen tools, and talking wallets and purses), and (5) phone and tablet apps (eg, magnification apps, color detection apps, money identification apps, object identification apps, scan and read apps, screen reading apps, voice recognition apps, location and GPS apps, and Braille apps).

Mashiata et al [11] classified ATs for visual impairment into four categories: (1) based on portability (eg, nonwearable devices such as smart canes and assistant robots and wearable travel aids such as head-mounted, ear aids, belt-mounted, blind shoes, glasses, and gloves), (2) based on navigation (eg, audio-tactile maps, indoor, indoor-outdoor, and outdoor such as smart city or urban navigation, vehicle detection, airport accessibility, shopping guide, and pedestrian navigation), (3) based on detection (eg, object recognition and obstacle detection, including vehicle detection, pedestrian detection, staircase, and daily life objects), and (4) based on smartphone assistance (eg, digital assistants, mobile apps, including voice maps, voice search, and mobile games).

Over recent decades, disability has stopped being viewed solely in functional terms. Frameworks such as the International Classification of Functioning, Disability and Health and the World Health Organization Quality of Life [12] now emphasize the importance of psychological and social dimensions in understanding and enhancing the quality of life for individuals with disabilities. However, much of the existing research on the impact of ATs has primarily focused on the functional outcomes associated with their use and attributed the poor uptake of these technologies to functional issues [13,14]. Two key points should be raised in relation to this. First, ATs continue to be designed from a biomedical, deficiency-oriented rather than a psychosocial, person-centered approach, failing to effectively fulfill users' needs [15]. Second, researchers have overlooked the role of psychosocial factors in the perception and use of ATs, which may better explain their acceptance and uptake, prompting the development of instruments such as the Psychosocial Impact of Assistive Devices Scale [13] to address this gap.

As with other disabilities, prior research has mainly focused on the functional outcomes of AT and rehabilitation interventions for people with visual impairments [16-18]; yet, there is a lack of a comprehensive review of the literature to understand the psychological and social impact of AT for this population. This review aims, therefore, to comprehensively examine the research investigating the short-, medium-, and long-term psychosocial impact of AT for people with visual impairments.

Objectives and Review Questions

This scoping review aims to answer the following questions: (1) What psychological and social outcomes are associated with the use of ATs among people with visual impairments? (2) What methods and instruments are used to measure the psychosocial impact and outcomes of ATs for people with visual impairments? (3) What are the key trends in the literature in relation to the population characteristics, countries of study, settings, type of ATs examined, impact period, and research methodologies used to assess the psychosocial impact of ATs for people with visual impairments?

Methods

Ethical Considerations

Ethics approval is not required for this study, as human participants were not involved.

Study Design

This scoping review will be conducted following the framework proposed by Arksey and O'Malley [19], which includes six stages: (1) identifying the research question; (2) identifying relevant studies; (3) study selection; (4) charting the data; (5) collating, summarizing, and reporting the results; and (6) consultation. Methodological recommendations from the Joanna Briggs Institute [20] and the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews) checklist [21] will also inform the process.

Stage 1: Identifying the Research Question

The primary research question guiding this scoping review is: What are the psychosocial impacts of ATs on people with visual impairments? This question arose from the recognition that while ATs are often evaluated for their functional efficacy, their broader psychosocial impacts have been less explored, despite these impacts potentially being equally or more important in encouraging the uptake and long-term use of these technologies and improving quality of life among users. This scoping review draws from theoretical frameworks such as the World Health Organization Quality of Life framework [12] and Schalock and Alonso's Quality of Life model [22] to conceptualize psychosocial impacts. That is, psychological outcomes refer to the impact of ATs on the mental and emotional state of the individual, including positive feelings (happiness and life

satisfaction), negative feelings (anxiety, depression, and stress), and self-esteem. Social outcomes refer to the impact of ATs on the individual's social interactions, support, and participation in community and societal activities.

Stage 2: Identifying Relevant Studies

An initial limited search was conducted by the research team to inform the development and refinement of the search strategy. A university librarian was also consulted at this stage to help identify the databases and refine the search strategy. The search included variations and combinations of the following key concepts:

- AT ("assistive technol*" OR "adaptive technol*" OR "assistive aid*" OR "assistive equipment*" OR "assistive device*" OR "assistive product*" OR "assistive service*" OR "assistive interv*" OR "sensory aid*").
- Visual impairment ("visual impair*" OR "vision impair*" OR "impaired vision" OR "sight impairment" OR "visual loss" OR "vision loss" OR "vision defect" OR "visual handicap" OR "blind" OR "blindness" OR "low vision" OR "partial* sight*" OR "partial vision" OR "visual* disorder*" OR "vision disord*" OR "visual* disab*" OR "vision disab*" OR "eye disord*").

Next, a full literature search of peer-reviewed journal papers and conference proceedings was conducted across 7 electronic databases, including CINAHL (EBSCO) and PsycINFO (EBSCO), as well as ACM Digital Library, IEEE Xplore, Scopus, Web of Science, and Google Scholar (first 100 records). During the initial limited search, PubMed was considered as a potential database but eventually excluded, as its results heavily targeted biomedical and clinical aspects, which did not align with the focus on psychosocial impacts. Instead, CINAHL was selected for its broader coverage of health care topics and more holistic aspects of care, including well-being and quality of life.

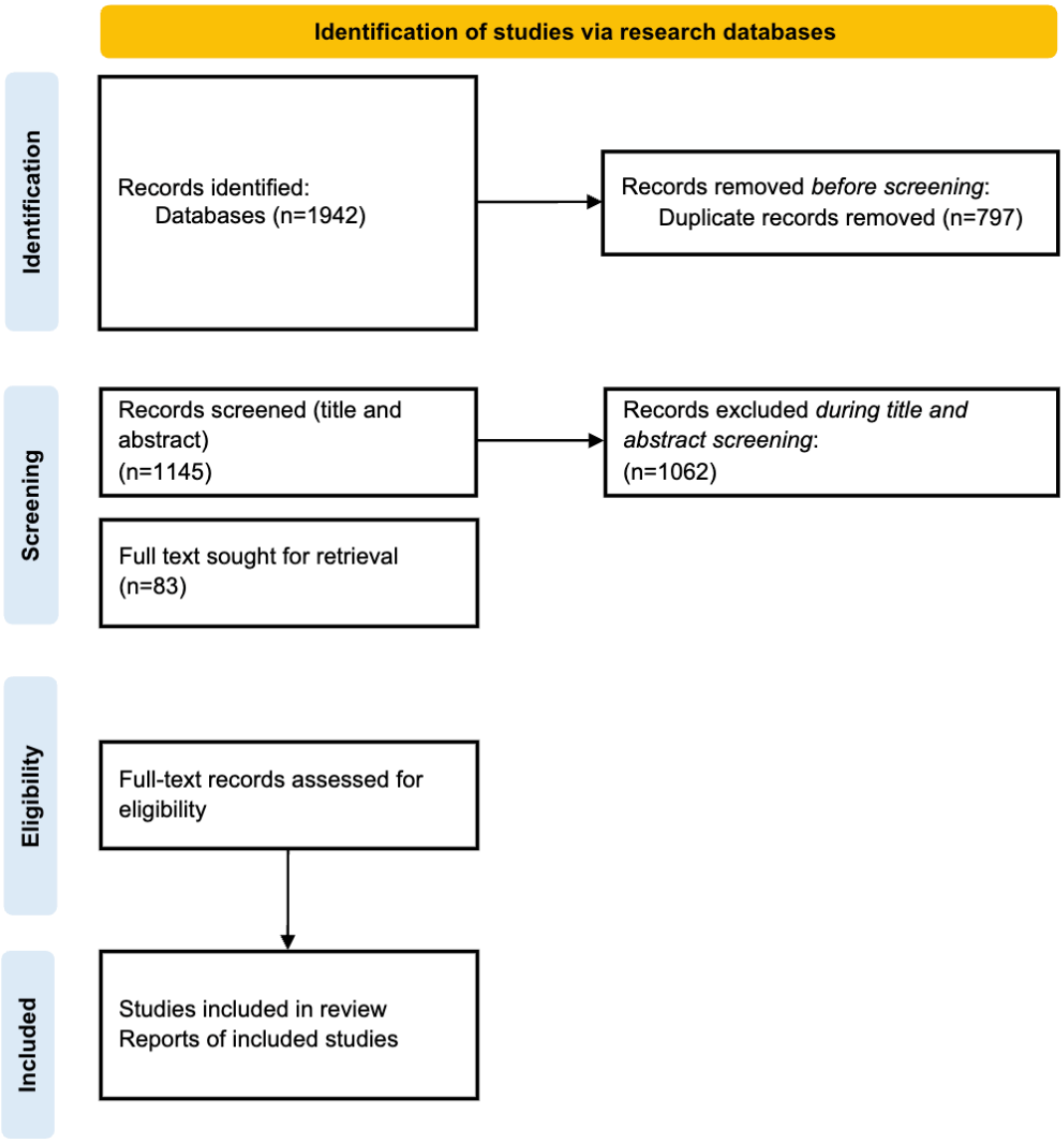
To focus on the most up-to-date literature and to capture the latest developments in the field of ATs for visual impairments, the search was limited to studies published in the past 5 years (2019-2024). Furthermore, the search was limited to studies written in English only. A full literature search was conducted in July 2024, which produced 1942 results.

Stage 3: Study Selection

A systematic approach will be used for study selection. Eligibility criteria have been developed to ensure the relevance and quality of included studies. From a *population* perspective, studies will be included if they focus on people with visual impairments, including children and adults, irrespective of the diagnosis and inclusion criteria used by individual studies. At a *concept* level, studies will be included if they (1) refer to the use of AT by people with visual impairments and (2) focus on the psychosocial impact or outcomes associated with the use of ATs. *Context-wise*, studies conducted in any country or setting, including health care, community, education, and work, and across all age groups will be considered. Primary research, including quantitative, qualitative, and mixed method studies reported in peer-reviewed journal papers or conference proceedings, will be included in this review. Conference abstracts only will be excluded. Secondary research (eg, literature reviews and meta-analyses) and nonempirical works (eg, theoretical papers, conceptual frameworks, opinion pieces, and editorials) may be consulted during the review process but will not be included. The review will only include research that includes the design or evaluation of an AT intervention focusing on impact.

Following the literature search, all retrieved studies will be collated and uploaded into a web-based literature review tool, Rayyan (Rayyan Systems Inc) [23], where duplicates will be removed. A random sample of 25 papers from the overall dataset will be first reviewed for pilot-testing of the source selector criteria. Following this, the reviewers will meet to discuss discrepancies and adapt the criteria based on the insights from the pilot test. Independently, 2 reviewers (RS and MB) will then conduct a screening of titles and abstracts to determine their potential eligibility for inclusion. The full texts of potentially eligible studies will be then retrieved and reviewed in detail for final inclusion. Reasons for excluding sources of evidence at the full-text stage that do not meet the eligibility criteria will be documented and reported in the scoping review. Any disagreements between reviewers (RS and MB) at each stage of the study selection process will be resolved through consensus or by consulting a third reviewer (CH). The search results and the study inclusion process will be reported in full in the final scoping review and presented in a PRISMA-ScR flow diagram (Figure 1 and Multimedia Appendix 1).

Figure 1. PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews) flow diagram illustrating the study selection process.



Stage 4: Charting the Data

Data from the studies included in the scoping review will be extracted using a standardized table to ensure consistency and comprehensiveness. The data extraction table will be piloted on a subset of studies and will be revised as necessary. The information to be extracted from each study includes the authors, year of publication, title, source of publication, type of publication, country of study, aim of the study, population and sample characteristics, research design, type of AT or intervention, setting, outcomes, instruments or impact measures, key findings, and the impact period categorized as immediate (less than 1 month), short-term (1 to 6 months), medium-term (6 to 12 months), and long-term (more than 12 months). To ensure the accuracy of the process, a second reviewer (MB) will cross-check the data extracted from at least 25% (n=7) of all included studies. Any discrepancies between reviewers will be resolved through consensus or consultation with a third reviewer (CH).

Stage 5: Collating, Summarizing, and Reporting Results

Descriptive statistics will be used to summarize the overall characteristics of the included studies. These will cover the number of studies, the distribution of studies by publication year, population characteristics, country of origin, study setting, type of ATs examined, impact period, and research methodologies used. Charts and diagrams will also be used to support data presentation. Tables will be constructed to synthesize the psychosocial outcomes reported in the included studies. Tables will detail the methods and instruments used to measure the psychosocial impacts of ATs, including information on specific tools or questionnaires, their reliability and validity, and the context of their app. Additionally, tables will summarize the main findings of the studies included in the review. Furthermore, a narrative summary will accompany the tabular or charted results, providing a description of the literature on the psychosocial impact of ATs on people with visual impairments, including key themes and trends observed. It will also identify gaps in the current body of knowledge, while

recommendations for future research will be made based on the identified gaps or inconsistencies.

Stage 6: Consultation

To expand the relevance and applicability of the findings arising from this scoping review, consultations will be conducted with stakeholders, including AT researchers, policy makers, and users. In particular, AT users will be provided with a summary of findings and invited to provide feedback through a written commentary. Their insights will inform the interpretation of results and the development of recommendations for practice and policy.

Results

This scoping review protocol was submitted to the Open Science Framework [24] on July 17, 2024. The database search was conducted in July 2024, and 1942 records were identified. During identification, 797 records were identified as duplicates and removed. Next, the title and abstract screening was conducted for 1145, of which 1062 records were excluded. Finally, 83 records were included for full-text screening. Data extraction and synthesis, as well as paper preparation, are currently underway. The paper should be submitted in February 2025.

Discussion

Expected Findings

The findings from this scoping review will shed light on the psychosocial impacts of ATs for people with visual impairments. The review will also explore the methods and instruments used to measure these outcomes and will identify key trends in the literature. These findings are expected to inform the development of a global evidence database mapping the impact of AT for people with visual impairments, with a view to extending it to other disabilities and long-term conditions, including other sensory impairments, mental health conditions, neurodevelopmental conditions, intellectual disabilities, and physical disabilities. The database is also expected to serve as a resource for researchers, clinicians, AT developers, policy makers, and other stakeholders, providing accessible and up-to-date evidence on the impact of AT. It is intended to facilitate evidence-based decision-making, support the development of guidelines, interventions, and policies, as well as identify gaps in the current research landscape. Findings will be presented at relevant conferences and shared with stakeholders (eg, disability and health care organizations, AT developers, and policy makers).

Strengths and Limitations

This scoping review is a comprehensive attempt to map the interdisciplinary literature on the psychosocial impact of AT for people with visual impairments. A full literature search of peer-reviewed journal papers and conference proceedings was conducted across 7 interdisciplinary electronic databases, including CINAHL (EBSCO) and PsycINFO (EBSCO) for literature from health care and psychology, as well as ACM Digital Library, IEEE Xplore for human-computer interaction, computing, and accessibility and AT-related literature, and Scopus, Web of Science, and Google Scholar (first 100 records) to include cross-disciplinary literature. The review will follow the PRISMA-ScR checklist that is specific for scoping reviews [21] to ensure a high level of quality and transparency. To this end, the scoping review protocol has been preregistered with the Open Science Framework [24].

One limitation of this scoping review is the exclusion of previous reviews and non–peer-reviewed publications. Additionally, the review only includes research published in English between 2019 and 2024. Due to the limited scope and time constraints of this review, a comprehensive quality assessment will not be conducted. Finally, this review does not include a full literature search on PubMed due to the clinical focus of search results from initial searches.

Acknowledgments

This research has been funded by the UK Research and Innovation Engineering and Physical Sciences Research Council UKRI (UK Research and Innovation) EPSRC (Engineering and Physical Sciences Research Council) ICT (Information and Communication Technologies) Public Engagement Grant (EP/W033674/1).

Data Availability

The datasets generated or analyzed during this study are available from the corresponding author on reasonable request.

Authors' Contributions

RS, MB, and CH conceptualized the study as a scoping review. MB and CH provided oversight for scoping review protocol development. RS and MB reviewed and edited the protocol, drafted the search strategy, wrote the manuscript, and designed Figure 1. All authors read, provided feedback, and approved the final manuscript for submission.

Conflicts of Interest

None declared.

Multimedia Appendix 1

PRISMA-Scr (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews) checklist. [DOCX File , 115 KB - resprot_v14i1e65056_app1.docx]

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Abbreviations

AT: assistive technology
PRISMA-ScR: Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews

Edited by A Schwartz; submitted 03.08.24; peer-reviewed by SS Senjam, A AL-Asadi; comments to author 22.09.24; revised version received 13.10.24; accepted 08.01.25; published 13.02.25.

Please cite as:
Szekely R, Holloway C, Bandukda M
Understanding the Psychosocial Impact of Assistive Technologies for People With Visual Impairments: Protocol for a Scoping Review
JMIR Res Protoc 2025;14:e65056
URL: https://www.researchprotocols.org/2025/1/e65056
doi:10.2196/65056
PMID:

Protocol

Social Determinants of Health Screening Tools for Adults in Primary Care: Protocol for a Scoping Review

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Abstract

Background: Social determinants of health (SDH) have been shown to be predictors of health outcomes. Integrating SDH screening tools into primary care may help identify individuals or groups with a greater burden of social vulnerability and promote health equity.

Objective: This study aimed (1) to identify the existing screening tools to assess social deprivation in adults in primary care settings; (2) to describe the characteristics of these tools and, where appropriate, their psychometric properties; (3) to describe their validity and reliability in those scales in which validation processes have been conducted; and (4) to identify evidence gaps and provide recommendations for future research.

Methods: This study protocol was structured according to the Joanna Briggs Institute methodology for scoping reviews and reported according to the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews) guidelines. Furthermore, since not all SDH assessment tools are published as scientific papers, we will use a slightly modified form of the scoping review framework to retrieve specific information about specific tools for screening SDH in primary care contexts. The following electronic databases will be searched by 2 reviewers: MEDLINE (via PubMed), CINAHL Plus, Web of Science, and Scopus. In addition, the following sources will also be searched for gray literature: DART-Europe E-thesis Portal, OpenGrey, and Google Scholar. After the revision of inclusion and exclusion criteria, the titles, abstracts, and full text of the included studies will be separately screened by 2 reviewers. A PRISMA-ScR flowchart will be used to depict the sources of evidence screened, and data charting will be used to gain in-depth knowledge. The findings of the scoping review will be presented in both narrative and tabular formats, summarizing the existing literature on tools used for SDH in primary care settings. A critical analysis will be undertaken to address the variability in tool validation, cultural adaptability, and integration into different health care systems. Finally, key gaps in the existing evidence will be explored, and research priorities will be proposed, emphasizing the need for screening tools that are culturally sensitive, scalable, and easily integrated into primary care workflows. This critically appraised information may be useful for implementing SDH screening tools in primary care settings and may contribute to future research addressing feasibility and validation studies in different primary health care systems.

Results: The study began in July 2024. Data collection is expected to be completed in April 2025, with publication expected in October 2025.

Conclusions: This scoping review will provide a comprehensive and critical description of the available tools aimed at screening SDH in primary care settings. Incorporating these tools into routine care has been recognized as a key strategy for addressing health inequalities, given the growing evidence base on the influence of SDH on health outcomes.

International Registered Report Identifier (IRRID): PRR1-10.2196/68668

(JMIR Res Protoc 2025;14:e68668) doi:10.2196/68668

KEYWORDS

social deprivation; social determinants of health; primary health care; social inequality; screening

Introduction

Background

According to the World Health Organization (WHO), social determinants of health (SDH) are the conditions in which people are born, grow, work, live, and age, along with the broader set of forces and systems that shape the conditions of daily life [1]. These determinants include a wide range of factors, such as income, education, employment, working conditions, housing, neighborhood environments, race, and gender [2]. On the other hand, health inequalities are defined as the systematic, avoidable, and unfair differences in health outcomes that can be observed between different groups of people, which are determined by the SDH [3].

In recent years, there has been a growing awareness of the significant impact of SDH on individual and population health outcomes. This has led to a transformation in health care practices and policies with greater recognition of the role of SDH in perpetuating health inequities and in providing a comprehensive understanding of a patient's health [4].

SDH have been shown to be the predictors of health outcomes, including hospital readmissions [5], emergency department visits [6], multimorbidity burden [7], depression prognosis [8], and lower adherence to preventive measures [9,10]. Identifying individuals or groups with a greater burden of social vulnerability or with the greatest disparities in a particular disease can guide future actions to promote health equity [11], implement tailored social interventions, and direct future research [12]. However, despite the clear evidence of the importance of SDH and the need to address its root causes, there are several issues to be considered. First, without multidisciplinary engagement and workflows, along with the availability of social resources for subsequent referral [13], expectations may be raised without solutions being provided, leading to a loss of patient trust. Second, without intersectoral collaboration, long-term strategies, upstream proposals, and public health policies and workflows, we could fall into perpetuating the "fantasy paradigm" [14]—a parallel fantasy world in which proximal, downstream, and easily tackled exposures are posited as potential solutions to health inequalities [15].

Primary care settings are ideal for addressing SDH because they are often the first, and sometimes only, point of contact for patients within the health care system. They are also the place for multiple consultations with a significant social burden, where longitudinal continuity of care is provided and where clinicians are aware of the community health resources [16]. The importance of SDH screening in primary care is underscored by the fact that social needs are often unrecognized in clinical settings, leading to suboptimal care and poorer health outcomes [17]. Therefore, integrating SDH screening tools into primary care is not only consistent with the principles of holistic and patient-centered care but also represents a crucial step toward addressing the root causes of health disparities [18-20].

There is considerable variability in the implementation of SDH screening tools in primary care settings [21]. The absence of standardized screening tools and protocols, along with varying levels of knowledge and training among providers, hinders the ability to identify SDH-related needs and intervene appropriately [22]. Furthermore, the diverse nature of SDH, which covers a wide range of domains and is influenced by individual-, community-, and policy-level factors, poses a significant challenge to the development of comprehensive screening tools [23]. These tools must be sensitive enough to capture the complexity of social determinants while also being practical for use in time-constrained primary care settings. A number of SDH screening tools have been developed and implemented with varying degrees of success. These tools range from brief questionnaires integrated into electronic health records to more extensive assessments conducted through patient interviews [14,21,24]. The development of these tools is often context specific, taking into account the patient population, health care setting, and available resources for follow-up interventions [25]. However, the variability in the content, format, and application of these tools across different health care systems underscores the need for a comprehensive synthesis of available tools aimed at assessing their effectiveness, validity, and feasibility [14].

Primary care providers face numerous barriers to implementing SDH screening, including time constraints, lack of training, and uncertainty about how to address identified needs [17,26]. There are also concerns that screening may reveal problems that providers are ill-equipped to deal with, leading to increased stress and workload without a clear pathway for patient referral and intervention [14]. Without collaboration between sectors such as social work or community resources in SDH screening and subsequent referral, primary care clinicians alone may not be able to cope [26]. Therefore, an important aspect of evaluating SDH screening tools is to consider not only their ability to identify social determinants but also their integration into care processes, the availability of resources to address identified needs, and their impact on patient outcomes [27].

Rationale for a Scoping Review

To avoid duplication of effort, a preliminary search conducted in July 2024 revealed that although several approaches to

synthesizing the literature on the use of tools to screen for SDH in clinical settings had been published [17,21,28] or were in progress (Parry et al [29]), many of the known tools had not been published in scientific papers and could only be found on institutional websites or through references to their use in the scientific literature (eg, EPICES score [30]) or book chapters. Therefore, several approaches to synthesizing the existing literature were considered, and scoping was found to be the most appropriate for the needs of this study according to the reasons for deciding to undertake a scoping review proposed by Arksey and O'Malley [31], namely that the use of SDH screening tools in primary care is an emerging issue, and different tools have been proposed because the generalizability across countries and primary care systems may not be possible, so mapping these tools is of scientific interest. In addition, a standard systematic review would leave out numerous tools that have not been published in traditional databases of the scientific literature, such as websites of health institutions, books, and so on. Therefore, suggesting lines of research and methodologies can be of scientific interest.

Study Aims

Our overall aim is to explore the literature describing the usefulness of SDH screening tools for adults in primary care settings. To achieve this, we will address the following specific objectives: (1) to identify existing screening tools for assessing social deprivation in adults in primary care settings; (2) to describe the characteristics of these tools, such as country, year of publication, and items included; (3) to describe their validity and reliability in those scales that have undergone validation processes; and (4) to identify evidence gaps and provide recommendations for future research.

Methods

Overview

In reviewing the existing literature, several approaches were considered, and a scoping review was found to be the most appropriate for the requirements of this study. Therefore, this study protocol was structured according to the 5-stage framework by Arksey and O'Malley [31]. In addition, the scoping review will be conducted according to the Joanna Briggs Institute methodology for scoping reviews [32] and reported following the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews) guidelines [33]. Furthermore, because not all the SDH assessment tools are published as scientific papers, we will use a slightly modified form of the scoping review framework outlined by Peters et al [34] to retrieve specific information about specific social deprivation screening tools in primary care contexts.

Identifying the Research Question

Some differences can be observed between these two approaches [33,34]. In essence, both approaches can be complementary, as the former is a checklist for reporting a scoping review compatible with the Population, Concept, and Context framework that we have chosen to describe the research question of our review (Multimedia Appendix 1). Our population will consist of adults (aged 18 years or older); our concept of SDH tools is understood as the conditions in which people are born, grow, work, live, and age, and the broader set of forces and systems that shape the conditions of daily life [1]; and as a contextual framework, the tools should be applicable to primary care settings.

Identifying Relevant Studies

The search strategy has been developed in collaboration with the research team and the participant librarians, adapting the PRISMA-ScR guidelines for literature search [35] to a scoping review. Two reviewers (JM-A and VM-V) independently searched the following electronic databases: MEDLINE (via PubMed), CINAHL Plus, Web of Science, and Scopus. The search strategy included terms related to the following descriptors, combined using Boolean operators: (1) SDH, (2) measurement tools, (3) validation studies, and (4) primary health care. All retrieved records will be imported into Mendeley (Elsevier) software, and duplicates will be removed. Textbox 1 provides the search strategy for the MEDLINE database as an example.

Textbox 1. Search strategy in MEDLINE.

Concept

- (tool [Title/Abstract]) OR ("questionnaire"[Title/Abstract])) OR ("scale"[Title/Abstract])) OR (measurement[Title/Abstract])) OR ("test"[Title/Abstract])) OR ("measure"[Title/Abstract])) OR ("assessment"[Title/Abstract])) OR ("index"[Title/Abstract])) OR ("indexes"[Title/Abstract]) OR ("score"[Title/Abstract]) OR (screening[Title])

AND

Social determinants of health

- (poverty[Title/Abstract]) OR (poverty[MeSH Terms])) OR (socioeconomic status[Title/Abstract])) OR (low socioeconomic status[Title/Abstract])) OR (low socioeconomic status[MeSH Terms])) OR (Social Deprivation[MeSH Terms])) OR (Social Deprivation[Title/Abstract])) OR (Social Vulnerability[Title/Abstract])) OR (Social Vulnerability[MeSH Terms])) OR (Social Determinants of Health[Title/Abstract])) OR (Social Determinants of Health[MeSH Terms])) OR ("social class"[MeSH Terms])) OR (social determinants[Title/Abstract])) OR (socioeconomic factors[MeSH Terms])) OR (socioeconomic factors[Title/Abstract])) OR (deprivation[Title/Abstract]) OR (drivers [Title]) OR (Social Drivers of Health [Title]) OR (social needs[Title])

AND

Validity

- (validity [Title/Abstract]) OR (Feasibility Studies [MeSH Terms] OR (Feasibility[Title/Abstract])) OR (applicability[Title/Abstract])) OR (screening[Title/Abstract])) OR (validation[Title/Abstract])) OR ("validation studies as topic"[MeSH Terms])) OR (health outcome predictor[Title])

AND

Context

- (Primary Health Care [Title/Abstract]) OR (Primary Health Care[MeSH Terms])) OR (primary care[Title/Abstract])) OR (Family Practice[Title/Abstract])) OR (Family Practice[MeSH Terms])) OR (general practice[MeSH Terms])) OR (general practice[Title/Abstract])) OR (clinical setting[Title]) OR (outpatient [Title]) OR (ambulatory [Title]) OR (Internal Medicine[Title])

The search strategy and index terms will be adapted for each electronic database or information source.

In addition, several approaches will be used to search the gray literature, understood as materials and research produced by organizations outside of traditional academic publishing. First, we will search the DART-Europe E-thesis Portal for access to dissertations and OpenGrey, a system for information on gray literature in Europe. We will also search using keywords in Google Scholar, and the first 200 results sorted by relevance will be screened for suitability according to the recommendations of Haddaway et al [36]. Furthermore, a supplementary search of the reference lists of studies selected for inclusion in the review will be conducted to identify additional relevant studies. This will be followed by a systematic citation search using CitationChaser [37] to compile studies citing the papers selected for inclusion. If further information is required regarding the studies of key papers, the authors will be contacted accordingly. Finally, an iterative approach will be used to search the websites of health institutions in the main countries that have implemented health policies related to social inequalities in health. Mendeley will be used as reference manager software.

Study Selection

The identified studies will be transferred to the web-based version of the Rayyan Systematic Review Tool [38] for further processing. Rayyan is a web-based tool designed to facilitate the screening process, which is a critical component of any systematic review. As recommended, two authors (JM-A and VM-V), after agreeing on a framework for screening papers according to the research objectives [33], will independently carry out the title and abstract selection of studies. Full papers will be obtained if the literature meets the inclusion criteria or if a decision cannot be made from the title or abstract alone. The review authors will resolve disagreements by consensus-based decision and, if necessary, by discussion within the group. In addition, we will record the specific reasons for the exclusion of each study.

For our scoping review, the inclusion criteria are given in Table 1. However, we will be aware that a reflexive process of the inclusion and exclusion criteria will be undertaken during the screening process, which will serve to consolidate the criteria [34].

Table 1. Inclusion and exclusion criteria based on the Population, Concept, and Context framework.

Scope parameters	Inclusion criteria	Exclusion criteria
Population	Adult participants (including older adults)	Pediatric population and adolescents
Concept	Screening tools for SDH[a] that include more than one dimension of SDH and screening tools with social deprivation indexes	Screening tools for only one dimension of SDH (eg, screening tools for only food insecurity)
Context	Primary care settings	Other specialty or emergent care setting
Types of evidence	Full-text papers of empirical research studies (eg, validation studies, randomized controlled trials, and observational studies), study protocols, full-text conference proceedings, papers written in English, documents retrieved from institutional websites, and PhD dissertations	Reviews[b], abstracts, posters, and papers for which we cannot obtain the full text or which are not written in English

[a]SDH: social determinants of health.

[b]Although systematic reviews will not be selected for inclusion, the studies included in these reviews will be reviewed to evaluate their possible inclusion in the scoping review.

Critical Appraisal

As scoping reviews are primarily aimed at identifying and exploring the existing literature on a topic, it has been stated that a quality assessment is not applicable [34]. In our case, as the methods used to develop the SDH screening tool may not always be standardized, conducting a quality assessment is likely to be unsuccessful. However, a critical review assessing their ability to be incorporated into care processes, their relationship to the availability of resources to address identified needs, and their impact on patient outcomes will be included in the *Results* and *Discussion* sections.

Charting the Data

A PRISMA-ScR [33] flowchart will be used to depict the sources of evidence screened, the assessment of documents' eligibility (which may include tools extracted from institutional documents, not just papers), and the tools included in the review, along with reasons for exclusions at each stage.

The data charting is specific to scoping reviews and differs from the data extraction processes commonly used in other types of research synthesis designs, where data extraction is a more structured process often including statistical procedures. In contrast, data charting in scoping reviews is a more comprehensive approach that incorporates narrative information to describe details about how, why, and where the study was conducted [39]. Accordingly, a consensus-based, data-charting form will be used by the 2 reviewers, who will independently extract the data, discuss the results, and iteratively update the data-charting form. This data-charting table will include descriptive variables (year of publication, study design, setting, target population, and data source) and information about the aims and structure (dimensions, items, and procedures for completing the questions) of the tool and setting characteristics.

Ethical Considerations

Ethical approval is not required for this review as it involves the analysis of publicly available empirical studies and the production of secondary data.

Expected Outcomes

Following the publication of this protocol, the search for SDH screening tools, removal of duplicates, and study selection will take place (estimated time: 2 months). The findings of this scoping review will be presented in both narrative and tabular formats, summarizing the existing literature on tools used for SDH in primary care settings. The narrative summary will describe the scope and nature of the identified screening tools including their structure (domains, number of items, and how the information should be obtained [eg, questionnaires and digital platforms]) and the contexts in which they are applied. The integration of these tools into clinical workflows, as well as any evidence of their effectiveness in improving patient outcomes, will also be considered.

Critical Analysis

Overview

The results will include a critical analysis of the strengths, limitations, and usability in primary care settings of the screening tools. This analysis will address the variability in tool validation, cultural adaptability, and integration into diverse health care systems. Potential biases or limitations in the implementation or outcomes of the tools, such as insufficient training of health care providers or limited follow-up on identified needs, will also be concerns to be discussed.

Research Gaps and Priorities

Key gaps in the existing evidence, such as social determinants not included in the tools, concerns about age or gender underrepresentation, and limited follow-up analysis of the usefulness of SDH screening on health outcomes, will also be critically examined. Finally, based on these findings, research priorities will be proposed, emphasizing the need for screening tools that are culturally sensitive, scalable, and easily integrated into primary care workflows (estimated time to complete these tasks: 6 months).

Dissemination of the Results

To ensure that the insights resulting from this review reach a variety of stakeholders, such as health care practitioners, policy makers, and academics, the findings will be disseminated using several dissemination strategies including reporting results in open-access journals and scientific conferences. In addition, stakeholders will be engaged at every stage of the review process to facilitate the adoption and implementation of evidence-based screening tools in clinical settings, thereby increasing their impact on health equity (estimated time: 6 months).

Results

The study began in July 2024. Data collection is expected to be completed in April 2025, with publication expected in October 2025.

Discussion

Principal Findings

This scoping review will provide a comprehensive and critical description of the available tools aimed at screening SDH in primary care settings. Incorporating these tools into routine care has been recognized as a key strategy for addressing health inequalities, given the growing evidence on the influence of SDH on health outcomes. Nonetheless, the absence of a comprehensive review makes it difficult for health care practitioners to select the most appropriate tools for their context and patient populations.

The importance of identifying and addressing the social needs of the patients attending health care settings has been highlighted by Gottlieb and Fichtenberg [40], and some scientific contributions have previously addressed some issues related to the implementation of SDH screening tools in clinical settings, such as the coverage and economic evaluation of these tools [41], the evaluation of interventions linking social and medical care [42], the barriers to the implementation of SDH in electronic health records [43], and its integration in nonspecific clinical settings [44]. In addition, a report from the US Preventive Services Task Force alerted on the importance of considering SDH in the recommendations of preventive interventions in primary care [19]. However, a catalog of currently available screening tools, their scope, structure, and dimensions is lacking. Furthermore, this review will assess the contextual elements such as resource accessibility and stakeholder involvement (patients, practitioners, and health care providers) that influence the implementation and effectiveness of these technologies in primary care. This review will map the body of literature to identify potential gaps and areas for additional research, including tool validation in varied populations, tool influence on clinical outcomes, and tool integration into larger care systems.

Including SDH screening tools for children in this review might seem to make our review more coherent, but it would greatly increase the complexity of the review. The tools for children and adults are very different. Overall, measuring SDH in children should emphasize developmental needs, relationships with caregivers, and early life conditions, whereas measures for adults tend to focus more on employment, social deprivation, and cumulative social conditions, as well as focus on the individual rather than indirectly asking the caregiver about the child's health [45]. Therefore, a review of SDH in the pediatric population requires a synthesis study, probably with a different methodological approach, focusing exclusively on this topic.

A key strength of this protocol lies in its systematic approach, which adheres to the current methodological frameworks for scoping reviews. This ensures that the review process will be transparent and reproducible, while allowing a broad range of study designs and inclusion settings. However, a limitation of this review is the potential for missing unpublished or non–English-language studies, which may result in an incomplete understanding of the global landscape of SDH screening tools.

Conclusions

This scoping review will provide a valuable synthesis of the available SDH screening tools applicable in primary care and identify critical gaps in the existing literature. This review will provide insights into the implementation of these tools, while identifying areas for further research, including validation in diverse populations. Ultimately, this work aims to support the integration of SDH screening into routine care, contributing to efforts to reduce health inequalities and improve patient outcomes.

Acknowledgments

This study was funded by the Research Network on Preventative Activities and Health Promotion (RD12/0005/0009) to VM-V. Additional funding was obtained from the Foundation for Biosanitary Research and Innovation in Primary Care (FIIBAP).

Authors' Contributions

JM-A and VM-V contributed to the conceptualization. JM-A and VM-V developed the methodology. JM-A, AEM, HMM, and VM-V performed the investigation. JM-A, VM-V, and AEM managed writing–original draft preparation. NJO, IDLMH, FSV, ACM, HMM, and SC handled writing–review and editing.

Conflicts of Interest

None declared.

Multimedia Appendix 1
PRISMA-P (Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols) checklist.
[DOCX File , 32 KB - resprot_v14i1e68668_app1.docx]

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Abbreviations

PRISMA-ScR: Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews
SDH: social determinants of health
WHO: World Health Organization

Edited by A Schwartz; submitted 12.11.24; peer-reviewed by E Magnan; comments to author 18.12.24; revised version received 12.01.25; accepted 17.01.25; published 19.02.25.

Please cite as:
Martínez-Alfonso J, Sebastian-Valles F, Martinez-Vizcaino V, Jimenez-Olivas N, Cabrera-Majada A, De los Mozos-Hernando I, Cekrezi S, Martínez-Martínez H, Mesas AE
Social Determinants of Health Screening Tools for Adults in Primary Care: Protocol for a Scoping Review
JMIR Res Protoc 2025;14:e68668
URL: https://www.researchprotocols.org/2025/1/e68668
doi:10.2196/68668
PMID:39969980

Protocol

Genetic, Socioecological, and Health Determinants of Extreme Longevity in Semi-Supercentenarians and Supercentenarians: Protocol for a Scoping Review

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Abstract

Background: The study of supercentenarians (individuals aged 110 years or older) offers valuable insights into aging, longevity, and the factors contributing to exceptional lifespans. These individuals often exhibit extraordinary cognitive and physical performance, which can inform strategies to improve the health of the general population. Research on centenarians (individuals aged 100 years or older), semi-supercentenarians (individuals aged 105-109 years), and supercentenarians covers themes like genetic factors, microbiome, inflammation, diet, lifestyle, and psychological aspects. These studies often focus on various aspects of extreme longevity, using varied objectives and methodologies, highlighting the need for a comprehensive synthesis to map the breadth of research and identify gaps in understanding this demographic.

Objective: This scoping review aims to map and synthesize existing evidence on the determinants of extreme longevity, focusing on individuals living beyond 105 years. This review seeks to categorize genetic factors associated with semi-supercentenarians and supercentenarians; explore the range of socioecological factors contributing to their longevity; and identify common themes such as health, functional capacity, cognition, mental health, behaviors, social support, quality of life, personality traits, environmental factors, and religiosity. Additionally, it aims to examine and describe the methodologies and assessment tools used in studies on extreme longevity and provide an overview of global demographic trends and patterns among supercentenarians, including geographic distribution, gender prevalence, and socioeconomic characteristics.

Methods: This scoping review follows the PRISMA-P (Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols) 2015 guidelines and the Population, Exposure, and Outcome framework. It includes observational and interventional, quantitative and qualitative studies on supercentenarians and semi-supercentenarians. Data will be sourced from databases like Scopus, PubMed, ProQuest, PsycINFO, and The Cochrane Library. The selection process involves abstract and full-text screening by two independent reviewers, with data extraction focusing on study characteristics, participant demographics, interventions or exposures, and key findings. A thematic analysis will identify patterns across various themes

Results: As of October 2, 2024, five databases were searched, yielding 844 studies. After removing duplicates, 706 studies remained. Following the first and second screening stages, 135 studies were found to be eligible. The study is expected to be completed by the end of February 2025.

Conclusions: By synthesizing evidence, this study will understand the global scope of supercentenarians, describe the main themes of research interest, and identify gaps. The findings are expected to contribute significantly to the body of knowledge on longevity, informing future research and public health policies. This scoping review aims to enhance the understanding of factors promoting healthy aging and extreme longevity, benefiting broader public health initiatives.

Trial Registration: PROSPERO CRD42024512298; https://tinyurl.com/4cmux7h4

(JMIR Res Protoc 2025;14:e63900) doi:10.2196/63900

KEYWORDS

supercentenarians; semi-supercentenarians; extreme longevity; genetic factors; socioecological factors; health determinants; aging research; scoping review; cognitive performance; data collection methods

Introduction

The study of supercentenarians—individuals who have reached the remarkable age of 110 years or older—holds immense scientific interest. These exceptional individuals provide valuable insights into aging, longevity, and the factors contributing to their remarkable lifespans. Limiting illness—both in duration and the number of individuals affected—becomes more critical as human longevity increases. Studying healthy humans with exceptional lifespans is meaningful in discovering clues to improve the general population's health. Centenarians (individuals aged 100 years or older), semi-supercentenarians (individuals aged 105-109 years), and supercentenarians (individuals aged 110 years or older) are excellent models for the study of healthy longevity. According to research, this aged population surprisingly maintain extraordinary cognitive and physical performance [1].

These studies provide valuable insights into various aspects of supercentenarian aging and use a variety of methodological frameworks for evaluating the determinants of extreme longevity. Currently, there exists a wide range of studies that investigate exceptional lifespans from diverse perspectives. Sebastiani et al [2] discussed genome sequencing in supercentenarians, revealing common and rare genetic variants that may contribute to exceptional longevity. Franzke et al [3] looked into "DNAging" and discovered that supercentenarians exhibit improved DNA repair and antioxidant defense mechanisms compared to younger cohorts. Santos-Lozano et al [4] discovered that both genetic and environmental factors are attributed to exceptional longevity in centenarians and supercentenarians. Some studies discussed morbidity in supercentenarians and found that cognitive and physical function decline is delayed in supercentenarians [5], while other studies investigated other factors contributing to super longevity in supercentenarians such as diet and lifestyle [6,7].

This scoping review aims to comprehensively synthesize the existing evidence to understand the determinants that contribute to extreme longevity in individuals living beyond 105 years, as well as the methodologies used for data collection.

This scoping review's main objectives are as follows:

1. To map and categorize the existing evidence on genetic factors associated with extreme longevity in semi-supercentenarians and supercentenarians;
2. To explore and synthesize the range of socioecological factors, including lifestyle behaviors, environmental exposures, and social support systems, that are associated with achieving extreme longevity;
3. To examine and describe the methodologies and assessment tools used in studies investigating extreme longevity; and
4. To provide an overview of global demographic trends and patterns among supercentenarians, including geographic distribution, gender prevalence, and socioeconomic characteristics.

Methods

Approach

This scoping review follows the Population, Exposure, and Outcome framework [8] and the PRISMA-P (Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols) guidelines published in 2015 (Multimedia Appendix 1) [9]. The population and outcome are as follows:

- Population: Semi-supercentenarians (aged 105 years or older)
- Exposure: Genetics and socioecological factors
- Outcome: Supercentenarian (aged 110 years or older)

Eligibility Criteria

Study Characteristics

This scoping review will include quantitative and qualitative studies in which supercentenarians and semi-supercentenarians are the focus of the study, including observational research (case-report, case-series, cross-sectional, case-control, and cohort studies) and interventional research (quasi-experimental studies and randomized controlled trials).

Types of Participants

This scoping review will target studies in which groups or subgroups of participants comprise male or female individuals aged 105 years and older.

The exclusion criteria will be studies involving participants younger than 105 years as the primary focus.

Setting and Time Frame

In this scoping review, articles will be screened initially without any time restrictions. Additionally, there will be no limitations on the study settings.

Report Characteristics

Only peer-reviewed studies with full-text availability in English will be included. There will be no restrictions on the date of acceptance or publication. Regarding publication status, only articles that are either published or in press will be considered.

The exclusion criteria will be articles not available in full text, non–English-language studies, and non–peer-reviewed studies (eg, gray literature)

Information Sources

Our sources of information will be limited to electronic databases. An electronic search will be performed through Scopus (including Scopus Secondary literature), PubMed, ProQuest, PsycINFO, and The Cochrane Library (Cochrane Database of Systematic Reviews, Cochrane CENTRAL, and

Cochrane Methodology Register). Additionally, the reference lists of primary studies included in the review and the reference lists of relevant, previously published reviews will be reviewed.

Search Strategy

The search syntax used in the different databases is shown in Table 1.

Table 1. Search syntax.

Database	Search query	Filters
Scopus Articles	TITLE-ABS-KEY (*supercentenarian* OR semi*supercentenarian) AND (LIMIT-TO (DOCTYPE , “ar”) OR LIMIT-TO (DOCTYPE , “no”) OR LIMIT-TO (DOCTYPE , “cp”) OR LIMIT-TO (DOCTYPE , “sh”) OR LIMIT-TO (DOCTYPE , “le”) OR LIMIT-TO (DOCTYPE , “ed”))	Articles, notes, conference papers, letters, and editorials; excluded reviews and book chapters
PubMed	“supercentenarian”[Title/Abstract] OR “semi*supercentenarian”[Title/Abstract] OR ((“Centenarians”[MeSH[a] Terms] OR “Centenarians”[All Fields] OR “centenarian”[All Fields]) AND “Centenarians”[MeSH Terms])	None
ProQuest	(supercentenarian* OR semi*supercentenarian supercenten*arian OR semi*supercentenarian) NOT (at.exact(“Literature Review” OR “Review”) AND PEER(yes)) Ending truncation: • Search query: supercentenarian* OR semi*supercentenarian Middle truncation: • Search query: supercenten*arian OR semi*supercentenarian Databases: • Coronavirus Research Database • ProQuest Dissertations & Theses Global • Publicly Available Content Database	Peer-reviewed studies; excluded literature reviews and reviews
PsycINFO	*supercentenarian* OR semi*supercentenarian	None
Scopus Secondary Literature (a secondary document is a document extracted from a Scopus reference list, but is not indexed by, or available in, Scopus)	TITLE-ABS-KEY (*supercentenarian* OR semi*supercentenarian)	None
Scopus Patents	TITLE-ABS-KEY (*supercentenarian* OR semi*supercentenarian)	None
Cochrane Database of Systematic Reviews	(centenarian):ti,ab,kw OR (supercentenarian):ti,ab,kw AND (semi-supercentenarian):ti,ab,kw	None

[a]MESH: Medical Subject Headings.

Details of the search records, such as the date of the search, database, keywords, number of studies identified, and the number of eligible studies, will be appropriately documented. The authors will follow the adapted PRISMA-P guidelines to report the screening results.

Study Records: Selection Process

The results from the database search will be entered into Zotero (Corporation for Digital Scholarship), where duplicate records will be removed. Abstract and full-text screenings of the studies will be conducted by two independent reviewers using the eligibility criteria as a guide. Any disagreements among reviewers following abstract screening will be resolved through discussions to reach a consensus. However, a third reviewer will be involved to address discrepancies at the full-text screening stage.

Data Extraction and Coding

Data extraction will be done through systematic categorization of information from the included studies. The information will be categorized into predefined fields to ensure uniformity and consistency. The extracted data will include the following categories:

- Study details: Title, author(s), year of publication, journal, and geographic location
- Study design: Observational (eg, case-report, case-series, cross-sectional, case-control, and cohort studies) or interventional (eg, quasi-experimental studies and randomized controlled trials) studies
- Study population: Demographics (age, gender, and socioeconomic background) and sample size
- Factors analyzed: Genetic determinants, socioecological factors (eg, lifestyle behaviors, environmental influences, and social support), and health outcomes
- Methodological details: Data collection methods, assessment tools, and analytical approaches
- Type of data: Quantitative, qualitative, or mixed methods

The extracted data will then be coded and classified into themes based on the study’s objectives and reported findings. Uniformity will be maintained by using a standardized data extraction template and regular discussions among reviewers

to resolve ambiguities and discrepancies during the coding process.

Data Synthesis

Thematic analysis will be conducted to synthesize findings from included studies, following the 6-phase framework by Braun et al [10]. This process includes familiarizing with the data, generating codes, identifying and reviewing themes, and producing the final synthesis. Themes will focus on age validation, demographics, health, functional capacity, cognition, behaviors, social support, quality of life, personality traits, environmental and genetic factors, and religiosity. Themes will be identified inductively to allow for novel insights while remaining aligned with the review objectives.

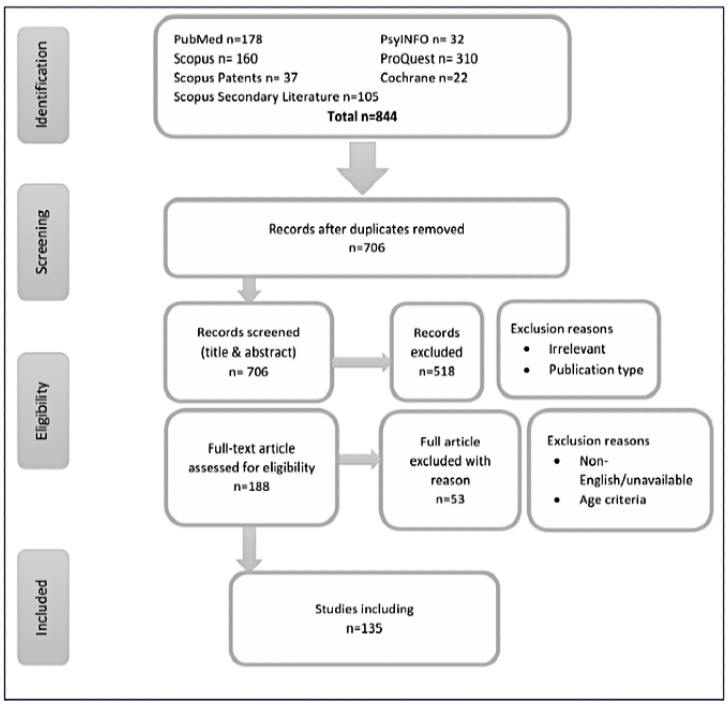
Reflexivity will be ensured through regular team discussions and documentation of assumptions to minimize researcher bias. Confirmability will be achieved by using two independent reviewers for coding, with discrepancies resolved through discussion or a third reviewer. Dependability will be ensured through a standardized coding process and team reviews of the thematic framework.

Credibility will be supported by providing detailed descriptions of themes. Transferability will be addressed by detailing the contexts and characteristics of the included studies and discussing broader implications for aging research.

Results

As of October 2, 2024, five databases were searched, and 844 studies were retrieved. After eliminating duplicates, 706 studies remained. Following the first stage of title and abstract screening, 518 studies were excluded and 188 studies remained. The remaining studies were subjected to full-text screening against the eligibility criteria, which resulted in eliminating 53 studies, leaving 135 studies to be included (Figure 1). The study is expected to be completed by the end of February 2025.

Figure 1. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow chart.



Discussion

Expected Findings

The study of semi-supercentenarians and supercentenarians is extremely valuable in shedding light on healthy aging and longevity [11]. Scholars have studied various areas and numerous factors suspected to contribute to extreme longevity. A study on Italian centenarians and supercentenarians used a multidimensional approach (genetic, demographic, and phenotypic characteristics) to better understand the complex interactions underlying longevity [12]. Other research concentrated on cognition and dementia. Recent research has identified the transcription factor *REST* as an important factor in extreme longevity and cognitive activity [13], while others found that supercentenarians show particularly mild neuropathological findings and thus exhibit remarkable resilience to age-related cognitive decline and dementia [14]. Genetic factors were also studied. A study found strong genetic components to longevity, with siblings of centenarians having significantly higher chances of reaching 90 years [15]. Psychosocial factors, including demographics, personality, and socioeconomic resources, were also found to significantly impact the health and quality of life of centenarians [16]. These are a few studies among many that contribute to the broader discussions on aging theories. On the other hand, more than 25 landmark centenarian and supercentenarian studies have been conducted by specialized organizations across different geographical regions, using diverse methodologies and data collection approaches [17-21]. Given the extensive research on semi-supercentenarians and supercentenarians, this scoping review will serve as a valuable resource for mapping the genetic and socioecological factors associated with individuals aged

105 and older. It will also identify and summarize the methods and assessment tools used to study the key factors contributing to extreme longevity.

A total of 135 studies has been included, reflecting a diverse body of research. However, the wide range of topics, methodologies, and findings highlights the need for a comprehensive synthesis to consolidate existing evidence and identify gaps for future investigation. This review provides an overview of current research on extreme longevity while pinpointing areas that require further study. This scoping review sets the foundation for future standardized research protocols in longevity studies. Additionally, the findings of this study will have important implications for aging-related health care strategies and interventions. Understanding the genetic and socioecological determinants of extreme longevity can lead to personalized health interventions that aim at promoting healthy aging. Policy makers and health care providers can use this evidence to design lifelong healthy behaviors programs and improve social and community support systems for older adults. The findings of this study will contribute to the body of literature on semi-supercentenarians and supercentenarians, inform future studies and interventions, and guide policy makers in the field of aging and public health.

Study Limitations

This scoping review has limitations that need to be acknowledged. There is a risk of selection bias. This scoping review only includes peer-reviewed, full-text articles in English, which may narrow the findings by excluding relevant studies published in other languages or in gray literature. Moreover, there is difficulty in making direct comparisons due to significant methodological differences, particularly in how longevity determinants are defined and the assessment tools used. Lastly, this scoping review as a study does not establish causal relationships between genetic, socioecological factors, and extreme longevity. Instead, it serves as a foundation by identifying gaps, trends, and inconsistencies in the existing research. It provides insights that can guide future longitudinal studies (which track individuals over time) and experimental research (which tests specific interventions) to better understand the causal mechanisms behind extreme longevity.

Acknowledgments

We acknowledge the use of the artificial intelligence tool ChatGPT (OpenAI) [22] for language enhancement in the preparation of this manuscript and in improving the clarity and coherence of the text. No funding was received for this research

Data Availability

Data are available upon request from the authors.

Authors' Contributions

Conceptualization: WAEKM, OA, SC
Methodology: WAEKM, OA, SC
Investigation: WAEKM, OA, SC
Writing - original draft: WAEKM
Writing - review & editing: WAEKM, OA, SC

Conflicts of Interest

None declared.

Multimedia Appendix 1
PRISMA-P (Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols) checklist.
[PDF File (Adobe PDF File), 114 KB - resprot_v14i1e63900_app1.pdf]

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Abbreviations

PRISMA-P: Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols

Edited by A Schwartz; submitted 02.07.24; peer-reviewed by S Minozzi; comments to author 29.10.24; revised version received 15.12.24; accepted 19.02.25; published 05.03.25.

Please cite as:
Abu El Kheir-Mataria W, Mahmoud Abdelraheem O, Chun S
Genetic, Socioecological, and Health Determinants of Extreme Longevity in Semi-Supercentenarians and Supercentenarians: Protocol for a Scoping Review
JMIR Res Protoc 2025;14:e63900
URL: https://www.researchprotocols.org/2025/1/e63900
doi:10.2196/63900
PMID:40053776

Protocol

Exploring Curriculum Considerations to Prepare Future Radiographers for an AI-Assisted Health Care Environment: Protocol for Scoping Review

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Abstract

Background: The use of artificial intelligence (AI) technologies in radiography practice is increasing. As this advanced technology becomes more embedded in radiography systems and clinical practice, the role of radiographers will evolve. In the context of these anticipated changes, it may be reasonable to expect modifications to the competencies and educational requirements of current and future practitioners to ensure successful AI adoption.

Objective: The aim of this scoping review is to explore and synthesize the literature on the adjustments needed in the radiography curriculum to prepare radiography students for the demands of AI-assisted health care environments.

Methods: Using the Joanna Briggs Institute methodology, an initial search was run in Scopus to determine whether the search strategy that was developed with a library specialist would capture the relevant literature by screening the title and abstract of the first 50 articles. Additional search terms identified in the articles were added to the search strategy. Next, EBSCOhost, PubMed, and Web of Science databases were searched. In total, 2 reviewers will independently review the title, abstract, and full-text articles according to the predefined inclusion and exclusion criteria, with conflicts resolved by a third reviewer.

Results: The search results will be reported using the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews) checklist. The final scoping review will present the data analysis as findings in tabular form and through narrative descriptions. The final database searches were completed in October 2024 and yielded 2224 records. Title and abstract screening of 1930 articles is underway after removing 294 duplicates. The scoping review is expected to be finalized by the end of March 2025.

Conclusions: A scoping review aims to systematically map the evidence on the adjustments needed in the radiography curriculum to prepare radiography students for the integration of AI technologies in the health care environment. It is relevant to map the evidence because increased integration of AI-based technologies in clinical practice has been noted and changes in practice must be underpinned by appropriate education and training. The findings in this study will provide a better understanding of how the radiography curriculum should adapt to meet the educational needs of current and future radiographers to ensure competent and safe practice in response to AI technologies.

Trial Registration: Open Science Framework 3nx2a; https://osf.io/3nx2a

International Registered Report Identifier (IRRID): PRR1-10.2196/60431

(JMIR Res Protoc 2025;14:e60431) doi:10.2196/60431

KEYWORDS

artificial intelligence; machine learning; radiography; education; scoping review

Introduction

Radiography is arguably one of the most technologically advanced health care disciplines, encompassing various technologies that continuously evolve with advancements in computing power and human knowledge [1,2]. Although the use of technology has always been extensive in the profession, recent technological advancements have focused on incorporating complex machine learning algorithms, which have led to a change in clinical protocols that affect patient outcomes and radiography practice [3-5]. Artificial intelligence (AI) technologies play an increasingly important role in clinical radiography with applications such as scheduling patients, image interpretation and reporting, vetting of examinations, patient positioning, image generation and reconstruction, radiation therapy dosimetry, and image postprocessing [4,6-8]. As the number of AI applications increases in clinical practice [9], it is postulated that the practitioner role may change and expand, and these new roles will require modifications to the competencies and educational requirements of current and future practitioners [4].

The increasing integration of AI technologies in radiography practice raises significant questions about the influences of AI technology on radiography practice and the subsequent ways in which radiography education may be required to change. Recent reviews have explored AI's current and potential applications in radiography practice [5] and examined the AI educational programs available to radiography staff globally [1]. Furthermore, research undertaken in the United Kingdom, Africa, and the Middle East exploring AI topics linked to education in radiography has focused on equipping practitioners for successful AI adoption [10] as well as the perceptions and attitudes of students and practitioners [11-16]. These conversations illustrate that there has been increasing exploration of various facets of AI in radiography, indicating that the emergence of AI technologies will continue to shape the future of radiography and radiography education.

Opinion statements and discussion pieces argue for the inclusion of AI education in undergraduate radiography curricula and appropriate education for current practitioners [3,4,17]. In addition, recommendations were made that higher education institutions must ensure that radiography curricula provide educational opportunities for patient-centered care in relation to AI integration to ensure competent and safe practice [2,3,6]. With increasing automation in clinical tasks, patient-centered care will gain more importance, highlighting the need for academic curricula to prioritize patient-centered care [2,4]. The evolving landscape of radiography, marked by the increasing integration of AI, raises important questions about how to best prepare future radiographers. Therefore, mapping the existing literature on the way that radiography education may need to change because of the integration of AI technologies in clinical practice is needed to grasp the current state of knowledge on the topic for future educational considerations. The aim of this scoping review is to explore and synthesize the literature on the adjustments needed in the radiography curriculum to prepare radiography students for the demands of AI-assisted health care environments.

Methods

Overview

The review will follow the Joanna Briggs Institute methodology for scoping reviews because it uses a rigorous and logical approach to scoping reviews [18,19]. The methodological guideline delineates 6 steps to map the extent of the literature on the research topic. These include (1) defining the research question, (2) developing the inclusion and exclusion criteria, (3) describing the search strategy, (4) searching the literature, (5) data extraction, and (6) analyzing the evidence and presenting the results [19]. The scoping review protocol is registered on the Open Science Framework [20]. The PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews) reporting guidelines and checklist [21] will be used to report the results (Multimedia Appendix 1).

Step 1: Defining the Review Question

The research question that will guide the scoping review is "How should the radiography curriculum be adapted to prepare radiography students for the integration of AI technologies in the health care environment?"

For this review, radiography refers to the four different radiography categories, including diagnostic radiography, diagnostic ultrasound, nuclear medicine technology, and radiation therapy.

Step 2: Study Selection

Inclusion Criteria

Overview

The types of studies to be considered for this review include quantitative, qualitative, mixed methods studies, scoping, literature, systematic reviews, opinion papers, letters, and conference papers. The selection of study types included in this review is justified based on the need for a comprehensive and nuanced understanding of the topic. The review will consider articles from any country or region, provided that an English translation of the article can be sourced or a translation app is available [22]. The Participants, Concept, and Context (PCC) framework will be used to systematically organize the scope of the review, ensuring it aligns with the objective and the relevant studies are included [18,19].

Population

The population consists of radiography students and educators. In addition, articles that form part of multidisciplinary health

professions' groups of which radiography forms a portion will also be included.

Concept

The concept focuses on how AI technologies are reshaping the clinical environment and the corresponding adjustments required in the radiography curriculum to prepare radiography students for this evolving landscape.

Context

This review will consider articles from academic and clinical settings in all countries.

Exclusion Criteria

Studies specifically related to other health professions' disciplines will be excluded. Furthermore, technologies discussed in the literature that lack AI will be excluded from consideration. All studies that align with the inclusion criteria, including the PCC, will be included in the review. In addition, articles for which the full text is not available through institutional subscriptions, interlibrary loans, or after contacting the corresponding author will not be included in the review. The authors will attempt to maximize access through the available institutional resources, but limitations may still apply. A full list of the eligibility criteria is provided in Table 1.

Table 1. Eligibility criteria for the scoping review.

PCC[a] Framework	Include	Exclude
Population	• All 4 radiography categories • Radiography educators • Radiography students	All other health professions' disciplines
Concept	• Studies that discuss AI[b] or AI-based tools in the context of radiography	Studies using technology that does not incorporate AI-based tools
Context	• Academic and clinical radiography education • Undergraduate radiography education • Postgraduate radiography education • Continuing professional development	Other health professions' education programs
Study characteristics	• The review will consider all types of study designs. • Sources printed in all languages • Full-text articles	Full-text not available

[a]PCC: Population, Concept, Context.

[b]AI: artificial intelligence.

Step 3: Search Strategy

The search strategy aimed to include published and unpublished literature. A preliminary search was performed on Scopus to identify articles on the topic in collaboration with a library specialist. The Scopus database was chosen because it is the largest indexing and abstract database and hosts a number of widely acknowledged Radiography journals. The search strategy was developed by examining the text found in the titles and abstracts of the relevant literature and the index terms and keywords used to describe the articles. The process entailed screening the titles and abstracts of 50 articles. Thereafter, the search strategy was refined iteratively through consultations with the librarian and between the authors. The detailed final search strategy for all databases, EBSCOhost, PubMed, Scopus, and Web of Science can be found in Multimedia Appendix 2. Gray literature was retrieved from the databases, including book chapters, conference papers, and letters. The total number of sources found was 2224 (Table 2).

Table 2. Electronic databases and gray literature results.

Electronic resources	Sources, n
EBSCO (Academic Search Premier, CINAHL, ERIC)	362
PubMed	1214
Scopus	267
Web of Science	112
Gray literature	269
Results	2224

Step 4: Selection of Evidence

Following the search, all citations were imported and managed using the Covidence online software [23]. All the duplicates were removed after the studies were imported into the software program. The primary investigator (CK) and a research assistant screened the studies during the title and abstract phase based on the inclusion and exclusion criteria to ensure that they are

relevant to the review [24]. The inclusion and exclusion criteria will be piloted on the first 20 articles to ensure that the criteria are applied consistently and that the relevant studies are included.

After the initial screening, a full-text screening of the selected articles will be performed to determine the literature to be included in the review. The reference list of all selected articles will then be hand-searched for additional studies that may be eligible according to the inclusion criteria. Following the full search, all citations will be captured. Any disagreements that arise between the reviewers at each stage of the selection process will be resolved through discussions, or with an additional reviewer and the changes will be noted and shared in the final scoping review report. Furthermore, reasons for the exclusion of sources of evidence at full-text screening will be recorded and reported in the scoping review.

Step 5: Data Extraction

To meet the aim and research question, the data will be organized according to the Joanna Briggs Institute template source of evidence details, characteristics, and results extraction instrument [22], incorporating key study information such as authors, study population, year of publication, study location, study design, and the key findings (Multimedia Appendix 3). This data extraction instrument was created and will be piloted to minimize potential bias. Piloting of the data extraction instrument will include a selection of 3-5 articles from the scoping review dataset and the two reviewers will perform independent data extraction to ensure that all the necessary data will be captured [21]. The instrument will be used to determine if the inclusion and exclusion criteria have been met during evidence selection. Modifications to the instrument may be made during the course of the literature search and the findings will be detailed in the scoping review report.

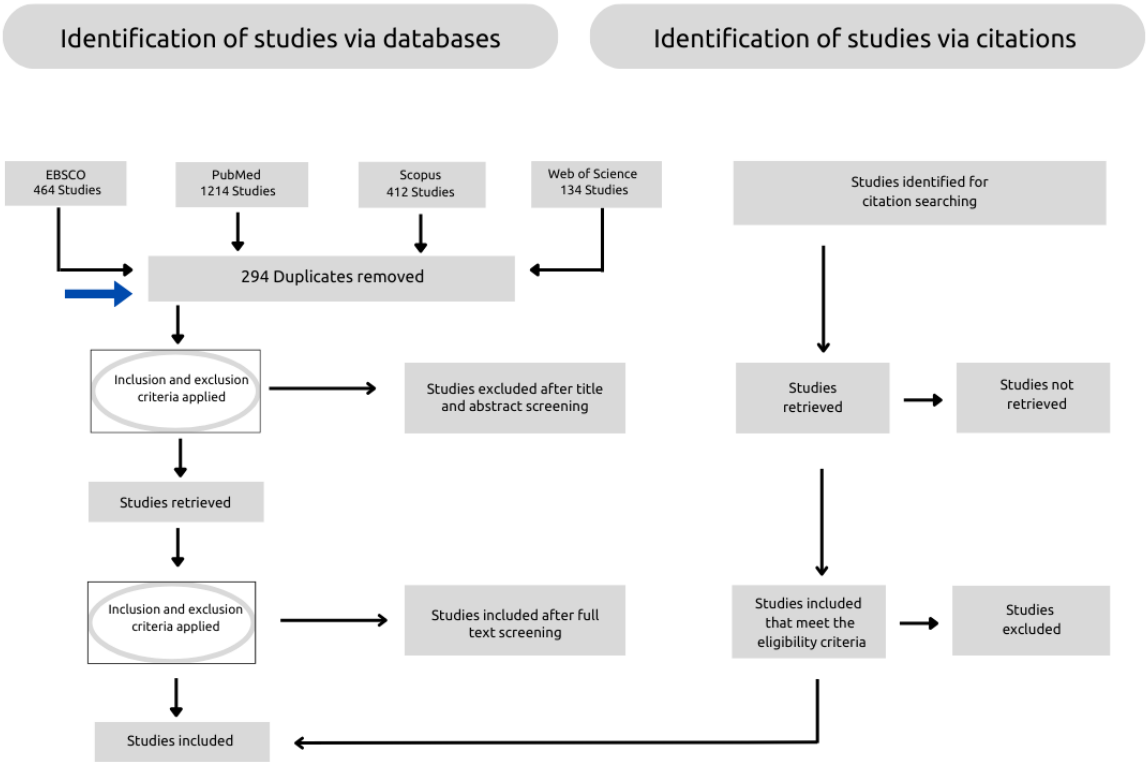
Step 6: Data Analysis

Scoping reviews should include a numerical summary outlining the types of literature that were retrieved and a thematic descriptive analysis [19]. The final themes of the scoping review will be developed using an iterative approach. A narrative description will then be used to synthesize the study findings using descriptive content analysis, and the identified themes will be reported.

Results

The final database searches were completed in October 2024 and in total produced 2224 items. Title and abstract screening of 1930 articles is underway after removing the 294 duplicates. The results will be presented in relation to the research question and the objective of the study. Furthermore, the results will be presented in 2 parts as proposed by Peters and colleagues [19]. The first part will consist of the results of the search and the inclusion of the studies will be presented with the PRISMA-ScR flow diagram (Figure 1). The blue arrow indicates the current status. The second part will consist of a narrative description that aligns with the objective of the scoping review. Data analysis and results may be further refined through the review process as the contents of the review are taken into consideration. Finalization of the scoping review is expected by March 2025. The results of the scoping review will be disseminated through publication in an accredited journal.

Figure 1. Flowchart of the PRISMA-ScR for the scoping review process. PRISMA-ScR: Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews.



Discussion

Addressing the call for an update to the radiography curriculum in response to new technological advancements such as AI is critical to prepare and equip current and future professionals for safe practice. This scoping review will map various studies and is anticipated to provide an overview of the adjustments needed in the radiography curriculum to prepare radiography students for the demands of AI-assisted health care environments. In return, the results will help to inform a variety of stakeholders, including radiography educators, radiography regulatory bodies, and radiography professional groups, to plan for needed changes in radiography education in response to the impact of AI-based technologies on clinical processes. To the best of our knowledge, this is the first scoping review to synthesize existing evidence of how the radiography curriculum might best prepare future practitioners for the demands of AI-assisted health care environments.

A strength of the scoping review is that all available studies of published data will be included. Current available literature focusing on how the radiography curriculum might need to change, considering the incorporation of AI technology in clinical practice, focuses on opinion and discussion pieces, and white papers [4,17,24]. In addition, some studies have highlighted the perceptions of educators and students on the incorporation of AI into radiography curricula; however specific methods of integration and a lack of implementation were noted [1]. Therefore, performing this review is warranted to help provide the necessary insights into changes to the curriculum that are aligned with the advances in technology.

A scoping review explores the breadth and not the depth of a topic, and the reviewers cannot comment on the quality of the studies included in the review. In addition, non-English articles may be excluded from this review, which can potentially lead to missing valuable work. However, for the search strategy, all languages are included and the number of studies for all languages will be documented. This process will show how many studies were identified but not included, promoting transparency in the selection process [22]. Furthermore, where possible translations will be sought to limit the omission of information.

This study will provide valuable insights into how the radiography curriculum should adapt to meet the educational needs of current and future practitioners to ensure competent and safe practice in response to AI technologies. Mapping the existing evidence is essential because the growing integration of AI-based technologies in clinical practice must be supported with appropriate education and training [1,4]. After collating and analyzing the findings of the scoping review, a manuscript containing the final analysis will be written and submitted for publication. In addition, this review will contribute toward a PhD in health professions education.

Acknowledgments

We would like to thank the librarian, Mr Yusuf Ras, for his contribution to the scoping review protocol.

Data Availability

All relevant data are available in the study or as multimedia appendices and will be made available upon request.

Authors' Contributions

CK conceptualized the scoping review, wrote the manuscript, and provided data. EA, PEH, and MV provided oversight for the scoping review protocol development.

Conflicts of Interest

None declared.

Multimedia Appendix 1
PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews) checklist.
[DOCX File , 140 KB - resprot_v14i1e60431_app1.docx]

Multimedia Appendix 2
Search strategy.
[DOCX File , 31 KB - resprot_v14i1e60431_app2.docx]

Multimedia Appendix 3
Data extraction tool.
[DOCX File , 19 KB - resprot_v14i1e60431_app3.docx]

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Abbreviations

AI: artificial intelligence
PCC: Population, Concept, and Context
PRISMA-ScR: Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews

Edited by T Leung; submitted 14.05.24; peer-reviewed by Z Salod, R Toomey, S Mao; comments to author 18.07.24; revised version received 31.10.24; accepted 05.12.24; published 06.03.25.

Please cite as:
Kammies C, Archer E, Engel-Hills P, Volschenk M
Exploring Curriculum Considerations to Prepare Future Radiographers for an AI-Assisted Health Care Environment: Protocol for Scoping Review
JMIR Res Protoc 2025;14:e60431
URL: https://www.researchprotocols.org/2025/1/e60431
doi:10.2196/60431
PMID:40053777

Protocol

Indigenous Community Views of Disability in Canada: Protocol for a Scoping Review

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Abstract

Background: Indigenous people do not necessarily view disability in the same way as do other groups. Indigenous concepts of disability are connected to their ancestral history, cultural customs, and environmental context. Some Indigenous languages do not contain a word equivalent to disability. Western approaches to disability seldom reflect the voices of Indigenous people.

Objective: The objective of this scoping review is to collate the perspectives, concepts, and understandings of disability in Indigenous communities in Canada and to map the factors that influence social approaches to disability from an Indigenous perspective.

Methods: Following the methodological framework for scoping reviews of Arksey and O'Malley, we will search electronic databases, including PubMed, Scopus, Web of Science, EBSCOhost ProQuest, Autochtonia, and APA PsycINFO. We will search gray literature through the Google search engine, conference abstracts, dissertation databases, government documents, and Indigenous organization websites. We will include quantitative, qualitative, and mixed methods studies in English and French. The included studies will describe Indigenous approaches to disability, as they are understood based on personal, cultural, and historical contexts. Two reviewers will use Covidence software (Cochrane) to remove duplicates, screen articles, record the step-by-step selection process, and extract data from the included articles. We will follow the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analysis extension for Scoping Reviews) guidelines. We will present the findings in tables, charts, narrative summaries, and through fuzzy cognitive mapping. We will contextualize the literature's findings by comparing them with the stakeholders in Quebec and provide a discussion to explore potential solutions for the identified factors.

Results: An initial limited search was conducted in January 2024. The study will be conducted in 2025. Publication of the results is expected in late 2025.

Conclusions: We anticipate that the findings from the scoping review will be useful for professionals, researchers, policy makers, and Indigenous communities themselves interested in co-designing and implementing evidence-informed disability programs and services, which will prevent mismatches between the programs and the sociocultural context. We will disseminate

the results of this review through workshops with the participating communities, direct engagement with relevant local stakeholders, and through conference presentations and publications in scientific journals.

Trial Registration: OSF Registries osf.io/9rzkx; https://osf.io/9rzkx

International Registered Report Identifier (IRRID): DERR1-10.2196/57590

(JMIR Res Protoc 2025;14:e57590) doi:10.2196/57590

KEYWORDS

Indigenous health; intercultural dialog; cultural safety; traditional medicine; disability

Introduction

The way disability is defined affects the types of disability services offered, who uses the services, and the way they work. The traditional biomedical model, despite frequent criticism, continues to influence Western approaches to disability [1,2]. This model views disability as an individual issue, characterized by abnormalities of the body or mind that medical science treats and social services cater for. In this mindset, experts are seen as the professionals responsible for either treating disabled individuals or coordinating services for them. Also focused on individual abnormalities and perhaps more criticized than the biomedical model for treating differences as medical issues and creating population categories, the moral model depicts disability either as a source of stigma and shame or, alternatively, as a sign of strength [3,4].

Social and inclusion models of disability reflect interactions between people with disabilities and attitudinal or environmental barriers that prevent their full and effective participation in society [5]. These approaches go beyond disability as a personal attribute to frame disability in terms of the conditions created by the social environment that cause people to experience barriers to performance in life situations. In the same way, the International Classification of Functioning, Disability, and Health (ICF) reinforces this view by emphasizing that disability results from the interaction between health conditions and contextual factors both environmental and personal [6,7]. The ICF highlights the importance of addressing not only impairments but also the external barriers that limit activity and participation [3,7,8]. Another approach explores not only physical or mental impairments but also the societal norms that define certain characteristics as disabilities. It's important to examine how social conditions exacerbate these stigmatized characteristics within specific populations [9-11]. A constructive step might be to engage with Indigenous communities to discuss the language and concepts surrounding disability, particularly whether colonialism and its resulting social disadvantages have transformed the social meaning of disability for Indigenous people [12,13].

Literature over the last 2 decades describes Indigenous perspectives and beliefs about disability [12,14-16]. Many Indigenous languages have no word for "disability," suggesting it is a term produced by western constructs [17], rather than anything negative or based on difference [18,19]. Articles about the intersection of indigeneity and disability highlight the importance of family ties, community networks and spirituality [14,16,18,20-24]. Although clearly different from western views, Indigenous worldviews of disability are not monolithic. Views vary between Indigenous cultures and, within any 1 culture, may not be static but responsive to the recovery of traditions and to adaptations [24,25].

With no published systematic review about Indigenous perspectives of disability from Canada, a review from Australia provides a substantial advance in the field [23]. This examined the understanding of disability within Australian Indigenous communities, highlighting that some disability services are shaped by western norms and assumptions that do not reflect their values. The review also notes that scholarly literature on Indigenous conceptualizations, experiences, and practices of disability remains relatively underdeveloped. Our review explores similar themes within the Canadian context. Our aim is to describe the concepts of First Nations, Métis, and Inuit, the 3 constitutionally recognized Indigenous groups in Canada who comprise approximately 5% of the country's population [26] and reflect unique cultural, environmental, and historical influences. Our review will focus on Indigenous points of view, summarizing the diverse narratives and choosing not to reproduce damage-centered approaches that contributed to pain and oppression [27].

We describe here the protocol for a scoping review, a starting point of a larger research program. This will compare and combine different knowledge sources to inform partnerships that address knowledge, policy, and implementation gaps for disability support services in Indigenous communities. The broader research initiative will encompass the following knowledge resources: (1) the scoping review detailed in this protocol; (2) perspectives from personnel of community-based initiatives and Indigenous-led organizations; (3) perspectives of Indigenous elders and knowledge keepers; and (4) perspectives from disability service providers, researchers, policy makers and people encountering disabling situations from the communities and their peers. The Weight of Evidence approach [28] uses fuzzy cognitive mapping [29] and will integrate these diverse sources of knowledge.

Methods

Study Design

We used the PRISMA-P (Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols) [30] checklist (Multimedia Appendix 1) for drafting the protocol. We will conduct the scoping review according to the guidelines proposed by Arksey and O'Malley [31] and the modifications proposed by Levac et al [32]. The 6-stage process includes identifying the research question, identifying relevant studies, developing

a study selection and data extraction method, charting the data, collating, summarizing, and reporting results, and contextualization with stakeholders. We will adapt the final step to function as a contextualization exercise, guided by the weight of evidence approach [28] that contrasts literature findings with contributions from stakeholders. The final report will follow the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-analyses extension for Scoping Reviews) [33].

Our team consists of 2 Indigenous researchers with expertise in Indigenous perspectives, psychosocial interventions, and inclusion. Other authors bring significant experience working with Indigenous communities in Canada and Mexico, as well as extensive expertise in working with people with disabilities in Nigeria, Zambia, Canada, and Colombia. We will do the first contextualization in the province of Quebec, as we describe below. We will verbally share discussions with our Indigenous researcher partners in Nunavik and Indigenous community members in the Saguenay-Lac-Saint-Jean region (Mashteuiatsh community) and the team leading the Nisidotam Inclusion Initiative in the Greater Montreal area. This ensures that Indigenous worldviews inform the approach, analysis, and findings, including the discovery and description of key knowledge gaps. We may make changes to the protocol, and we will detail and justify any modifications in the final report.

Stage 1: Identifying the Research Question

Our research questions are as follows:

1. What does the literature reveal about Indigenous perspectives, concepts, and understandings of disability in Indigenous communities in Canada?
2. What are the key factors that influence disability among Indigenous communities in Canada?

Inclusion Criteria

The participants, concept, and context (PCC) framework will guide the inclusion of eligible studies in this scoping review [34].

Participants

This review will consider sources that include the First Nations, Inuit, and Métis in Canada as the population of interest. We will include the recognized names of Indigenous peoples as search terms in this review.

Concept

This review will consider studies on Indigenous perspectives, concepts, and understandings of disability in Canada, as well as the factors influencing disability among Indigenous people.

Context

This review will consider studies or reports conducted in any Canadian province or territory, as well as those with a substantial focus on the Canadian context.

Types of Sources

This scoping review will consider peer-reviewed and gray literature. Mixed methods, quantitative, and qualitative studies are eligible for inclusion. The publication date range will be unrestricted.

Stage 2: Identifying Relevant Studies

We will consider sources that describe or reflect Indigenous perspectives on disability, whether they are published in peer-reviewed journals or as gray literature. The study or report must be located within Canada or have a significant component of the Canadian context.

We will design a structured search strategy for the electronic databases PubMed, Scopus, Web of Science, EBSCOhost (Bibliography of Indigenous Peoples in North America), ProQuest (Canadian Business and Current Affairs Database), Autochtonia, and APA PsycINFO to identify relevant published studies. We will develop the strategy using Boolean operators, filters, and truncation for each database. We will search for relevant articles using a mixture of search terms and keywords. We will consider adapting the filter developed by the University of Alberta to retrieve studies related to Indigenous people [35]. The research team will draft and refine a search strategy with the support of a professional librarian. We will pilot the search strategy to check the appropriateness of the keywords and databases. As an example, Multimedia Appendix 2 presents the search strategy for Scopus database.

The search for potentially relevant documents in the gray literature will follow 4 different searching strategies [36]: (1) search gray literature databases such as the Canadian Research Index and the Indigenous Studies Portal at the University of Saskatchewan; (2) use customized Google search engines to examine the first ten pages of results. Combine keywords using simple Boolean operators or hand search relevant subsections of sites; (3) Target Indigenous associations and websites for relevant information; and (4) Consult with experts proficient in research synthesis and aware of relevant documents to gather additional insights. We will contact both Indigenous and non-Indigenous scholars to include multiple sources and ensure our search is as inclusive as possible.

We will hand-search the references for the included articles to identify any additional relevant articles. We will limit the search to articles published in English or French. We will not apply restrictions based on the year of publication or study design.

To stay updated of current work in the field, our scoping analysis methodology will allow us to continually circle back to take newer articles through the screening process and potentially include them in our analysis.

Stage 3: Study Selection

We will export the list of references into Covidence software (Veritas Health Innovation) [37] to conduct title or abstract and full-text screening, first using the software to remove duplicates. Two independent researchers will screen study titles and abstracts against the inclusion and exclusion criteria to identify potentially relevant articles for full-text review. Two reviewers will then conduct a full-text review to confirm the final selection of articles. We will resolve disagreements by consensus or by consulting a third reviewer. A PRISMA (Preferred Reporting

Items for Systematic Reviews and Meta-analyses) flow chart will show the study selection procedure.

Stage 4: Charting the Data

Two reviewers will use the Covidence data charting framework to extract the relevant data from the included articles. They will pilot the draft data extraction sheet on a random sample of 5 articles. They will use a free use application to chart the data. The first part of the data extracted will include the authors, study title, source or journal, publication type, year of publication, objectives of the study, study design, geographic location, Indigenous group, description of participants, language, findings on perspectives, concepts, understandings, and terminology used about disability. The second part will list all the factors that influence disability from the Indigenous perspective and their relationships. We will present a 3-column edge list, a tabular format to represent relationships in a fuzzy cognitive map. The columns will include causes (originating node), outcomes (landing node), and the sign of the relationship (–1 or +1) [29]. Additional columns will indicate supporting evidence for the relationship and corresponding reference. We will use 1 row for each relationship. If the evidence is quantitative, we will include relationships that are significant at the 95% confidence level. If the evidence is qualitative, we will include quotes, arguments or texts supporting the relationship. We will adjust and refine the data extraction form as needed throughout the data extraction process and document any modifications in the review report. Data extractors will resolve disagreements through discussion.

Stage 5: Collating, Summarizing, and Reporting Results

We will present the results of the review as a qualitative description, incorporating tables, figures, and maps where appropriate. We will present the findings of the scoping review in a fuzzy cognitive map to illustrate the perspectives, concepts and understandings of disability and the factors that influence disability from an Indigenous perspective.

Fuzzy cognitive mapping visually represents knowledge, helping clarify the complex factors that influence outcomes or decisions [38,39]. These maps show assumed causal relationships that can be based on data or unwritten knowledge [40] between concepts or factors (nodes) and the outcomes, connected by arrows or edges [38,39,41]. The source of knowledge assigns different values to the edges, indicating the direction of the causal relationships and quantifying the strength of their influence on the outcome [28,38,39,41,42].

We will create a map for each article included in the review. We will identify whether the influence of a reported factor is positive or negative (+1 or –1) and depict it in a 3-column edge table as described above. If the study shows that an increase in one factor leads to an increase in another factor, we will assign a positive relationship (+1). If it shows a decrease in the second factor, we will assign a negative relationship (–1) [42].

After creating an individual table for each included study, we will calculate the fuzzy transitive closure for each study using the open access software CIETmap (V.2.2) to determine the strength of influence one factor has on others through direct or indirect relationships [43].

We will use Harris' discourse analysis approach to weigh each relationship based on its relative frequency across all the transitive closure maps [44,45]. Factors appearing in multiple maps will be weighted as having a stronger causal influence than those appearing in only 1 or 2 studies [41,45]. By dividing each relationship's occurrence by the highest frequency, we will obtain values between 0 and 1, where values closer to 1 indicate more influence. We will create a composite map of all factors and relationships identified in the scoping review, with relationship weights based on their relative frequency [45]. Multimedia Appendix 3 illustrates an example of a fuzzy cognitive map.

We anticipate refining and expanding the data presentation approach as the nature of the available literature becomes known. We will highlight areas where evidence is lacking and make recommendations for decision-making, practice or further research.

We will report the review methods and findings according to the PRISMA-ScR guidelines. We will disseminate the results of the scoping review in a peer-reviewed publication and present and discuss them in relevant forums, workshops, conferences, and community spaces. Potential limitations of the review include that we may miss studies reported in Indigenous languages and that some local knowledge may not be accessible despite best efforts to search the gray literature.

Stage 6: Contextualization

We will contextualize with stakeholders in the final step of the scoping review [31,32], which is part of a broader participatory research project on disability among Indigenous peoples of Canada. We will adapt the "weight of evidence" approach [28] to contrast and combine the synthesized evidence from the literature with the experiential knowledge of stakeholders, including Indigenous scholars, elders, knowledge keepers, cultural advisors, individuals with disabilities from the communities and their peers, as well as members of community-based and regional organizations representing people with disabilities or First Nations and Inuit in Quebec. We will invite them to share their perspectives, concepts, and understandings of disability in Indigenous communities, and to create maps of the factors that influence disability from an Indigenous perspective.

We will adapt the fuzzy cognitive mapping protocol recommended by Andersson and Silver [39]. A facilitator and a notetaker will support each stakeholder mapping session.

After the stakeholders create their own maps, they will compare them with the composite map from the scoping review. We will combine the scoping review map with the users' maps to update the literature with stakeholder perspectives. The scoping review and the stakeholder maps will serve as the basis for engaging them to explore solutions for the identified issues.

Results

The preliminary database search was conducted in January 2024. The study is scheduled for 2025, and its results will be published in open-access, peer-reviewed journals by the end of 2025.

Discussion

Principal Findings

The proposed scoping review will identify and map evidence on Indigenous concepts, perspectives, and understandings of disability as well as the key factors that influence disability in Canada. This review offers space for perspectives outside Western paradigms, facilitating a subsequent intercultural dialogue. This dialogue allows stakeholders with different cultural backgrounds to engage in respectful, dynamic communication to address a concern [46], in this case, the conceptualization of disability in Indigenous communities. The review might encourage a more inclusive, comprehensive, and culturally safe understanding of disability. It will contextualize the existing literature in the rich heritage of Indigenous Peoples in Quebec, Canada, including their perspective of disability and the implications of this for disability policy in this province. It will serve as a prototype for contextualizing the literature in the specific belief systems of Indigenous groups in other provinces and beyond Canada.

To our knowledge, no previous literature review has covered this topic in Canada. However, a review published by Australian authors significantly advances the understanding of disability services and disability conceptualization within Indigenous communities.

Strengths and Limitations

This scoping review has several strengths. First, we will include gray literature. By doing so, we will add valuable insights and ensure we don't miss findings and diverse perspectives that may not be found in peer-reviewed academic sources. Second, by contrasting and integrating evidence from the literature with the knowledge of Indigenous communities and people with disabilities through fuzzy cognitive maps, the scoping review will provide a thorough overview. Third, the participatory nature of the exercise will engage all stakeholders in interrogation of the literature and the codevelopment of a uniquely provincial and inclusive perspective. In this important sense, participation in the review process can be a first step in the intercultural dialogue.

The scoping review will have certain limitations. Some studies in Indigenous languages might be missed, and certain local knowledge may remain inaccessible, despite diligent attempts to include gray literature. The review will not include a quality assessment of the studies, which may introduce a risk of bias. We will provide a description of the methodologies and different criteria used to facilitate the contextualization of the findings. Potential limitations could include challenges in language use during fuzzy cognitive mapping for stakeholders, operator bias (influence of facilitators), as well as issues with coding and weighting [29]. To address this, we will train facilitators in protocols to reduce these recognized weaknesses. We are aware that the inclusion of multiple interpretations, factors, and varying levels of methodological rigor across different groups could decrease the precision of results.

Future Directions

By mapping the literature and identifying knowledge gaps, this scoping review will be a first step toward identifying research priorities and developing effective policies and interventions for Indigenous groups with disabilities. Future directions include repetition of the contextualization exercise in other Canadian provinces, generating provincially specific reviews that take account of Indigenous views in that province and the provincial agencies concerned with Indigenous people living with disability.

In addition to scientific publication and conference presentations, we will share the findings through workshops with participating communities and civil society organizations working in disability in Quebec.

Acknowledgments

The authors would like to thank Genevieve Gore from the McGill University Library for assistance with the development of the search strategy and Julian Robbins from the Centre for Addiction and Mental Health (CAMH) for his feedback on this protocol.

Authors' Contributions

All authors contributed to drafting the initial protocol, critically reviewed it for intellectual content, and subsequently revised it for publication. All authors reviewed and approved the submission of the final manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
PRISMA-P (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols) 2015 checklist.
[DOCX File , 34 KB - resprot_v14i1e57590_app1.docx]

Multimedia Appendix 2

Search strategy for scopus.
[DOCX File , 13 KB - resprot_v14i1e57590_app2.docx]

Multimedia Appendix 3
Example of a fuzzy cognitive map.
[DOCX File , 26 KB - resprot_v14i1e57590_app3.docx]

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Abbreviations

ICF: International Classification of Functioning, Disability, and Health
PCC: participants, concept, and context
PRISMA: Preferred Reporting Items for Systematic Review and Meta-Analysis
PRISMA-P: Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols
PRISMA-ScR: Preferred Reporting Items for Systematic Review and Meta-Analysis extension for Scoping Reviews

Edited by A Schwartz; submitted 21.02.24; peer-reviewed by J Smith-Merry, V Tomas; comments to author 11.03.24; revised version received 15.11.24; accepted 21.01.25; published 10.03.25.

Please cite as:
Rojas-Cárdenas A, Cleaver S, Sarmiento I, Rock J, Grenier Y, Charrier F, Gosselin RA, Cockcroft A, Andersson N
Indigenous Community Views of Disability in Canada: Protocol for a Scoping Review
JMIR Res Protoc 2025;14:e57590
URL: https://www.researchprotocols.org/2025/1/e57590
doi:10.2196/57590
PMID:

Protocol

Measuring Adult Health and Well-Being Outcomes Associated With Nature Contact in Parks and Other Forms of Protected Areas: Protocol for a Scoping Review

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Abstract

Background: Growing evidence shows various health and well-being benefits from nature contact in parks and other forms of protected areas. However, the methods to measure these outcomes lack systematic identification, critical appraisal, and synthesis. Researchers working in this area would benefit from a clear framework highlighting key considerations when selecting measurement tools, along with a summary of the measures used, and insights into the limitations of generalizing existing research findings.

Objective: The objectives of this scoping review are 2-fold. First, we aim to identify the instruments used to measure mental health and well-being outcomes of adults associated with direct nature contact in parks and other forms of protected areas. Second, we aim to evaluate the psychometric properties associated with the validity of these instruments to better understand the strengths and weaknesses of current measurement approaches.

Methods: Following PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews) guidelines, 8 scholarly databases were searched (PubMed, Web of Science, PsycINFO [via ProQuest], ERIC [via EBSCOhost], CINAHL [via EBSCOhost], GreenFILE [via EBSCOhost], OVID, and GEOBASE) on January 4, 2023, for literature measuring the mental health and well-being outcomes associated with nature contact in protected areas. Sources were screened by reviewers based on clear inclusion or exclusion criteria relevant to the research questions: peer-reviewed English language studies measuring mental health and well-being focused on adults (aged 18+ years) with direct, in-person nature contact in parks and protected areas. Data will be extracted, analyzed, and represented according to 3 domains. This includes study details, characteristics of the measurement instruments, and their validity.

Results: The results of the study and submission of a manuscript for peer review are expected in April 2025. The results of the scoping review are expected to contribute to an understanding of the diverse methods used to measure mental health and well-being related to nature contact in protected areas. Expected findings will include an organized summary of existing quantitative and qualitative instruments for measuring mental health and well-being outcomes, including appraisal of the instrument's psychometric properties.

Conclusions: To the authors' knowledge, this will be the first scoping review undertaken on measures used to assess mental health and well-being outcomes related to nature contact in parks and protected areas context, offering a starting point from which to critically examine the validity and consistency of such methods. Findings will aid in identifying the strengths and weaknesses of current measurement approaches to mental health and well-being outcomes of nature contact and may be used to guide future research on this topic, helping researchers choose the best tool to assess outcomes.

International Registered Report Identifier (IRRID): DERR1-10.2196/63338

(JMIR Res Protoc 2025;14:e63338) doi:10.2196/63338

KEYWORDS

nature contact; human health; mental health; well-being; parks; protected areas; outcomes

Introduction

Overview

There is a growing body of research investigating the role of nature in human health and well-being, with numerous studies reporting improvements to physical, psychological, emotional, cognitive, social, and spiritual well-being from time spent in nature [1-4]. Within this context, parks and other forms of protected areas offer unique opportunities to connect with nature, and considerable research has highlighted the increasingly recognized health benefits afforded by these settings [5-8].

Globally, there are more than 295,000 protected areas covering 16.1% of the earth's terrestrial or freshwater area and 8.2% of its marine area [9]. There is also a highly ambitious global initiative to protect 30% of earth's land or freshwater and marine area by 2030, as per the United Nations Convention on Biological Diversity Kunming-Montreal Global Biodiversity Framework [10]. If this goal is achieved, the designation of parks and other forms of protected areas would represent the fastest and largest land or freshwater and ocean allocation in the history of the modern conservation movement. Protected areas differ from most urban green space and local-regional parks in that they have legislated management objectives to conserve nature and provide opportunities for human enjoyment. The International Union for Conservation of Nature (IUCN) defines a protected area as "a clearly defined geographical space, recognized, dedicated and managed, through legal or other effective means, to achieve the long-term conservation of nature with associated ecosystem services and cultural values" [11].

Protected areas can include national and subnational protected area designations, such as national parks, state or provincial parks, and a variety of other designations that fit within the IUCN definition. It is estimated that such areas receive more than 8 billion visits annually [12], underscoring their significance as an essential ecosystem service. It is also estimated that parks and protected areas provide health services valued at US $6 trillion annually worldwide (representing 8% of global gross national product) [13]. Evidence establishing the significance of protected areas to human health and well-being continues to grow at the same time that many nations are committing to significantly expand protected areas networks by 2030. Given these joint trends, this proposed review offers a timely stock take that will help direct the current state of knowledge toward a stronger evidence-informed practice related to the use of parks and protected areas as a nature-based mental health service.

In addition to being timely, the proposed review will provide an important new tool for researchers who face numerous challenges investigating the impact of nature on human health and well-being. Previous research has examined the impact of nature on human health, demonstrating that mental health and well-being outcomes are the most frequently studied [2]. Despite a growing wealth of research, steps to critically evaluate and provide decision support to researchers and practitioners at the level of instrumentation are lacking. The dearth of current decision support presents a critical gap as well-being is a wide-ranging concept, with still wider-ranging options related to measurement. Well-being can capture relatively transitory emotion and mood states, more stable aspects of positive identity such as self-acceptance and self-esteem, broad global evaluations such as subjective life satisfaction, and improvement in clinical conditions such as anxiety and depression.

The need for this review is underscored by a past systematic review conducted by Cooke et al [14]. While not specific to nature-based interventions, Cooke et al [14] identified more than 40 different instruments for measuring well-being that varied widely in length, psychometric properties (ie, validity), and use cases. Linton et al [15] argue that such variability may in part be due to a lack of agreed upon criteria of what an instrument should contain. As noted, despite the current variety, ongoing creation of new instruments, and proliferation of their use in nature-based contexts, there has been no systematic or critical examination of the methods used to measure health and well-being outcomes associated with nature contact in parks and other forms of protected areas. This is a critical knowledge gap that the proposed scoping review will address.

Researchers working in this area would benefit from a clear framework identifying the features to consider in measurement selection as well as a summary of the measures that have been used and their validity. A framework of this type would provide a clearer picture of aspects of well-being that have and have not been investigated or replicated and limits to the generalizability of the research to date. To support further research and decision-making related to outcome-based management in parks and other forms of protected areas, the proposed scoping review seeks to address two objectives: (1) to identify the instruments used to measure mental health and well-being outcomes of adults associated with direct nature contact in parks and other forms of protected areas and (2) to evaluate the psychometric properties associated with validity of the instruments used to measure mental health and well-being outcomes associated with direct nature contact.

Existing Reviews

The current protocol was informed by an initial review of existing peer-reviewed literature to identify potentially comparable knowledge syntheses. To capture the current state of research related to mental health and well-being outcomes from nature contact, we gathered and documented scoping reviews published within the past decade that focused on an adult population. A search was conducted in Google Scholar to locate relevant scoping reviews, using variations of keywords that included "nature contact," "mental health," "well-being," and "scoping reviews." Table 1 outlines details of 7 relevant knowledge syntheses. All identified studies focused on

constructs related to mental health and well-being. While 6 of the identified studies were specific to health and well-being outcomes related to nature contact, by contrast, none were specific to the unique context of parks and protected areas.

Table 1. Summary of comparable existing knowledge syntheses.

Citation	Title	Objective	Review of measurement instruments	Specific to outcomes from nature contact	Specific to parks and protected areas
Cooke et al (2016) [14]	Measuring Well-Being: A Review of Instruments	Identify and critically evaluate the psychometric properties of instruments measuring well-being and related constructs	Y[a]	N[b]	N
Wendelboe-Nelson et al (2019) [16]	A Scoping Review Mapping Research on Green Space and Associated Mental Health Benefits	Identify the variations across existing literature in the associations between green space and health benefits	Y	Y	N
Christiana et al (2021) [17]	A Scoping Review of the Health Benefits of Nature-Based Physical Activity	Summarize existing literature on the positive association between nature exposure, physical activity, and health outcomes	N	Y	N
Wilkie and Davidson (2021) [18]	Prevalence and Effectiveness of Nature-Based Interventions to Impact Adult Health-Related Behaviors and Outcomes: A Scoping Review	Document the use of nature-based interventions as a strategy to change adult health-related behaviors and outcomes	N	Y	N
Charles-Rodriguez et al (2022) [19]	The Relationship Between Nature and Immigrant's Integration, Wellbeing and Physical Activity: A Scoping Review	Summarize existing research related to nature exposure, immigrant well-being, and physical activity	N	Y	N
Nejade et al (2022) [2]	What is the Impact of Nature on Human Health? A Scoping Review of the Literature	Summarize evidence relating nature-based interventions to health outcomes and examine enablers of nature contact	N	Y	N
Overbury et al (2023) [20]	Swimming in Nature: A Scoping Review of the Mental Health and wellbeing Benefits of Open Water Swimming	Summarize existing evidence relating to mental health and well-being benefits of open water swimming	N	Y	N

[a]Y: yes.

[b]N: no.

Cooke et al [14] reviewed 42 different instruments used to measure aspects of psychological well-being, psychosocial well-being, and psycho-physical well-being. The study categorizes these instruments according to 4 well-being categories (hedonic, eudaimonic, quality of life, and wellness) and a fifth category of composite measures. Evidence of reliability and validity of each instrument is tracked and reported, and authors report a substantial degree of variability in the reporting of evidence related to validity. Results do not report on patterns in the use of instruments according to intervention types or environmental contexts.

In 2 recent reviews, authors documented nature-based interventions and associated health and well-being outcomes. Wilkie and Davidson [18] examined 52 studies including a categorization of environmental settings, exposure times, and theoretical frameworks. They also report on targeted behaviors and outcomes, which includes mental health and well-being in 79% of studies reviewed and physiological health outcomes in 63% of studies. Results track specific outcomes (eg, self-esteem) that were measured but no details around measurement instruments. Nejade et al [2] similarly reviewed 39 papers that provided evidence of mental and physical health outcomes from nature-based health interventions. The forms of natural outdoor environments included green spaces, blue spaces, and mixed green-blue spaces, ranging from urban parks to wetlands, national parks, or reserves (n=2). The study provides a categorization of nature-based health interventions and activities, reports the mental and physical effects of engagement with natural outdoor environments, and discusses barriers and enablers of such engagement. Instruments used to assess health and well-being outcomes are not assessed.

Despite the proliferation of studies revealing the health and well-being benefits associated with nature contact, there is a clear need to identify and understand the specific instruments being used to assess these benefits. This is especially true in the context of nature contact in parks and other forms of protected areas, where rapid growth in visits to such areas is occurring alongside unprecedented national commitments to protect land or freshwater and marine area the world over. Research is needed to identify the most effective tools for assessing health and well-being outcomes vis-a-vis diverse research contexts (eg, types of environments, activities, and sociodemographic considerations) so that evidence-based policies and guidelines, as well as program outcomes, can be assessed consistently and effectively.

Methods

Research Design and Guiding Frameworks

This scoping review has been registered with the Open Science Framework [21] and developed in accordance with the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews) guidelines [22]. The completed PRISMA-P checklist is available in Multimedia Appendix 1.

Scoping reviews are broader in nature than systematic reviews, allowing researchers to examine the extent, range, and nature of research activity in a chosen area as opposed to finding the best evidence possible to a tightly defined research question [23]. A scoping review was considered the most appropriate method to address the research objectives due to the capacity to answer broad questions and summarize findings to identify gaps in the literature [2,24]. The scoping review applies Arksey and O'Malley's [25] five-stage process by (1) identifying the research questions, (2) identifying relevant studies, (3) selecting for studies in the final review, (4) charting the data, and (5) collating, summarizing, and reporting the results. Levac et al [26] expands on this framework to include a sixth optional consulting stage, which the research team deemed unnecessary for the purpose of this study.

Each stage of the scoping review was guided by the Population, Concept, and Context (PCC) framework to establish cohesion between the research questions, search strategy, and inclusion criteria (Textbox 1). The PCC framework is recommended for scoping reviews as a less restrictive alternative to the Population, Intervention, Comparator, and Outcome framework typically applied to systematic reviews [27]. Throughout this process, the purpose of the scoping review will be referred to, and critically discussed by the research team, to ensure that all decisions align with the research objectives and, ultimately, inform both research and practice.

Textbox 1. Developing a scoping review protocol with Population, Concept, and Context.

- P (Population): adults (aged 18 years or older)
- C (Concept): mental health, subjective well-being, emotional health, psychological health, restoration, coping, attention, mood, and indigenous well-being (including spirituality)
- C (Context): direct contact with parks and protected areas (spatial scope)

Search Strategy

A comprehensive search strategy was developed by a multidisciplinary team of 6 researchers in collaboration with an experienced university librarian. Following the recommendations of the Joanna Briggs Institute [28] for developing a search strategy, a limited preliminary search was conducted in Google Scholar using keywords related to the research objectives that included "mental health," "mental well-being," and "protected areas." This preliminary search produced 22 peer-reviewed papers that were deemed relevant to the review topic. The titles and abstracts of each paper were screened, along with the key terms used to describe the papers. This preliminary review allowed the research team to identify a robust set of key terms for the search strategy. The full literature index used to develop the search terms for this scoping review can be found in Multimedia Appendix 2. The protected areas terminology used in the literature search reflects the internationally recognized IUCN definition of protected areas and protected area categories, including specialized applications (ie, marine-protected areas). In addition, to inform the development of the search strategy, a search in the APA (American Psychological Association) Dictionary of Psychology identified relevant terms related to mental health, well-being, and subjective well-being.

Searches were conducted in 8 scholarly databases (PubMed, Web of Science, PsycINFO [via ProQuest], ERIC [via EBSCOhost], CINAHL [via EBSCOhost], GreenFILE [via EBSCOhost], OVID, and GEOBASE) known to contain journals focusing on human health and the natural environment. The search hedge contained terms related to domains of protected areas, nature engagement or exposure, and human mental health and well-being (Table 2). The search targets the intersection of environmental settings (protected area), with actions or events (nature engagement or exposure), and associated outcomes (mental health and well-being). Protected areas are recognized not only as spaces designated for conservation but also as venues for nature engagement. There is substantial evidence linking nature engagement with improved mental health and well-being, including benefits associated with protected areas [8,29-32]. The search terms were grouped by the Boolean operator "OR" to enhance the accuracy and relevance of results by accounting for as many concepts as possible and then combined using the Boolean operator "AND" to ensure that only relevant literature that contains all listed search concepts would be generated. The proximity operator "NEAR/20" was used to identify terms within 20 words of each other, regardless of their order. To

promote transparency and replicability in future research, the full search strategy for each of the 8 databases is available in Multimedia Appendix 3.

All database searches were conducted on January 4, 2023. To limit the scope of the searches, the selected databases were filtered to include only peer-reviewed journal papers published in English. No date filters were used to limit results to ensure that all relevant studies were included. By excluding a date limiter, the search strategy is more likely to identify trends over time, for instance, when certain instruments were first used to measure mental health and well-being in a parks and protected areas context.

Table 2. Primary search hedge subsequently adapted by scholarly database.

Concept	Search terms
Protected area classification	"protected area*" OR "national park*" OR "conserv* area*" OR "provincial park*" OR "state park*" OR "wildlife area*" OR "wildlife sanctuar*" OR "tribal park*" OR "nature reserve*" OR "marine reserve*" OR "marine sanctuar*" OR "conserv* territor*" OR "protected landscape*" OR "protected seascape*" OR "habitat management area*" OR "species management area*" OR "natural area*" OR "wilderness" NEAR/20
Nature engagement	exposure OR access* OR time OR engag* OR visit* OR being OR activity OR exercis* OR experience* AND
Mental health and well-being	"well-being*" OR "psychological restoration" OR "psychological health" OR "restorative*" OR "life satisfaction" OR coping OR "stress hormone" OR cortisol OR "mental health" OR "subjective well*" OR cognit* OR stress* OR emotion* OR anxiety* OR anxious* OR depress* OR mood* OR "state of mind" OR "frame of mind" OR brain* OR mind* OR "self-esteem"

Study Selection Process

All studies identified by our search strategy were uploaded into the reference manager software Zotero (Corporation for Digital Scholarship) [33]. Study details were then imported into the scoping review software Covidence (Veritas Health Innovation Ltd) [34] where duplicates were removed. The screening (and data extraction process) was piloted by 2 independent reviewers (JB and RB). These reviewers screened a random sample of 20 sources to ensure relative consistency and understanding of the proposed inclusion or exclusion criteria.

All studies were screened by 2 independent reviewers (CER and RB) at 2 levels. At the first level, the title, keywords, and abstracts of each source were assessed against the following criteria listed in Textbox 2. Where both reviewers agreed based on explicit content that a criterion was not met, the study was removed. Where there was disagreement or a lack of explicit content to make a judgement, the study moved to level 2 for full text review using the same inclusion or exclusion criteria.

Textbox 2. Inclusion and exclusion criteria.

Inclusion criteria

- Relevant to the research questions.
- Measures mental health and well-being.
- Protected area context.
- Focuses on direct contact (being physically present) with protected areas.
- Peer-reviewed papers (accessible for retrieval).
- Focuses on adults (aged 18 years or older).
- Available in English.

Exclusion criteria

- Not relevant to the research questions.
- Measures only other forms of health and well-being (physical, social, etc).
- Nonprotected area context.
- Focuses on nondirect forms of contact with protected areas (virtual reality, photograph viewing, etc).
- Books, book chapters, or reviews: conference proceedings, dissertations, theses, systematic or scoping reviews, gray literature, news articles, social media content, opinion papers, and inaccessible peer-reviewed papers.
- Includes children (younger than 18 years).
- Not available in English.

At the level of full-text screening, the research team attempted to retrieve the full-text files of all potentially relevant studies through available university library services. If unable to retrieve the full text through the library services, a member of the

research team contacted the corresponding authors to obtain a full-text file. Sources that remained unavailable were removed from the review. Once again, 2 independent reviewers (JB and RB) screened the full-text files applying the same inclusion or exclusion criteria that were used at level 1. Disagreements between reviewers at each stage of the selection process were addressed through discussion, involving a third reviewer to resolve conflicts as necessary.

Data Extraction and Analysis

Data will be extracted using Covidence by 2 independent reviewers (JB and RB) and compared for quality assurance to reduce bias. Any discrepancies that arise will be discussed and conflicts will be resolved by a third reviewer (CER). The proposed data extraction form (Table 3) will be used to identify and extract relevant variables that best address the research objectives. Extracted data from each paper will include descriptive information (eg, author names, title, and year of publication) and study methodology (eg, location, study design, sample, measurement instrument, and timing). Data pertaining to any quantitative or qualitative instruments used to measure mental health and well-being outcomes will also be extracted (eg, dimensions of well-being measured, instrument name, number of items, response scale, and end user engagement). Where a study includes more than 1 instrument of interest, each instrument will be recorded separately.

Table 3. Proposed data extraction template, indicating fields for which researchers will extract data with sample outputs.

Domains	Data extraction fields	Sample outputs
Characteristics of the study	• Reference • Study location • Protected area designation • Study design • Measurement form • Timing of measurement • Time spent in nature	• Full citation of listed study • Canada • National Park • Mixed methods, etc • Questionnaire, interview, etc • While in protected area • Two days, 1 week, etc
Details provided about the quantitative instruments in each study	• Dimensions of well-being • Instrument name • Source • Number of items • Scale size • Substantive validity • Structural validity • External validity	• Affect (eg, feeling, emotion, attachment, or mood) • Positive and Negative Affect Schedule (PANAS) • Author (year) • 20 items • 5-point scale • n=1 (100%) • n=1 (100%) • n=0 (0%)
Details provided about the qualitative instruments in each study	• Dimensions of well-being • Instrument name • Source • “End user” engagement • Multiple researchers involved in theming process • Member checks	• Affect (eg, feeling, emotion, attachment, or mood) • Semistructured interview • Author (year) • n=1 (100%) • n=0 (0%) • n=0 (0%)

Drawing on validity criteria from Simms [35], information that the researchers provide about the quantitative measurement instruments in the “Methods” section of each study will be assessed for 3 aspects of construct validity: substantive validity, structural validity, and external validity. Substantive validity is information about whether a measure is theoretically linked to the construct being studied. Structural validity is information about the degree to which the scores of a scale are an adequate indication of what the items measure, while external validity is information about whether the study findings can be generalized to other contexts [35,36]. Each study will be scored as either yes (1), the validity information was provided, or no (0), the validity information was not provided.

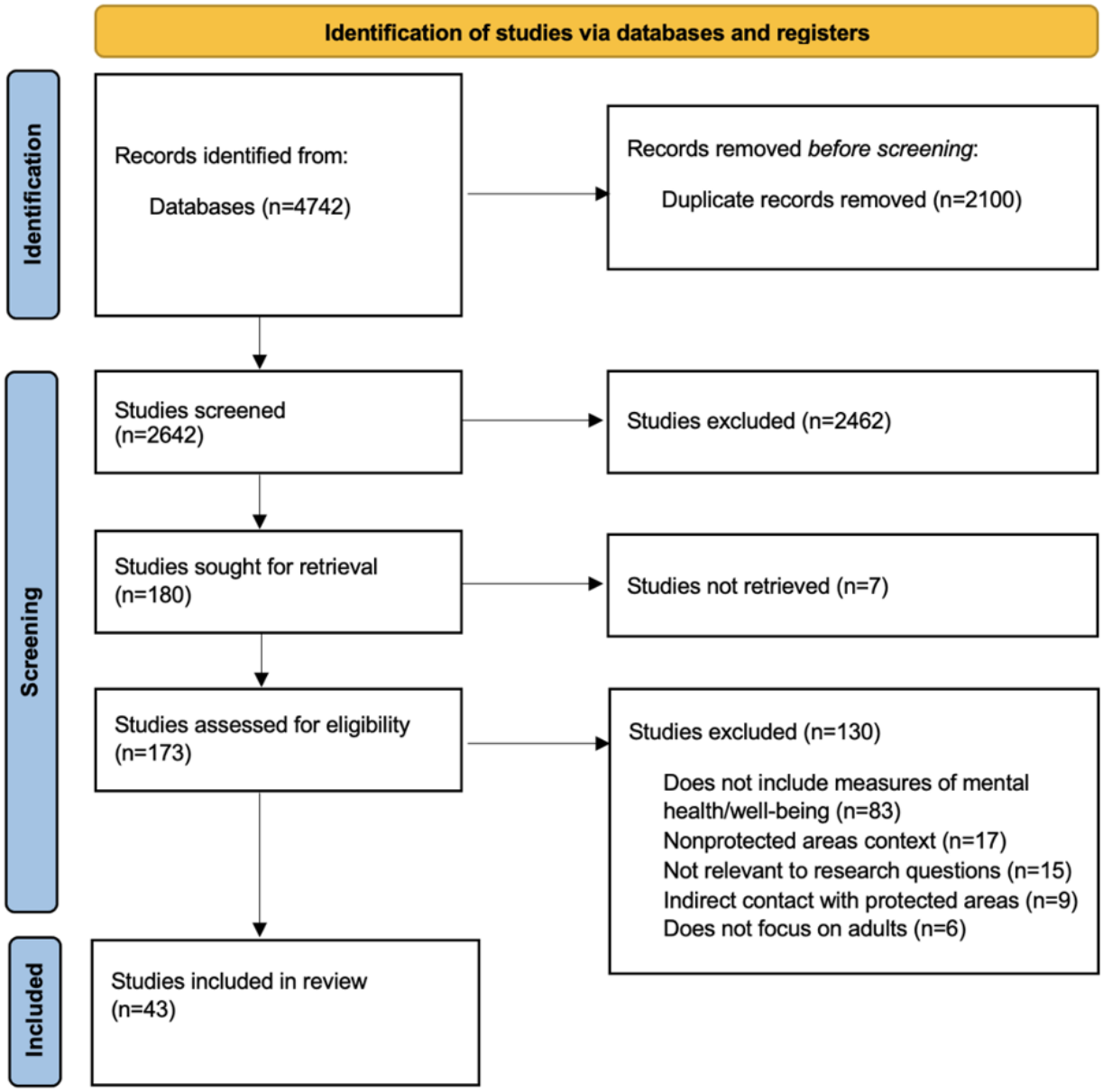
A quality appraisal will also be conducted on qualitative measurement instruments used in reviewed studies. This appraisal indicates whether multiple reviewers were involved in the theming process and checks were performed. Similar to the quantitative instruments, each criterion will be scored as yes (1) or no (0) based on whether studies provide evidence that these activities were incorporated into the methodology.

Results

Preliminary results of the study selection process are reported here using a PRISMA diagram (Figure 1) in accordance with PRISMA-ScR guidelines [28]. Searches in the 8 scholarly databases on January 4, 2023, yielded an initial 4742 studies (1 merged). From these initial studies, 2642 unique studies were identified for title and abstract screening, after the removal of 2100 duplicates. Through title and abstract screening, 180 studies were selected for full-text review, eliminating 2462 studies as they did not meet the previously outlined inclusion criteria. The full-text papers were sought for retrieval (7 were unavailable), resulting in 173 studies assessed for eligibility through the full-text review process. A total of 43 papers were selected for the final analysis. This pool is larger than those in other scoping reviews on adjacent topics [1], which affects the scope and time frame of the analysis. An updated search was conducted on December 11, 2024, yielding an additional 8 papers to be included in the analysis, for a total of 51 papers.

The results of the final scoping review and submission of a manuscript for peer review are expected in April 2025.

Figure 1. PRISMA flow diagram of the study selection process showing results and exclusions.



Discussion

Overview

This protocol details the methodology for a scoping review of the instruments that measure health and well-being linked to nature contact in protected areas, including their psychometric properties. Existing reviews have focused primarily on constructs related to mental health and well-being of adult populations associated with nature contact, although none specifically identify parks or protected areas. The volume of studies retrieved through the selection process suggests a robust evidence base regarding the health and well-being benefits of nature contact, with a likely diversity of measurement tools used. The review will identify, evaluate, and compare measures to provide a comprehensive overview of the quantitative and qualitative methodological instruments and tools used in research to date.

Strengths and Limitations

The scoping review is subject to limitations, in that it does not include gray and white literature, as well as studies that are not available in English. Given this, some relevant sources may be missed. Peer-reviewed papers not indexed in the searched databases may also be missed, but this limitation was deemed acceptable, given the need to manage the scope of the project. In addition, the extent to which the psychometric properties of an instrument can be evaluated is limited to the information provided within the included studies, which may be lacking descriptions of scale development. A deeper investigation would require looking elsewhere for additional resources, which is

beyond the scope of this review. Nevertheless, this review will provide a strong evidence base on which to build future research.

Conclusions

To the authors' knowledge, this will be the first scoping review undertaken on measures used to assess mental health and well-being outcomes related to nature contact in a parks and protected areas context. Findings will aid in identifying the strengths and weaknesses of current measurement approaches to mental health and well-being outcomes of nature contact and may be used to guide future research on this topic. For example, nature prescriptions—a health care program comprising written directives by health professionals for visits to natural settings (either individually or in groups) relying heavily on parks and other forms of protected areas—now exist in at least 6 countries [37]. Canada has more than 12,000 health care professionals prescribing nature in parks, and China's national health strategy includes a commitment to build more than 1000 forest therapy facilities nationwide [38].

Given the unprecedented interest and growth in nature-based health care commitments, it will be necessary to identify and use methods that effectively consider contextual factors. Relevant factors can include demographics (age, gender, and ethnicity) and activities, durations, and environments prescribed. All of these factors must be documented to best ensure reliability and validity when evaluating the outcomes (or benefits) and efficacy of nature prescription programs. This proposed review is also very timely, given the projected growth in the global estate of protected areas as per the United Nations Convention on Biological Diversity Kunming-Montreal Global Biodiversity Framework (detailed in the "Introduction" section).

Adherence to the PRISMA-ScR guidelines will ensure that the findings of this scoping review are of high quality and replicable. Furthermore, by providing insights into the validity of the measurement instruments used, we provide an opportunity to strengthen the methodological quality of future studies. The outlined scoping review will have significant implications for researchers, policy makers, and practitioners working at the nature conservation and human health interface. This review will provide a means to both understand previous research and undertake innovative research initiatives related to mental health and well-being outcomes associated with nature contact in parks and protected areas.

Acknowledgments

Funding to support this work was provided by the Parks Canada Agency (GC1727) and the John McMurry Research Chair in Environmental Geography at Wilfrid Laurier University.

Data Availability

The datasets generated and/or analyzed during this study are available from the corresponding author on reasonable request. The datasets will be reported in the final scoping review manuscript.

Authors' Contributions

JB and RB drafted the first manuscript and contributed to data curation and analysis. CER, LL, MWG, and CJL revised the manuscript. CJL and CER also contributed to study conceptualization, funding acquisition, and supervision of the process. All authors contributed to study design and reviewed and edited the final manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol.
[DOC File , 58 KB - resprot_v14i1e63338_app1.doc]

Multimedia Appendix 2
Index of relevant articles that informed the development of the search strategy.
[DOC File , 50 KB - resprot_v14i1e63338_app2.doc]

Multimedia Appendix 3
Search strategy for 8 scholarly databases.
[DOC File , 36 KB - resprot_v14i1e63338_app3.doc]

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Abbreviations

APA: American Psychological Association
IUCN: International Union for Conservation of Nature
PCC: Population, Concept, and Context
PRISMA-ScR: Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews

Edited by A Schwartz, T Leung; submitted 19.06.24; peer-reviewed by H Zong; comments to author 27.09.24; revised version received 21.11.24; accepted 22.02.25; published 24.03.25.

Please cite as:
Bueddefeld J, Reining CE, Lavallee L, Brady R, Groulx MW, Lemieux CJ
Measuring Adult Health and Well-Being Outcomes Associated With Nature Contact in Parks and Other Forms of Protected Areas: Protocol for a Scoping Review
JMIR Res Protoc 2025;14:e63338
URL: https://www.researchprotocols.org/2025/1/e63338
doi:10.2196/63338
PMID:40126537

Protocol

Experiences of Birth Attendants on Upward Obstetric Emergency Referrals in Low- and Middle-Income Countries: Protocol for a Scoping Review

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Abstract

Background: Every day, approximately 800 women die from pregnancy-related causes, alongside 2.6 million stillbirths and 2.8 million neonatal deaths annually. Inadequate referral by skilled birth attendants hinders timely access to necessary emergency obstetric care, challenging progress toward the maternal health Sustainable Development Goal (SDG) 3. The COVID-19 pandemic further disrupted care in low- and middle-income countries, forcing women to rely on traditional birth attendants, thereby affecting the referral system. It is crucial to understand the experiences of both skilled and traditional birth attendants regarding upward referrals in emergency obstetric care to identify barriers and facilitators within these systems in low- and middle-income countries.

Objective: This study aims to map existing evidence on the experiences of skilled and traditional birth attendants regarding upward referral systems in emergency obstetric care within low- and middle-income countries.

Methods: We will conduct a scoping review guided by the Joanna Briggs Institute's methodological framework. Studies will be included if they report on experiences with upward referral in obstetrical emergencies. We will consider studies published in English and French from 2016 to July 2024. The literature search will be conducted in databases including PubMed, EBSCOhost (Academic Search Complete and CINAHL with full text), Scopus, Web of Science, and Google Scholar. Identified citations will be managed using EndNote version 21 (Clarivate Analytics) and Rayyan. Two independent reviewers will screen eligible studies and resolve disagreements through discussion with a third reviewer. Data will be extracted using a validated form and analyzed through content analysis, with findings presented narratively. This protocol aligns with the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews) guidelines. The review will offer a comprehensive narrative of upward referral systems in obstetrical emergencies, focusing on transitions from traditional birth attendants to health care facilities and from lower to higher levels of health care.

Results: The preliminary search was completed in August 2024, and the database search will be conducted within the next 6 months. Findings will be disseminated through medical education conferences and publications.

Conclusions: This review contributes a comprehensive narrative of upward referral systems in obstetrical emergencies, aiming to enhance understanding and improve transitions from traditional birth attendants to health care facilities and between different health care levels. It could significantly impact maternal and neonatal care by identifying the referral experiences of both skilled and traditional birth attendants. The insights may inform interventions that integrate traditional birth attendants into health care

systems, potentially reducing maternal and neonatal mortality. The results will guide future research aimed at developing a model to improve upward referrals for obstetric emergencies in sub-Saharan Africa.

Trial Registration: Open Science Framework 4HAVZ; https://osf.io/4havz

International Registered Report Identifier (IRRID): PRR1-10.2196/64886

(JMIR Res Protoc 2025;14:e64886) doi:10.2196/64886

KEYWORDS

referral systems; upward referral; obstetric emergencies; traditional birth attendants; skilled birth attendants; low- and middle-income countries; birth attendants; obstetric; middle-income countries; scoping review protocol; pregnancy; neonatal deaths; deaths; obstetric care; health care; medical education; mortality; Africa; pregnant; women's health

Introduction

Pregnancy and childbirth can pose risks to both the mother and fetus [1], sometimes leading to life-threatening situations known as obstetric emergencies [2]. In such cases, specialized care is necessary and provided through a well-established referral system [3], typically an upward referral, which refers to the process by which health care providers at lower levels of the system seek assistance from specialized or better-equipped providers [4]. This system ensures a smooth transfer of patients between different levels of health care facilities, optimizes service delivery, and reduces the risk of complications [5] that can lead to mortality. Skilled birth attendants (SBAs) and traditional birth attendants (TBAs) are crucial in this process [6,7]. Alongside pregnant women, these frontline caregivers navigate the complexities of pregnancy and childbirth, often requiring swift intervention to ensure positive maternal and neonatal outcomes. However, the varying experiences of different stakeholders can negatively impact the obstetric referral process [8].

Every day, approximately 800 maternal deaths occur due to pregnancy-related causes [8], alongside 2.6 million stillbirths and 2.8 million neonatal deaths annually [9]. The global community is committed to improving health care quality to address these alarming statistics [8]. In line with Sustainable Development Goal (SDG) 3, which aims to ensure healthy lives and well-being for all, specific targets highlight the urgency of action. SDG 3, Target 1, aims to reduce the global maternal mortality ratio (MMR) to below 70 maternal deaths per 100,000 live births by 2030. Target 2 seeks to prevent the deaths of newborns and children younger than 5 years to fewer than 25 deaths per 1000 live births and reduce neonatal mortality to 12 deaths per 1000 live births [9]. However, challenges remain, especially in low- and middle-income countries (LMICs) [8], which are defined as countries with a gross national income per capita ranging from US $1086 to US $4255 [10]. Despite the United Nations' recognition of the right to access the highest attainable standard of physical health, including the integration of referral systems [11], obstetric emergencies continue to pose significant threats to the health and lives of mothers and newborns worldwide [8]. TBAs historically played a pivotal role in maternal health care before the formalization of midwifery, but interest in their role has diminished over time [6,12]. Since the 2000s, the focus has shifted toward skilled birth attendance, sidelining TBAs in routine deliveries due to their ineffectiveness in reducing maternal mortality [7]. Nevertheless, a significant proportion of women in LMICs continue to seek TBA services, highlighting their enduring importance [13].

In contrast, SBAs are recognized as a key strategy for reducing high maternal mortality rates and are pivotal indicators of progress in maternal mortality reduction efforts [7]. Addressing high maternal mortality rates through referral systems requires a comprehensive understanding of the experiences of pregnant women, SBAs, and TBAs [7]. However, the current health care system operates in fragmented silos, hindering collaboration between different systems. This lack of integration undermines efforts to combat maternal mortality, despite some pregnant women preferring TBA practices over Western medicine [12].

Research based on the Three Delays Model by Thaddeus and Maine highlights challenges affecting the timeliness of obstetric referrals within health care facilities. These challenges occur at both patient and institutional levels, impacting the referral process [7]. They include difficulties in identifying and reaching health care facilities, often involving TBAs in the referral process, and obstacles in receiving adequate care, often linked to SBAs who are responsible for essential obstetric care during pregnancy [14].

To improve maternal health outcomes, it is crucial to explore and understand the experiences of women, TBAs, and SBAs. Understanding stakeholders' perceptions and navigation of the referral process can help identify gaps in service delivery, such as limited access to emergency obstetric care facilities or communication challenges between health care providers and pregnant women. Addressing these challenges can enhance the efficiency and effectiveness of obstetric referral systems, ensuring timely access to needed care for women.

Although previous studies and reviews have examined referrals in obstetric emergencies [1-3,5,8,14] since the adoption of the SDGs, none have focused on the experiences of upward obstetric emergency referrals in LMICs for both SBAs and TBAs, advocating for integrated referral systems that can save the lives of mothers and babies. Therefore, this review aims to provide a comprehensive overview of the current state of birth attendants' experiences with referral systems in obstetric emergencies in low-income countries.

Methods

Study Design

Using the steps of the Joanna Briggs Institute (JBI) Scoping Review Methods [14], the researchers will examine and map the available literature related to the experiences of birth attendants with upward obstetric emergency referrals in LMICs. This scoping review protocol has been developed and registered with the Open Science Framework. The protocol will be implemented, and the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews) guidelines will be used to guide the reporting.

Main Objective and Review Questions

The main objective of this review is to examine available evidence regarding birth attendants' experiences with upward referral systems in emergency obstetric care in sub-Saharan Africa (SSA) since the inception of the SDGs. Based on the objective of this review, the following research questions have been developed:

1. What are the publication characteristics of evidence on upward obstetric referrals?
2. What are the experiences of birth attendants regarding upward obstetric emergency referrals in LMICs?

The objective of this scoping review is part of the PhD study titled "Developing a Model to Enhance Effective Upward Referral of Obstetric Emergencies from Community Health Centres in Oliver Tambo District, Eastern Cape, South Africa: A Grounded Theory Inquiry."

Eligibility Criteria

The eligibility criteria for this review will be based on the JBI mnemonic for formulating systematic review questions, which describe the population, concept, and context of the study [14]. Textbox 1 summarizes the criteria.

Textbox 1. Eligibility criteria.

Inclusion criterion:

- Population:
  - Skilled birth attendant: a professional health care worker who attends to pregnant women
  - Traditional birth attendant: an unskilled person who attends to pregnant women
- Concept:
  - Upward referral of women during labor and childbirth
  - Referral of women during pregnancy
  - Referral from traditional birth attendants to a health care facility
- Context:
  - Low- and middle-income countries
- Study designs:
  - Qualitative designs
  - Quantitative designs
  - Mixed methods designs
  - Conference proceedings abstracts
  - Gray literature
- Time period:
  - From January 2016 to July 2024

Exclusion criterion:

- Population:
  - Professional health care workers who do not attend to pregnant women
  - Unskilled individuals who do not attend to pregnant women
- Concept:
  - Referral of women outside the pregnancy and childbirth experience
  - Neonatal emergencies
- Context:
  - High-income countries
- Study designs:
  - Letters to the editor
  - Reviews
- Time period:
  - After July 2024

Population

The scoping review will include all relevant peer-reviewed and gray literature focused on upward referral systems in emergency obstetric care in LMICs. The population sample for the review will consist of birth attendants including SBAs and TBAs.

Concept

The concept will be guided by the following: Experiences, perceptions, and upward obstetric emergency referrals**.** According to the World Health Organization (WHO) [15], “referral can be defined as a process in which a health worker at one level of the health care system, having insufficient resources (eg, drugs, equipment, and skills) to manage a clinical

condition, seeks the assistance of a better or differently resourced facility at the same or higher level to assist in or take over the management of the client's case." Furthermore, an obstetric emergency is defined as a complication or situation of a serious and often dangerous nature, developing suddenly and unexpectedly, and demanding immediate attention in order to save lives [8].

Context

The context of this review will focus on LMICs within emergency obstetric care settings.

Types of Sources

This scoping review will include both experimental and quasi-experimental study designs such as before-and-after studies and interrupted time-series studies. In addition, analytical observational studies, including prospective and retrospective cohort studies, case-control studies, and analytical cross-sectional studies, will be considered for inclusion. Descriptive observational study designs, including case series, individual case reports, and descriptive cross-sectional studies will also be included. Qualitative studies focusing on qualitative data, including, but not limited to, designs such as phenomenology, grounded theory, ethnography, qualitative description, action research, and feminist research, will be considered for inclusion. Furthermore, text and opinion papers will also be considered in this scoping review.

Search Strategy

An initial limited search in PubMed and ScienceDirect was undertaken to identify papers on the topic. The text words from the titles and abstracts of relevant papers, along with the index terms used to describe them, were used to develop a full search strategy (Table 1).

Table 1. Preliminary search strategy.

Date	Database	Search query	Results, n
January 29, 2024	PubMed	((“obstetric labor complications”[MeSH Terms] OR (“obstetric”[All Fields] AND “labor”[All Fields] AND “complications”[All Fields]) OR “obstetric labor complications”[All Fields]) AND (“referral and consultation”[MeSH Terms] OR (“referral”[All Fields] AND “consultation”[All Fields]) OR “referral and consultation”[All Fields] OR (“hospital”[All Fields] AND “referrals”[All Fields]) OR “hospital referrals”[All Fields]) AND (“developing countries”[MeSH Terms] OR (“developing”[All Fields] AND “countries”[All Fields]) OR “developing countries”[All Fields])) AND (2016/1/1:2024/1/31[pdat])	11
July 3, 2024	Science Direct	referral OR referral process OR referral pathway OR care pathway) AND obstetric labour complications AND Developing countries	712

Second, a systematic search will be conducted across 4 remaining electronic databases, namely EBSCOhost (including Academic Search Complete and CINAHL with full text), Scopus, Web of Science, and Google Scholar.

The search strategy, including all identified keywords and index terms, will be adapted for each included database or information source or both. Peer-reviewed journals will be reviewed for primary studies with a clear empirical base, using qualitative, quantitative, and mixed methods addressing the research question. Studies will be identified by searching literature from January 2016 to July 2024. In addition, papers will be searched through the “cited by” search feature as well as through citations included in the reference lists of included papers. The search terms will include referral system, LMICs, obstetric emergency, SBAs, and TBAs. Boolean operators (AND, OR) will be used to separate keywords, and Medical Subject Headings (MeSH) terms will be included during the search. The search syntax will be modified as needed. Reference lists of selected papers will also be searched for additional papers of interest. The services of an experienced subject librarian will be used to ensure that a robust search strategy is followed. The search strategy will be piloted to check the appropriateness of selected electronic databases and keywords. To compile all relevant evidence sources, identify, and remove duplicate records, the EndNote X21 reference manager will be used to import and manage eligible studies.

Source of Evidence Selection

Following the search, all identified citations will be collated and uploaded into EndNote version 21, and then imported into the Ryann systematic review app, where duplicates will be removed. Following a pilot test, titles and abstracts will be screened independently by FZJ and ELMK for assessment against the inclusion criteria for the review. Potentially relevant sources will then be retrieved in full. The full text of selected citations will be assessed independently by FZJ and ELMK to determine whether they meet the inclusion criteria. Reasons for the exclusion of sources of evidence in the full text that do not meet the inclusion criteria will be recorded and reported in the scoping review. Any disagreements between the reviewers at each stage of the selection process will be resolved by OBB. The results of the search and study inclusion process will be fully reported in the final scoping review and presented in a PRISMA-ScR flow diagram [16].

Data Extraction

Data will be extracted from the papers included in the scoping review by FZJ and ELMK independently, using a data extraction tool developed by the reviewers. The data extracted will be informed by the formulated review questions and will include—in addition to paper details such as authors, year of publication, design, and setting—specific details about the participants or population, reasons for referral, challenges experienced, support identified related to the referral, and further recommendations for upward obstetric emergency referrals.

Before data extraction, the tool will be pilot-tested independently by FZJ and ELMK. The draft data extraction tool will be modified and revised as necessary during the process of extracting data from each included evidence source. Any modifications will be documented in the scoping review. OBB will afterwards check that no relevant information has been omitted. The information to be extracted using this tool is detailed below (Textbox 2).

Textbox 2. Initial data extraction tool.

Criteria:

- Authors or year of publication or both
- Research design
- Study setting
- Nature of population or sample
- Reasons for referral
- Challenges experienced related to the referral
- Support experience related to the referral
- Recommendations related to the referral

Data Analysis

Knowledge and experiences of skilled and traditional BAs regarding referral in obstetric emergencies to combat maternal and child mortality rates will be extracted from this review. The data will be analyzed to develop a comprehensive model for effective referral in resource-constrained settings.

Data summarization and reporting will adopt a fundamental descriptive approach, using content analysis [17]. A narrative approach will present the findings from the included studies, using thematic content analysis to describe the themes that are relevant to experiences with referral systems in obstetric emergencies in low- and middle-income countries. In addition, any other emerging themes will be reported.

Ethical Considerations

This study was approved by the university's ethics committee for BioMedical Research (ethics approval BREC/00006633/2024).

Results

As of August 2024, the preliminary search was completed, and the database search will be conducted within the next 6 months. Findings will be disseminated through medical education conferences and publications.

Discussion

Principal Findings

It is anticipated that this review will map out the different experiences of birth attendants regarding upward referral in obstetric emergencies. It is also anticipated that the experiences of SBAs are different from those of TBAs. These insights will enrich the body of knowledge related to referrals in LMICs. The findings have the potential to aid in improving care for mothers and newborns in several ways. First, the study will synthesize information on referral systems in obstetric emergencies within resource-constrained health care settings. Second, it will identify referrals from both SBAs and TBAs to health care facilities. This information could support the development of interventions that advocate for including TBAs in health care systems to reduce maternal and neonatal deaths. Third, the review's findings will inform a future study aimed at developing a model to enhance effective upward referral of women with obstetric emergencies during labor in an SSA country.

Comparatively, researchers [1,2] have highlighted logistical challenges in emergency referrals, concentrating on gaps in primary care systems and delays in reaching tertiary facilities. This study, on the other hand, provides a more comprehensive understanding of the systemic and interpersonal dynamics influencing emergency referrals in LMICs. The dual focus on both TBAs and SBAs is unique, as it addresses an unexplored area in studies such as [7], which observed that traditional and formal care providers act as fragmented health structures, preventing collaboration. However, in LMICs, a significant proportion of women continue to seek TBA services, highlighting their enduring importance [13]. Therefore, the insights generated could serve as a foundation and guidance for future research aimed at developing a model to improve upward referrals for obstetric emergencies in SSA.

Policy and Practical Implications

The scoping review aims to provide insights into the experiences of both SBAs and TBAs regarding upward referral systems in emergency obstetric care. It will be instrumental in identifying key gaps and challenges in the referral process.

By linking the anticipated results to the SDGs, particularly SDG 3 on good health and well-being, the review highlights the critical role of improving referral systems to reduce maternal and neonatal mortality. The review will inform policy makers about effective strategies to enhance referral processes, ensure timely access to emergency obstetric care, and better integrate TBAs into the health care system.

Health care providers are expected to benefit from the insights this scoping review will provide regarding training needs for

effective referrals and collaboration between SBAs and TBAs. This will improve referral practices and ensure smoother transitions of care.

Furthermore, the review will emphasize the importance of community involvement in supporting and understanding the referral process. Recommendations for engaging communities through educational campaigns and support systems may strengthen the overall referral network.

Potential Challenges and Limitations

The review includes only studies published in English and French, which may exclude relevant research in other languages and limit the comprehensiveness of the findings. Furthermore, it focuses on studies published and indexed in selected databases, potentially overlooking unpublished research.

Conclusion

This review contributes a comprehensive narrative on upward referral systems in obstetrical emergencies, aiming to enhance understanding and improve transitions from TBAs to health care facilities and between different health care levels. It could significantly impact maternal and neonatal care by describing the referral experiences of skilled TBAs in obstetric emergencies. The insights may inform interventions that integrate TBAs into health care systems, potentially reducing maternal and neonatal mortality. The results will guide future research aimed at developing a model to improve upward referrals for obstetric emergencies in an SSA country.

Acknowledgments

The authors would like to thank Dr Cedric Mbobnda Kapche for critically reviewing this manuscript.

Data Availability

All data generated and analyzed will be included in the published scoping review article and will be available upon request.

Conflicts of Interest

None declared.

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Abbreviations

JBI: Joanna Briggs Institute
LMIC: low- and middle-income countries
MeSH: Medical Subject Headings
MMR: maternal mortality ratio
PRISMA-ScR: Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews
SBA: skilled birth attendant
SDG: Sustainable Development Goal
SSA: sub-Saharan Africa
TBA: traditional birth attendant
WHO: World Health Organization

Edited by A Schwartz; submitted 30.07.24; peer-reviewed by NJ Norehan Jinah, FH Mfidi; comments to author 02.09.24; revised version received 16.10.24; accepted 11.12.24; published 10.04.25.

Please cite as:
Juqu FZ, Baloyi OB, Mbobnda Kapche EL, ten Ham-Baloyi W, Chironda G, Xulu-Kasaba ZN
Experiences of Birth Attendants on Upward Obstetric Emergency Referrals in Low- and Middle-Income Countries: Protocol for a Scoping Review
JMIR Res Protoc 2025;14:e64886
URL: https://www.researchprotocols.org/2025/1/e64886
doi:10.2196/64886
PMID:

Protocol

Health Care Social Robots in the Age of Generative AI: Protocol for a Scoping Review

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Abstract

Background: Social robots (SR), sensorimotor machines designed to interact with humans, can help to respond to the increasing demands in the health care sector. To ensure the successful use of this technology, acceptance is paramount. Generative artificial intelligence (AI) is an emerging technology with the potential to enhance the functionality of SR and promote user acceptance by further improving human-robot interaction.

Objective: We present a protocol for a scoping review of the literature on the implementation of generative AI in SR in the health care sector. The aim of this scoping review is to map out the intersection of SR and generative AI in the health care sector; to explore if generative AI is applied in SR in the health care sector; to outline which models of generative AI and SR are used for these implementations; and to explore whether user acceptance is reported as an outcome following these implementations. This scoping review supports future research by providing an overview of the state of connectedness of 2 emerging technologies and by mapping out research gaps.

Methods: We follow the methodological framework developed by Arksey and O'Malley and the recommendations by the Joanna Briggs Institute. Our protocol was drafted using the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-analyses extension for Scoping Reviews). We will conduct a systematic literature search of the online databases MEDLINE, Embase, CINAHL (Cumulative Index to Nursing and Allied Health Literature), Web of Science, and IEEE Xplore, aiming to retrieve relevant data items via tabular data charting from references meeting specific inclusion criteria which are studies published from 2010 onwards, set in the health care sector, focusing on SR with physical bodies and implemented generative AI. There are no restrictions on study types. Results will be categorized, clustered, and summarized using tables, graphs, visual representations, and narratives.

Results: After conducting a preliminary search and deduplication in the second quarter of 2024, we retrieved 3176 preliminary results. This scoping review will be supplemented with the next methodological steps, including retrieving the results in a reference management tool as well as screening titles, abstracts, and full text regarding specific inclusion criteria. The completion of these steps is scheduled for the second quarter of 2025. Limitations based on the heterogeneity of the included studies and the general breadth of a scoping review compared to a systematic review are to be expected. To reduce bias, we adopted a system of dual reviews and thorough documentation of the study selection.

Conclusions: The conducted preliminary search implies that there are a sufficient number of heterogeneous references to complete this scoping review. To our knowledge, this is the first scoping review on generative AI in health care SR.

International Registered Report Identifier (IRRID): PRR1-10.2196/63017

(JMIR Res Protoc 2025;14:e63017) doi:10.2196/63017

KEYWORDS

robotics; social robots; artificial intelligence; generative AI; human-robot interaction; health care sector; PRISMA

Introduction

Background

Social robots (SR) are interactive robots designed to engage with humans in a social or collaborative manner, often mimicking human behaviors, communication, and social cues [1-3]. SR are already being used in geriatric care, rehabilitation, and the care of people with cognitive disabilities [4]. Since much progress has been made regarding the development of SR in recent years [5], it is to be expected that they will find widespread use in the health care sector in the next few years [6]. Between 2005 and 2010, 1300 units of "Paro," an artificial seal for therapy of patients with dementia [7], were sold in Japan [8]; as of 2013, "Paro" was adopted in 80% of local care institutes in Denmark [9]. These examples illustrate that SR could be a way of responding to the needs of people in need of care and of filling the gap between the supply and demand of health care professionals. Other examples for SR that can be applied in the health care sector are "Cruzr" [10], a service robot [7,10]; "NAO" [11], a household robot [7,11]; or "Lio" for older adult care [7,12].

For SR to be effectively integrated and successful, their acceptance is paramount. Simply introducing these innovative robots is not sufficient if individuals are hesitant or unwilling to interact with them [13]. Lum [14] emphasizes that the fundamental challenge for the practical application of SR is the willingness of people to accept them in their everyday lives. In democratically constituted, liberal societies, acceptance is deemed a factor for a successful take-up of a technology by the population [15]. While positive effects such as assistance with everyday tasks [16,17], maintaining of individual autonomy [17-19], or increase of happiness [18] are associated with the use of SR in older adult care, their acceptance is noted to vary [6], with acceptance toward the SR depending on the area of their application [15]. With the ongoing development and practical use of SR, the question of their acceptance as a possible component of people's everyday routines moves further into focus [6,14].

Dialog management is positioned as one of the main goals of human-robot interaction (HRI) [20], increasing user satisfaction and task efficiency [20,21]. In this context, generative artificial intelligence (AI) like OpenAI's ChatGPT [22], being extensively trained on conversational dialog [23,24], could be used to translate instructions given in natural language into actions executable by a SR [25,26], improving multiparty interactions [21]. Since late 2022, there has been a significant growth in the field of generative AI [27], a technology which will have an impact on all industry sectors with the potential to change how people work and to increase productivity [28]. We believe that by implementing generative AI in SR, usability and user acceptance, key elements of HRI, could be vastly increased. Speech, gesture, mimic recognition, robot customizability, intuitive operation, and interaction among others, are aspects we believe to highly benefit from the potential of generative AI. We expect this emerging technology to largely influence the use and functionality of SR, facilitating their widespread use in the health care sector. Health care professionals, patients, and other persons in need of care could benefit from such advanced robots fulfilling a wide array of valuable tasks. With this scoping review, the authors intend to map out if and how these emerging technologies are interconnected.

Definitions and Terms

Social Robots

Sarrica et al [29] point out that there is a wide array of various definitions for SR, which are partially built on existing definitions or introduce new concepts. For example, Bendel [7] refers to SR as sensorimotor machines explicitly designed to be used in the immediate vicinity of and for direct interaction with humans. A machine is defined as an assemblage of parts that transmit forces, motion, and energy to one another in a predetermined manner [30], consequently implying the necessity of a physical body as well as the presence of sensors and motors for interaction with and perception of the environment by a robot in a narrow sense. While Bendel [7] presents the option to broaden the concept of robots and include software robots like chatbots within SR by relativizing the sensorimotor and physical components, scientific definitions overall tend to describe SR as semiautonomous or autonomous physical bodies, with "machines" and "physical" being some of the main dimensions underlying different definitions [29]. As Kuipers et al [31] point out, the creation of robots with a human-like competence of real-world manipulation is a major challenge of research, since the ability to physically change the surrounding world is of utmost relevance to humans [32]. In the context of care, the burden of physical work is high and further increasing [33,34]. Against this background, we consider only SR with a physical body for this review to ensure a high level of comparability of the results.

Generative AI

Generative AI is a type of AI able to generate content [28]. It is based on different kinds of underlying models, for example, generative adversarial networks, encoder-decoder networks, neural networks, or transformers [27]. Subtypes of generative AI are large language models, deep neural networks which are pretrained with millions of parameters on large amounts of unlabeled text [35]. This training enables them to learn the relationship between words or portions of words [28]. Unlike decision tree models, which use algorithms to create predictions or rules based on incoming data, generative AI uses specific algorithms trained on large amounts of data to generate new, previously unseen content [27]. This generated content can be manifold, for example, human-like texts, images, and music [27]. Compared to a conversational AI, which can provide users with human-like responses in a conversation, generative AI can not only generate such responses but generate the content of

these responses as well [36]. These responses can even surpass the original programming of the generative AI [36]. Since late 2022, the field of generative AI has grown significantly [27,37]; pretrained and then task-specifically modified large language models became the dominant pattern in the field of natural language processing [38-44], with examples being Google's BERT (Bidirectional Encoder Representations from Transformers) [38] and OpenAI's GPT-3 [39]. Generative AI gained increasing public focus since the release of ChatGPT in late 2022, while the concept of generative models of AI began to be recognized since the 2010s [27]. One of the goals in the development of ChatGPT was to facilitate a better reciprocal understanding of the communication between human users and robots [45].

Acceptance

Acceptance, acceptability, adoption as well as other related terms in the context of technology acceptance are often used interchangeably [46], describing the same overall concept. Acceptability is described as the user's willingness toward the use of a system [47]. User acceptance can be defined as "the demonstrable willingness within a user group to employ (information technology) for the tasks it is designed to support" [48]. The aforementioned terms are occasionally used exchangeable with other concepts of human-computer interaction like user satisfaction [49]. User acceptance can be specified as the users' intention to use a future technology, their willingness to integrate it into their daily life [50], and the prospective judgment of this new technology [51]. Beetz et al [15], specify acceptance of assistive robotics as being based on trust. Human-related aspects such as cultural background, living conditions, or expectations toward the functionality of a robot as well as criteria of the robot itself such as design [6,32], language capability, or range of functions are relevant for the acceptance of an SR [6]; specifically, an anthropomorphic approach on the design of SR is deemed to be of high relevance [14]. In the literature, the terms facilitators and barriers are commonly used to describe factors of technology uptake in general, for example, facilitators of the implementation of SR can be mobility aspects [52], being physically accessible [52,53], or offering an economic advantage [54]. Davis [55] developed the Technology Acceptance Model to describe why a person does or does not use a technology. A person's attitude toward using a technology depends on the technology's perceived usefulness and its perceived ease of use, the behavioral intention to use a technology depends on the aforementioned attitude toward using and the perceived usefulness directly [55]. Thus, this model implicates a complex relationship between the user's subjective ability to accept, and the quality of a technology of being acceptable. Based on a revision of this model [56], Heerink et al [57], proposed the Almere Model for technology acceptance of SR by older adult users, examining 12 areas related to HRI: anxiety, attitude toward technology, facilitating conditions, intention to use, perceived adaptiveness, perceived enjoyment, perceived ease of use, perceived sociability, perceived usefulness, social influence, social presence, and trust [57]. The Almere Model integrates the multi-dimensionality of acceptance formation by relating robot-specific factors to their subjective perception by humans.

Literature Gap

To address the intersection of SR and generative AI, we conducted a preliminary search for systematic reviews, scoping reviews, or protocols for reviews in the online databases MEDLINE, Embase, CINAHL, Web of Science, and IEEE Xplore based on our search strategy presented in stage 2. For example, some of these reviews focus on AI in the health care sector in general [58-101]; other reviews focus on social or surgical robots in the health care sector in general [102-118]; a few highlight the use of AI in surgical robots [119,120] or the use of chatbots [80,88,121] in the health care sector; Clabaugh and Matarić [122] conducted a systematic review on enablers of autonomy of SR; Huang et al [123], conducted a systematic review on antecedents and consequences of the application of intelligent SR; Hung et al [124], published a protocol for a systematic review on the facilitators and barriers to the use of robots equipped with AI in older adult care; Lee et al [125] conducted a systematic review and meta-analysis on the effect of AI-equipped SR on cognitive function.

However, none of these reviews focus specifically on the implementation of generative AI in SR in the health care sector and the interconnectedness of these 2 emerging technologies.

Aim

The aim of this scoping review is to map out if and how 2 emerging technologies: generative AI and SR are interconnected. This scoping review is based on an overview of relevant publications that have considered the implementation of generative AI in physical health care SR. We intend to explore whether generative AI is applied in SR in the health care sector, what models of generative AI and SR are used for this implementation, in which setting these implementations take place, and if user acceptance is among the reported outcomes following these implementations.

Methods

Study Design

In this review, we follow the methodological framework developed by Arksey and O'Malley [126] and the recommendations by the Joanna Briggs Institute [127]. We apply the following stages here: (1) identifying the research question, (2) identifying relevant studies, (3) selection of studies, (4) data charting, and (5) collating, summarizing, and reporting the results. To report our results, we use the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews), attached in (Multimedia Appendix 1), and, where applicable, PRISMA-P (Preferred Rpeorting Items for Systematic Reviews and Meta-Analyses Protocols; Multimedia Appendix 2).

Research Team

The research team conducting this review consists of a medical student researcher interested in the fields of medical sociology and medical data science, PL; a researcher with a background in health economics, CG; a professor for digitalization working in the field of digital transformation and applications, DF; the head of information literacy education and systematic review,

medical library, CD; a professor for medical data science and an expert on human-computer interaction, FB; and a senior researcher working in the field of medical informatics and health care organization and innovation, TS.

Stage 1: Identifying the Research Question

The main research questions of this protocol are as follows: (1) Are generative AI models implemented in SR in the health care sector? The following subquestions are posed: (2) Which models of generative AI and SR are used for these implementations? (3) What are the settings of these implementations? (4) Has the acceptance of SR been reported as an outcome following these implementations?

Answering these questions can support future research by mapping out potential research gaps and providing an overview of the state of connectedness of 2 emerging technologies, SR, and generative AI.

Stage 2: Identifying Relevant Studies

To identify relevant studies, a systematic literature search of the electronic databases MEDLINE (via Ovid; 2010 onwards), Embase (via Ovid; 2010 onwards), CINAHL (via EBSCOhost; 2010 onwards), Web of Science (2010 onwards), and IEEE Xplore (2010 onwards) will be conducted. The selection of these databases follows the recommendation of a member of the research team (CD), an information specialist of the medical library of Charité, covering a broad and interdisciplinary field including computer science, social and behavioral sciences, and medicine. To construct our search queries, we followed the guidelines of the Peer Review of Electronic Search Strategies (PRESS) [128]. Textbox 1 presents the main search terms underlying these search queries. An initial search query was built with Ovid for MEDLINE. The online tool Polyglot Search Translator [129] is used to adapt this search query for the databases Embase, CINAHL, and Web of Science. For IEEE Xplore, the initial search query is adapted manually to account for the different syntax and limit of search terms per search clause. Duplicates will be deleted by using the online tool Systematic Review Accelerator [130] after the corresponding results have been documented and managed using the reference managing software EndNote (Clarivate).

The search terms are based on the expertise of the research team, an internal focus group, and an additional use of the AI chatbot, ChatGPT (OpenAI) to detect further relevant synonyms and terms. These terms are combined using the appropriate Boolean operators AND Specialty OR to generate the search queries. The exact search queries for MEDLINE, Embase, CINAHL, Web of Science, and IEEE Xplore are referenced in (Multimedia Appendix 3).

Textbox 1. Overview of the main search terms.

Social robot

- Social robot
- Interactive robot
- Companion robot
- Humanoid robot
- Personal robot
- Emotional robot
- Assistive robot
- Service robot
- Communicative robot
- Socially assistive robot
- Socially interactive robot
- Care robot
- Household robot
- Pleasure robot
- Sex robot
- Anthropomorphic robot
- Autonomous robot
- Therapy robot
- Entertainment robot
- Robotics

Generative AI

- Generative AI
- Generative artificial intelligence
- Artificial intelligence
- AI
- Large Language Model
- LLM
- Foundation Model
- Deep Neural Network
- Machine Learning
- ChatGPT
- OpenAI
- YouChat
- Stable Diffusion
- DALL-E
- Runway
- Midjourney
- MusicLM
- VALL-E
- ElevenLabs
- Codex

- AlphaCode
- GitHub Copilot
- Emotion recognition
- Speech recognition
- Gesture recognition
- Facial expression analysis

Health care sector

- Health care
- Health care Sector
- Health service
- HCS
- Medical Sector
- Hospital
- Clinic
- Nursing home
- Rehabilitation
- Primary care
- Speciality care
- Mental health
- Public health
- Long-term care facility
- Physician
- Nursing
- Allied health professions
- Medical practitioner
- Care
- Medical device
- Health informatics
- Patient
- Person in need of care
- Invalid
- Convalescent
- Sick person
- Elderly
- Elderly person
- Elderly care
- Nursing home
- Nursing personnel
- Aged

Stage 3: Study Selection

The PCC (Population, Concept, and Context) Framework was used as a basis for the inclusion criteria. The population is SR with physical bodies; the concept is the implementation of generative AI in SR; and the context is the health care sector or SR intended for the health care sector. The framework underlying this scoping review is presented in Textbox 2,

inclusion and exclusion criteria to be used in this scoping review are highlighted in Textboxes 3 and 4.

The screening process is divided into 2 subsequent steps: an initial title and abstract screening, and a secondary full-text screening. At least 2 reviewers (PL and TS) will conduct the primary title and abstract screening independently, using the eligibility criteria. Then, the secondary full-text screening of all references included in the title and abstract screening will be conducted by at least 2 members of the research team (PL and TS) independently, using the same eligibility criteria. In the secondary screening, disagreements will be resolved by discussion and consensus of 3 members of the research team (PL, TS, and CG). Any restrictions regarding study design, time frame, or language are not intended. A PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram will be used to show a graphic representation of the process of study selection.

Textbox 2. Overview of the Population, Concept, and Context framework of this review.

- Population: social robots (SR) with physical bodies.
- Concept: implementation of generative artificial intelligence in SR.
- Context: in the health care sector or SR intended for the health care sector.

Textbox 3. Overview of inclusion criteria.

- Studies focusing on social robots (SR) with physical bodies are considered.
- Generative artificial intelligence must be implemented in these SR.
- Studies set in the health care sector are considered, or studies focusing on SR intended to be used in the health care sector.
- Studies published since 2010 are considered, as the concept of generative models of artificial intelligence began to be recognized in the 2010s [27].
- No restrictions concerning study design (ie, reviews or case studies are included), time frame, or language

Textbox 4. Overview of exclusion criteria.

- Social robots without physical bodies are excluded (ie, chatbots or artificial intelligence avatars).
- Surgical robots are excluded.
- Studies published before 2010 are not considered.
- Studies focusing on social robots outside of or not intended for the health care sector are not considered.

Stage 4: Data Charting

The variables that are to be extracted are based on recommendations by 2 members of the research team (DF and FB). We extract data describing the specifications of the applied SR and model of the implemented generative AI, the characteristics of this Implementation and HRI, as well as general information regarding for example, but not limited to, studies' populations, reported outcomes, or country of origin. Textbox 5 conceptualizes the items we aim to extract from the included studies.

The authors will create preliminary data charting forms in Microsoft Excel, which will undergo independent pilot testing using a sample of publications (for example 10 articles). After achieving consistent results and obtaining approval from at least 2 researchers of the team (DF, FB), data charting will be conducted by one team member (PL) for all included full-text articles. A total of 2 other team members (CG and TS) will verify the charted data to ensure the inclusion of all relevant information. A draft of a data charting form is attached in (Multimedia Appendix 4). A team member (CD) will provide support for this process.

Textbox 5. Overview of data extraction items.

Items and description

- Author and year: name of first author, year of publication.
- Study type: What type of study was conducted (eg, randomized controlled trial, cohort study, case-control study, qualitative study, etc)?
- Study design: framework, methods, and procedures applied to answer the research question.
- Origin: where the study was conducted.
- Population and sample size: which and how many participants were in the study.
- Aim: purpose of the study.
- Make of social robot (SR): model and developer of SR.
- Shape of SR: traits of the physical body of SR (eg, number of appendices, anthropomorphic or animal-like shape).
- Mobility of SR: ability of SR to move.
- Autonomy of SR: whether the SR is autonomous or controlled remotely.
- Interface of SR: means of communication or interaction with SR (eg, speech, display, touchscreen, gestures, facial expressions, emotion recognition, remote control, haptic, etc).
- Human-robot interaction: specific traits of interaction with SR (eg, duration, tasks, and intention).
- Model of generative artificial intelligence (AI): specific model of implemented generative AI.
- Use of generative AI: what the implemented generative AI is used for.
- Element of health care sector: sub-sector of the health care sector in which SR was applied (eg, inpatient or outpatient sector, nursing home, day care, home care, etc).
- Outcome acceptance: if user acceptance has been reported as a study outcome.
- Acceptance measurement: tools or models used to measure user acceptance.

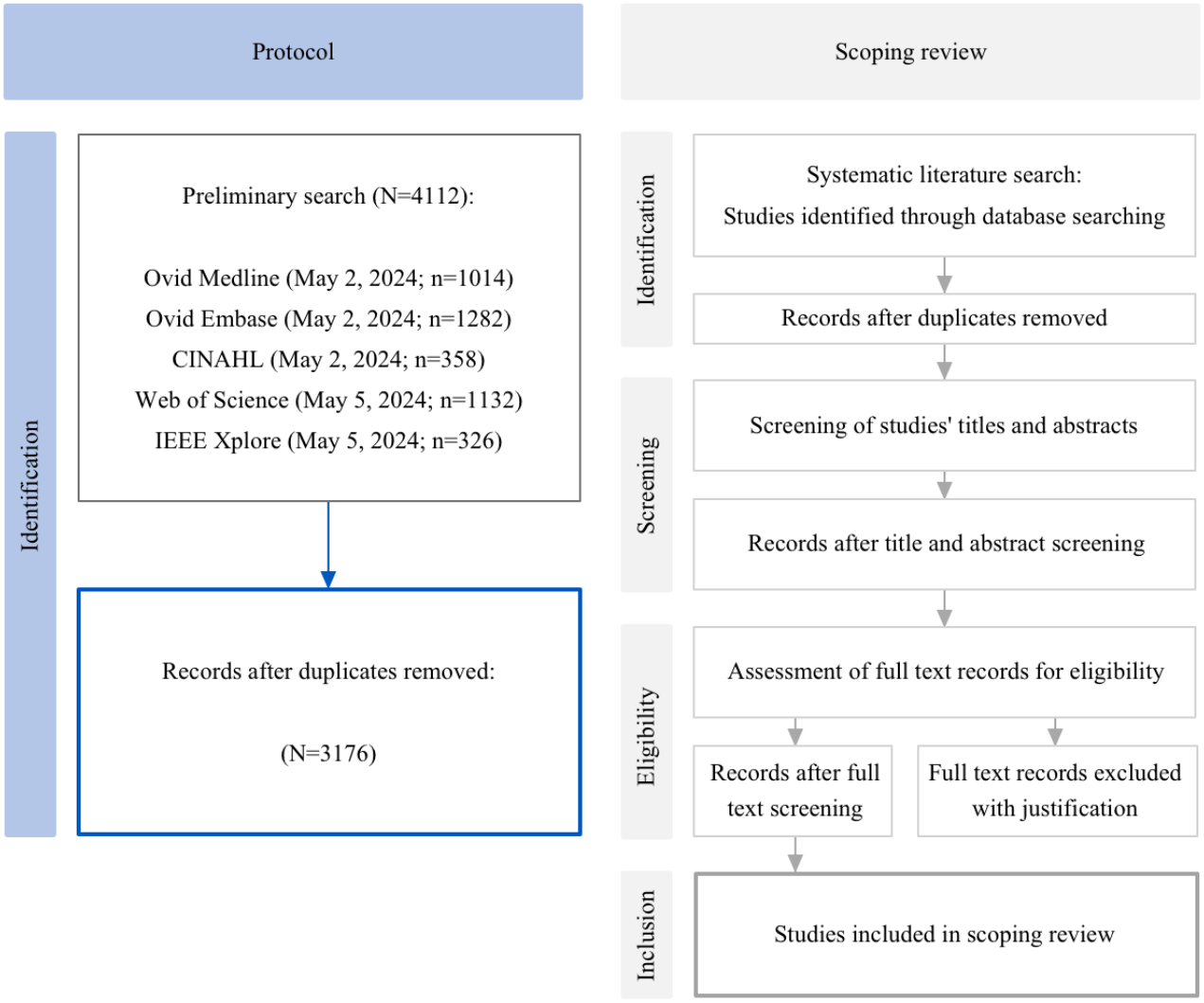
Stage 5: Collating, Summarizing, and Reporting the Results

The studies will be collated, categorized, summarized, and reported based on the data items extracted in the former step, for example, the type of SR, the context of HRI, the use of generative AI, the country of origin, derived acceptance-promoting aspects, etc. To synthesize the results, we will cluster similar publications by classifying the collected data items. The findings of this synthesis will be presented through a series of adequate tables, graphs, and visual representations, as well as corresponding narrative summaries. While we intend to use the main categories of data items from the former steps, we anticipate and remain open to discovering further categories, as well as expanding or modifying existing ones, as this review progresses. A team member (CD) will provide guidance for this stage.

Results

A preliminary literature search was conducted in the second quarter of 2024 to screen relevant existing literature as well as to verify no other scoping reviews of the same focus have been published. This preliminary search of the electronic databases MEDLINE, Embase, CINAHL, Web of Science, and IEEE Xplore was based on the search strategy presented in Stage 2 of this protocol. In this preliminary search, we retrieved a total of 4112 references, of which 3176 remained after deduplication. Figure 1 presents a flow diagram of our preliminary search for this protocol, and of the subsequent scoping review. Following these preliminary results, we deem the literature sufficient to conduct this scoping review. To our knowledge, this is the first scoping review on the implementation of generative AI in Health care SR. We intend to complete the following methodological steps of the scoping review by the second quarter of 2025.

Figure 1. Flow diagram of this protocol's preliminary search and subsequent scoping review.



Discussion

Principal Findings

The authors anticipated to retrieve relevant studies, gaining an overview of scientific literature to decide if it is feasible to conduct a scoping review on this topic. We anticipated the results to be sufficient in number, since generative AI and SR are emerging technologies of high relevance. The preliminary search provided 3176 results after deduplication. Based on these preliminary results, we anticipate that there is sufficient literature to conduct this scoping review. To our knowledge, no other reviews of the same scope have been published.

Limitations

Based on the methodology of this protocol, some limitations can be derived. The authors aim to synthesize results from publications that are expected to have widely heterogeneous populations, origins, outcomes, and overall methodologies. For example, different age groups or cultural backgrounds of participants limit our ability to generalize the findings of this review. In general, scoping reviews tend to be inherently limited by focusing on breadth rather than depth [131]. Also, the selection of databases, search terms, inclusion criteria, and studies based on the research team's experience might pose a source of possible bias. To reduce overall bias, we adopted a system of dual reviews, discussing conflicting results with senior researchers of the team, and thoroughly documenting the process of study selection.

Conclusions

This scoping review on the interconnectedness of 2 emerging technologies will outline the implementation of generative AI in health care SR, and to map out and categorize which models of generative AI and SR are used in these implementations. Based on relevant literature and the expertise of the research team, it is the authors' intention to answer the primary and secondary research questions: (1) Are generative AI models implemented in SR in the health care sector? (2) Which models of generative AI and SR are used for these implementations? (3) What are the settings of these implementations? (4) Has the acceptance of SR been reported as an outcome following these implementations? While there are previous reviews on either AI or SR in general in the health care sector, there is merely a scant number of reviews on AI-equipped social or surgical robots, and there are, to our knowledge, no other reviews of the same scope as our review. Conducting this scoping review supports future research by mapping out further research gaps

and by providing an overview of the state of the connectedness of SR and generative AI, a relatively new technology with vast potential.

Acknowledgments

The authors would like to thank Meghan Forrest, and the Medical Library of Charité – Universitätsmedizin Berlin for providing methodological guidance and support.

We used the generative AI tool ChatGPT by OpenAI as stated in Stage 2 to detect further search terms, which then have been revised by the research team.

Data Availability

The datasets generated or analyzed during this study are available from the corresponding author on reasonable request.

Conflicts of Interest

None declared.

Multimedia Appendix 1
PRISMA-ScR checklist.
[PDF File (Adobe PDF File), 317 KB - resprot_v14i1e63017_app1.pdf]

Multimedia Appendix 2
PRISMA-P checklist.
[DOCX File , 33 KB - resprot_v14i1e63017_app2.docx]

Multimedia Appendix 3
Search queries for MEDLINE, Embase, CINAHL, Web of Science, and IEEE Xplore.
[DOCX File , 22 KB - resprot_v14i1e63017_app3.docx]

Multimedia Appendix 4
Draft of a data charting form.
[XLSX File (Microsoft Excel File), 7 KB - resprot_v14i1e63017_app4.xlsx]

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Abbreviations

AI: artificial intelligence
BERT: Bidirectional Encoder Representations from Transformers
HRI: human-robot interaction
PRESS: Peer Review of Electronic Search Strategies
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRISMA-P: Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols
PRISMA-ScR: Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews
SR: social robot

Edited by A Schwartz; submitted 03.07.24; peer-reviewed by A Khosla, X Cheng; comments to author 29.11.24; revised version received 13.12.24; accepted 24.12.24; published 14.04.25.

Please cite as:
Lempe PN, Guinemer C, Fürstenau D, Dressler C, Balzer F, Schaaf T
Health Care Social Robots in the Age of Generative AI: Protocol for a Scoping Review
JMIR Res Protoc 2025;14:e63017
URL: https://www.researchprotocols.org/2025/1/e63017
doi:10.2196/63017
PMID:

Protocol

Remote Lifestyle Intervention to Reduce Postpartum Weight Retention: Protocol for a Community-Engaged Hybrid Type I Effectiveness-Implementation Randomized Controlled Trial

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Abstract

Background: Maternal obesity is associated with significant racial disparities. People who identify as non-Hispanic Black and Latinx are at the highest risk related adverse short- and long-term health outcomes (eg, hypertension in pregnancy and postpartum weight retention). Remote lifestyle interventions delivered during and after pregnancy hold promise for supporting healthy weight outcomes; however, few are tested in groups of people who self-identify as non-Hispanic Black and Latinx or address the neighborhood-level and psychosocial factors driving maternal health disparities. Implementing remote lifestyle interventions within community-based programs that serve birthing people may optimize trust and engagement, promote scalability and sustainability, and have the broadest public health impact.

Objective: The goal of this trial is to test the effectiveness of a culturally adapted remote lifestyle intervention (Healthy for Two–Home Visiting) implemented within home visiting compared to usual home visiting services on postpartum weight retention among pregnant or postpartum individuals, in particular those who identify as non-Hispanic Black and Latinx. Facilitators and barriers to implementation of the intervention within home visiting will be examined.

Methods: We describe the rationale and protocol for this hybrid type I effectiveness-implementation randomized controlled trial. In this paper, we highlight the community-engaged approach and trial design features that enable the implementation of the intervention within home visiting and demonstrate its applicability to the target population. Participants will be 360 pregnant individuals with overweight or obesity enrolled between 20 and 33 weeks of gestation and randomized 1:1 to Healthy for Two–Home Visiting or usual home visiting services. The primary outcome is weight retention at 6 months post partum, calculated as 6-month postpartum weight minus earliest pregnancy weight (≤18 wk of gestation). The measures of implementation include intervention feasibility, acceptability, reach, adoption, and fidelity. Throughout the paper, we highlight the community input used to improve intervention effectiveness and study implementation and as a strategy to promote maternal health equity.

Results: This study was funded in June 2021, and recruitment began in April 2023. As of November 2024, we enrolled 90 participants. Data collection to assess the intervention's effectiveness is expected to end in June 2026. Implementation evaluation is expected to conclude in December 2026.

Conclusions: This hybrid type I effectiveness-implementation randomized controlled trial integrates a culturally adapted remote lifestyle intervention into early home visiting services to examine its effectiveness on postpartum weight retention compared to usual home visiting. We anticipate that the study results will enable an understanding of the drivers of successful implementation

within a community-based setting to maximize the future sustainability and dissemination of a strategy for reducing long-term obesity and other maternal health disparities.

Trial Registration: Clinicaltrials.gov NCT05619705; https://clinicaltrials.gov/study/NCT05619705

International Registered Report Identifier (IRRID): DERR1-10.2196/62847

(JMIR Res Protoc 2025;14:e62847) doi:10.2196/62847

KEYWORDS

pregnancy; obesity; postpartum weight retention; remote lifestyle intervention; home visiting; mobile health; mHealth app; community-engaged research; implementation science; health disparities; maternal health

Introduction

Background

Maternal obesity is a persistent public health concern, with widening racial and ethnic inequities [1-3]. In the United States, 57% of women who self-identify as non-Hispanic Black and 47% of women who self-identify as Latinx, Hispanic, or of Spanish origin (hereinafter referred to as Latinx) have obese status compared to 38% of people who identify as non-Hispanic White [4]. Nearly 50% of pregnant people who identify as non-Hispanic Black or Latinx exceed the recommended guidelines for gestational weight gain (GWG), contributing to adverse maternal and infant health outcomes (eg, hypertension in pregnancy, preterm birth, and maternal mortality) [5-8], as well as an estimated economic impact of up to US $32 billion from conception through the offspring's first 5 years of life [9]. It is imperative to focus public health prevention efforts on non-Hispanic Black and Latinx pregnant individuals who are most susceptible to worsening obesity (ie, postpartum weight retention [PPWR]) [10-13] and other long-term health problems, including cardiovascular disease [14-17]. Pregnancy offers an opportunity to initiate healthy behaviors that limit GWG and its associated health risks because individuals are motivated to have a healthy baby [18]. This ideal window for health promotion extends to the period after birth when it is critical to sustain healthy changes and improve care transitions, especially among individuals with known barriers to health care access and quality [19]. These individuals have increased exposure to negative social determinants of health (eg, environmental, financial, cultural, and linguistic barriers; racism; limited health literacy; and inadequate insurance coverage), which impacts postpartum visit attendance [20,21] and further exacerbates health risk [22-24].

Counseling and lifestyle interventions during and after pregnancy are a recommended and well-established strategy for limiting GWG [25-28] and reducing PPWR [29-32], and their implementation is being tested in real-world settings; for example, our team is testing a remote health coaching intervention to limit GWG integrated into prenatal care clinics [33,34]. However, there are several evidence gaps. First, few interventions have been tested in racial and ethnic minority groups [32,35], with especially low representation of Latinx individuals [36]. Second, few interventions have been implemented and tested in community-based settings where pregnant and postpartum individuals considered high risk access safety net services. Finally, interventions that address health-constraining social factors that contribute to disparities in maternal health outcomes are limited [31,37,38].

Importantly, implementing effective remote lifestyle interventions within community-based programs that pregnant individuals access and trust may optimize their benefits, promote scalability and sustainability, and have the broadest public health impact. Home visiting is an evidence-based public health strategy targeting pregnant individuals considered high risk and families with children aged up to 5 years. Home visitors provide health education, promote positive parenting and early learning, and link families with needed community resources and social support [39]. Early home visiting has been shown to prevent child abuse and neglect, improve maternal and child health, enhance family socioeconomic status, and promote child development and school readiness [40]. Early home visiting is an ideal setting for delivering lifestyle interventions for pregnant and postpartum individuals because home visitors are uniquely positioned to address social and environmental factors impacting health behavior (eg, neighborhood food availability and walkability) [39]. A recent randomized trial testing a lifestyle intervention embedded in early home visiting services showed lower GWG and PPWR up to 12 months, greater achievement of 5% weight loss, smaller waist circumference, and reduced sugar intake at 12 and 24 months [41], as well as greater success in reducing access to sugar-sweetened beverages in the home up to 24 months [41,42].

Objectives

The goals of this paper are to (1) describe the design of this hybrid type I effectiveness-implementation randomized controlled trial testing the effectiveness of the Healthy for Two–Home Visiting (H42-HV) remote lifestyle intervention integrated into home visiting compared to usual home visiting services on PPWR among pregnant and postpartum individuals; (2) highlight the design features of this trial that enable its implementation within home visiting and the applicability of the intervention to the target population, in particular those who identify as Latinx and non-Hispanic Black; and (3) highlight our application of a community-engaged approach to the conceptualization and design of the study to improve intervention effectiveness and study implementation and as a strategy to promote maternal health equity.

Methods

Study Design, Aims, and Hypothesis

We designed this hybrid type I effectiveness-implementation randomized controlled trial to test the effect of the H42-HV lifestyle intervention integrated into home visiting from mid- to late pregnancy (20-33 wk) through 6 months post partum, compared to usual home visiting services, among pregnant and postpartum individuals with overweight or obesity. The primary outcome is PPWR calculated as 6-month postpartum weight minus prepregnancy (≤18 wk of gestation) weight. Additional measures of effectiveness include GWG and maternal health behaviors, wellness, and health care use. Our main hypothesis is that participants in the H42-HV arm will have lower PPWR than those in the usual home visiting services arm.

Hybrid type I effectiveness-implementation trials assess the primary outcome of clinical effectiveness and evaluate implementation strategies of the intervention as secondary outcomes to better understand facilitators and barriers to real-world dissemination. This hybrid approach could efficiently and in a timely fashion inform the pathways from translation of evidence into practice upon establishing the effectiveness of the intervention, guide future sustainability efforts, and facilitate greater subsequent public health impact [43,44]. To this end, the study will also examine home visiting organizational factors that could impact the implementation of the intervention. We will use the practical, robust implementation and sustainability model (PRISM) framework [45] and domains from the Consolidated Framework for Implementation Research (CFIR) [46] to assess intervention feasibility, acceptability, reach, adoption, and fidelity.

The protocol has been registered with ClinicalTrials.gov (NCT05619705).

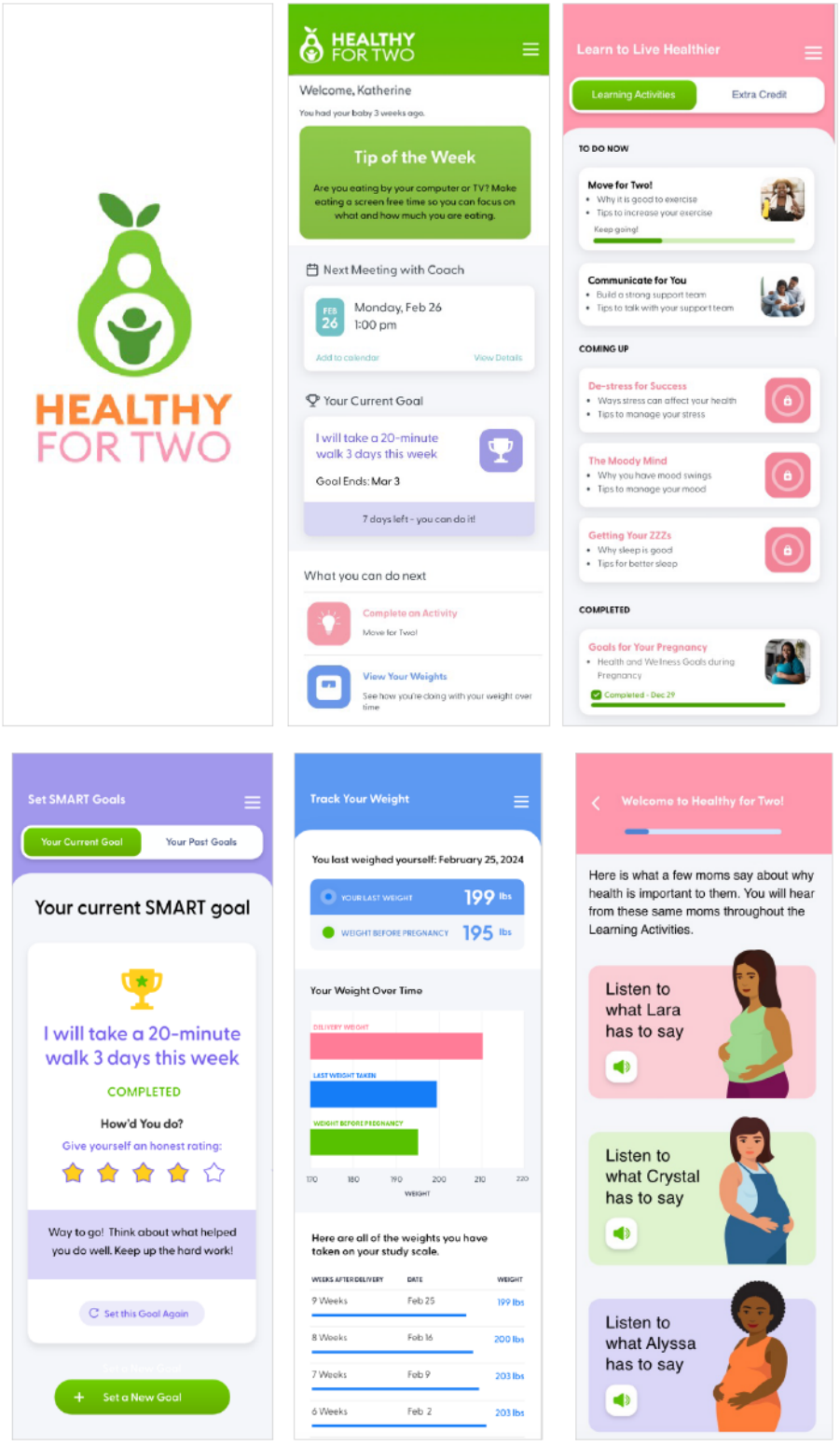
Application of a Community-Engaged Approach

We used a community-engaged research approach to inform the conceptualization and design of the study, including the adaptation of the H42-HV intervention and its integration into early home visiting services. On the basis of the continuum of community engagement in research [47], our level of engagement is best characterized as community participation because the community was actively engaged with a defined role in all stages of the research process. Prior studies clearly demonstrate the importance of early and sustained stakeholder involvement to develop and implement remote health interventions for underserved populations [48-50]. The study principal investigators (WLB and KMB) engaged home visiting stakeholders while developing the proposal and, once funded, used a variety of strategies to establish and sustain 2-way engagement, communication, and information sharing. All aspects of the study were enhanced by feedback from a diverse group of stakeholders who serve individuals identifying as Latinx or non-Hispanic Black, including regional and state leaders in home visiting and participating home visiting program managers and home visitors. Stakeholders also included current or recently pregnant individuals who identify as Latinx or non-Hispanic Black and participate in home visiting services.

During the conceptualization phase, we met with state and program leaders to gather information about the relevance of the intervention and its alignment with state and program public health priorities. We also explored the feasibility and acceptability of implementing the intervention within the home visiting setting. In the planning phase of the study, we established a translation and cultural adaptation team of primarily native Spanish-speaking maternal and child health professionals (ie, dietitian, midwife, and nurse) and health professional students (ie, those studying nursing and medicine) to translate and adapt the H42-HV intervention for Spanish-speaking individuals (the adapted version is called Sanos los Dos).

Once funded, we established a coordinating council with home visitors, leaders from participating programs, and Spanish- and English-speaking community members. Regular meetings with the coordinating council informed all aspects of the study protocol as well as implementation measures, recruitment processes, intervention adaptation, and safety protocols. We asked for specific feedback about the referral process, recruitment materials (flyers and videos), intervention approach and messaging, cultural adaptability, and community resource needs through semistructured one-on-one interviews (6 with home visiting program leaders and 7 with coordinating council members). We performed end-user testing of the H42 mobile health (mHealth) app (Figure 1). We conducted 6 interviews with parents and 2 with home visitors, applying a process known to impact the usability and engagement of culturally adapted digital health tools [49,51].

Figure 1. Healthy for Two mobile health app.



Overall, the feedback highlighted facilitators and barriers to the integration of the H42-HV intervention into home visiting programs and identified strategies for recruitment, adaptations to meet the language and cultural needs of individuals who identify as Latinx and non-Hispanic Black, and effective coordination between the home visitor and health coach. We describe how we addressed feedback from the coordinating council and the additional stakeholders in each of the following subsections.

Home Visiting Programs and Setting

In the formative phase of the trial, we engaged with 7 home visiting programs from across 5 counties in Maryland, United States, that serve predominantly pregnant and postpartum individuals who identify as Latinx or non-Hispanic Black, speak English and Spanish, and have low incomes and literacy levels. Once we launched recruitment, we invited additional early home visiting programs to refer participants to be screened and enrolled in the study. We did not limit ourselves to a particular

model of home visiting and included evidence-based and non–evidence-based models [39]; for example, the partnering home visiting models include but are not limited to Healthy Families America, Healthy Start, Nurse Family Partnership, and Babies Born Healthy. Depending on the model, home visitors are either nurses or paraprofessionals. Participating home visiting models enroll families in early pregnancy and follow them 6 months to 5 years post partum, but the frequency and intensity of home visits vary by model.

Participant Eligibility

As this is an effectiveness trial, we apply the broadest eligibility criteria to enhance generalizability [43,44,52]: age ≥18 years, singleton pregnancy between 20 and 33 weeks of gestation, and planning to enroll in home visiting services at 1 of the study's participating sites. We are focusing this study on individuals who are overweight or obese (BMI ≥25 kg/m^2) before pregnancy as they are at the highest risk for future cardiometabolic disease [53], and we are excluding conditions that may impact an individual's ability to medically or physically participate in the intervention if randomized to that arm (eg, advised not to exercise by provider or diagnosed with type 1 diabetes). Textbox 1 presents additional eligibility criteria.

Textbox 1. Eligibility criteria.

Inclusion criteria

- Age ≥18 y
- 20-33 wk of gestation
- Prepregnancy BMI ≥25 kg/m^2 (calculated based on self-reported prepregnancy height and weight)
- Able to provide informed consent
- English or Spanish speaking
- Intention to enroll in early home visiting services at a participating site
- Ability to complete telephone-assisted screening and electronic consent

Exclusion criteria

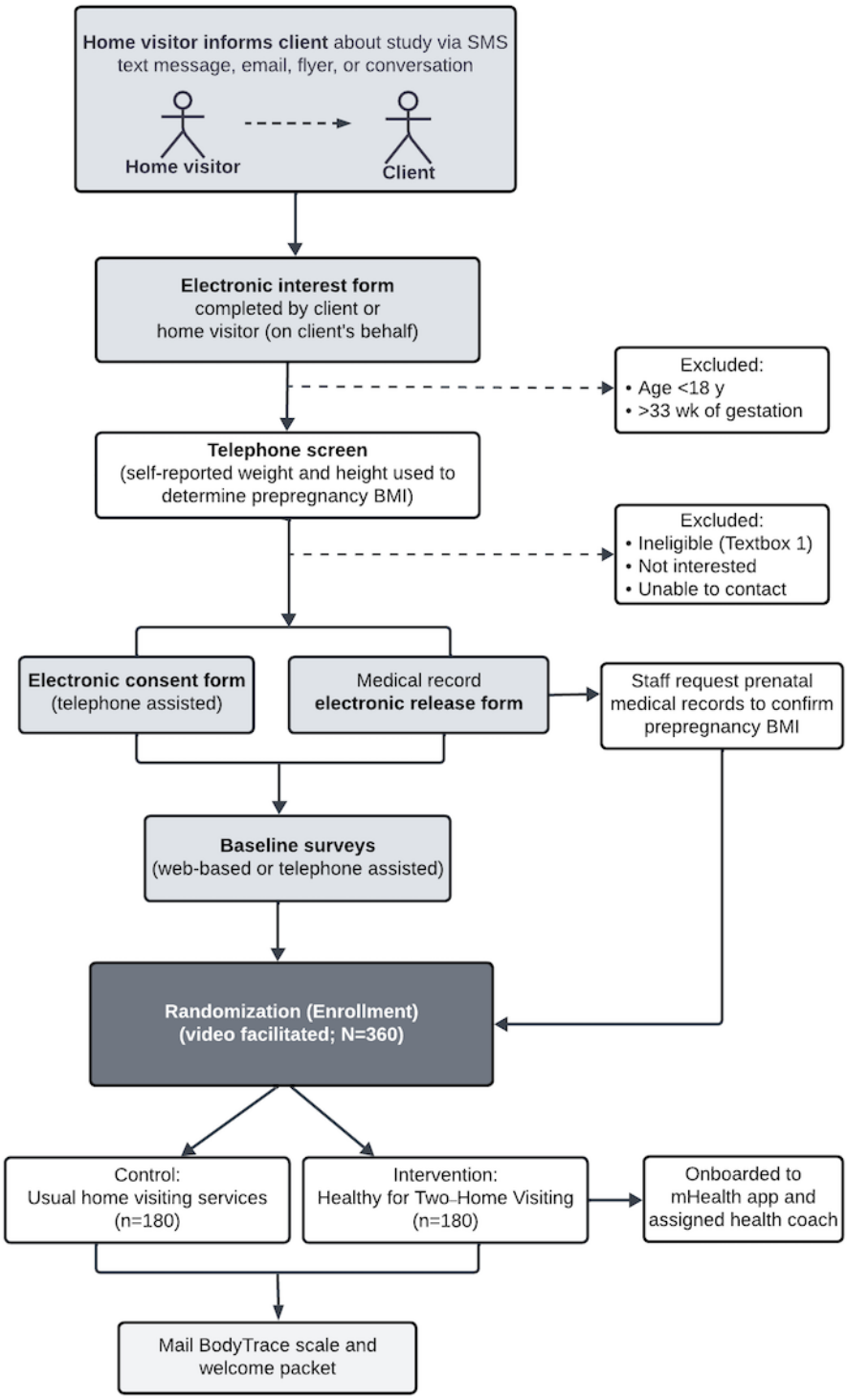
- Diagnosed with type 1 diabetes
- Pregnant with multiple fetuses
- Advised not to engage in exercise by medical provider
- Not cleared by the study's clinicians or home visiting program staff
- Planning to relocate outside of Maryland in the next year
- Active substance abuse (except marijuana)
- Psychiatric or substance use–related hospitalization in the past year
- Active eating disorder

Evidence shows that starting an intervention early in pregnancy has the greatest impact on pregnancy outcomes and GWG [54,55]. However, many home visiting programs rely on several steps to occur before services can begin, that is, entry in prenatal care, referrals from clinic, screening by outside agency for eligibility, and outreach by home visiting program. In response to input from participating home visiting programs, we selected a broad enrollment window during pregnancy (20-33 wk of gestation) and will continue intervention delivery through 6 months post partum. Given state and program leader feedback about the potential for home visiting enrollment in late pregnancy, we selected the primary outcome as return to prepregnancy weight or below because PPWR is a risk factor for future obesity.

Screening and Recruitment

With feedback from home visiting program partners (refer to the Application of a Community-Engaged Approach subsection), we designed the role of home visitors to be low touch and aligned with the procedures they already use in their program and visits. Figure 2 outlines the study design and recruitment procedures. Home visiting staff inform potentially eligible clients about the study via conversation, email, or SMS text message using a "toolkit" of different materials available in English and Spanish to accommodate program, staff, and client needs and preferences (eg, suggested dialogue, paper flyers or postcards, and an informational video lasting 2-3 min). All recruitment materials include a link and QR code to an "electronic interest form" (to be completed by clients or home visitors on their behalf) that requests basic eligibility information to preemptively exclude clients aged <18 years and >33 weeks of gestation, as well as additional details to facilitate the next steps of the screening process.

Figure 2. Study design and recruitment procedures. mHealth: mobile health.



Upon receiving a completed "electronic interest form," research staff reach out to the potential participant via telephone to further assess interest and screen for eligibility. After confirming eligibility, research staff complete a telephone-assisted electronic consent process that includes obtaining a signed authorization for the release of medical records, including prenatal and infant records as well as claims data. After consent is obtained, study staff immediately request prenatal clinic records for height and prepregnancy weight measurements to confirm BMI criteria, and participants complete web-based or telephone-assisted baseline data collection surveys. Once these steps are complete, consented participants meet virtually with staff for a video-facilitated randomization (enrollment) visit. At randomization, participants receive instructions for taking home weight measurements using a study-provided smart scale shipped to their home; intervention participants are oriented to the H42 mHealth app and provided the name of their health coach. In response to home visitors' interest in the result of each client they refer (ie, ineligible, unable to contact, or enrolled), we provide them with the option to "opt in" to live email updates on referral outcomes.

Randomization and Blinding

A total of 360 participants will be randomized 1:1 to the H42-HV arm or comparison arm. Randomization is stratified by home visiting program region+primary language served (ie, central Spanish or English, capital Spanish or English, eastern Spanish or English, southern Spanish or English, or western Spanish or English) and BMI (≥30 kg/m^2 vs 25-29.9 kg/m^2) and within each stratum using randomly varying block sizes of 2, 4, and 6. The randomization scheme was generated using Stata (version 17.0; StataCorp LLC) and imported into REDCap (Research Electronic Data Capture; version 14.0.31; Vanderbilt University) [56,57]. Assignment remains masked until a participant is randomized. Due to the nature of this lifestyle intervention, participants, home visitors, the intervention team, and the safety monitor will not be blinded to randomization assignment after randomization. Until the end of the trial, all nonintervention study staff and coinvestigators, including the principal investigators and data collectors, will remain blinded, with the exception of the lead biostatistician.

H42-HV: Intervention Design and Approach

Overview

The intervention was adapted from our previously designed and pilot-tested remotely delivered lifestyle intervention (called Healthy for Two/Healthy for You) to limit GWG and PPWR in a racially diverse population with low literacy [33,34]. The person-centered intervention uses a standard behavioral approach to weight management [58], teaching strategies aligned with social cognitive theory, such as self-monitoring, goal setting, and problem-solving [59]. The overarching goal of the H42-HV intervention is for participants to have lower PPWR 6 months after delivery.

Intervention Components and Adaptations

Overview

We used an iterative approach for translating and adapting intervention content and technologies using feedback from our key stakeholders (refer to the Application of a Community-Engaged Approach subsection). In addition to shifting intervention timing and focus to the postpartum period, we reframed messaging about program goals to achieving "overall health and wellness" versus a "healthy weight." Consistent early feedback from home visitors suggested that strong internalized weight biases among their clients may impact intervention engagement and acceptability. Weight stigma is pervasive in health care settings, has detrimental impacts on overall health and the use of health care services [60,61], and has more recently been regarded as a social determinant of poor birth outcomes [62]. Textbox 2 summarizes the adapted components of H42-HV.

Textbox 2. Healthy for Two–Home Visiting intervention components.

Person-centered health coaching (English or Spanish)

- 10 total telephone or video meetings (4 pregnancy, 6 postpartum) lasting approximately 30 min using a person-centered approach, plus 2 as-needed "boosters"
- Starts between 20 and 33 wk of gestation and continues through 6 mo post partum
- Coaches have access to a mobile health (mHealth) coaching interface to view participant app engagement and health progress (refer to the H42 mHealth App subsection)

Self-weighing via a home smart scale

- Participants self-weigh at least once weekly on a cellular-enabled home smart scale
- Paper and electronic "wellness journal" available to self-monitor diet and exercise

H42 mHealth app (hosts web-based learning and goal-setting activities, smart scale weight displays, and 2-way participant-coach messaging; promotes engagement via dynamic in-app messages and email reminders)

- Learning activities: 10 educational modules focused on diet, exercise, social support, stress, mood, and sleep. Learning methods include the following: simple, brief education on core topic; audio quotes from 3 ethnically diverse mothers describing personal challenges or successes and behavioral strategies that help them meet health and wellness goals; 5 simple multiple-choice quiz questions to reinforce key concepts; open-ended free-text questions, ranging from 4-9 total per learning activity, to promote goal-oriented thinking, problem-solving, and identification of barriers and successes.
- Add-on learning: videos and external links covering topics such as breastfeeding, gestational diabetes, and smoking cessation
- Goal setting activity: tool that aids participants in setting their own specific, measurable, achievable, relevant, and time-bound (SMART) goals and rating their progress
- Weight display: real-time view of home smart scale weights with feedback to support goal of returning to prepregnancy weight
- Coach-participant messaging: synchronous communication stream primarily used for scheduling and delivery of individualized intervention content (ie, PDF files, images, etc)
- Home page: personalized summary to facilitate intervention adherence (ie, date and time of upcoming coach meetings, most recent coach message, reminders to weigh) and engagement (ie, seasonal health or wellness "Tip of the week")
- Coach and coach manager interface: coach interface with dynamic access to participant weight data and engagement with app (ie, SMART goals, free-text entries); coach manager interface with real-time access to participant and group-level data for individualized case management and ongoing support and management of all coaches

Person-Centered Health Coaching

The cornerstone of the H42-HV intervention is *health coaching* using an evidence-based person-centered approach [63] aimed at enhancing participants' intrinsic drive to make health-related behavior changes (diet, exercise, and stress management). Participants complete up to 12 coach meetings (10 planned plus 2 as-needed "boosters") via video or telephone when they join the study (between 20 and 33 weeks of gestation) through 6 months post partum. Coaches aim to complete 4 meetings during pregnancy and 6 meetings post partum, with flexible cadence to account for varying enrollment dates. The frequency of coach meetings is consistent with similar interventions showing an effect on PPWR [29,33,64] and based on evidence that moderate- (ie, ≥6 contacts) to high-intensity (ie, ≥12 contacts) lifestyle interventions have the greatest effect on GWG [26,65]. Coaches receive enhanced training on weight bias and cultural sensitivity as well as supporting behavioral changes in the context of common social and environmental barriers such as food insecurity and neighborhood safety.

Health Behavior Tracking (Self-Weighing via Home Smart Scale)

Participants are instructed to weigh themselves weekly on a *cellular-enabled home smart scale* (Body Trace; BodyTrace, Inc) [66] that transmits live data to the H42 mHealth app and coach interface described in detail in the next subsection. Coaches emphasize that self-weighing is a core tool to assess progress, similar to monitoring one's exercise minutes and the type and amount of food and drinks consumed. Participants have the option to track and share diet and exercise behaviors with their coach as well as daily ratings of their mood and sleep using a simple paper "wellness journal" or "electronic wellness journal" delivered daily or weekly via SMS text message or email.

H42 mHealth App

Our team designed the *web-based mHealth app* (Figure 1) *and coach interface* based on intervention content tested in past trials [33,34]. The H42 mHealth app is accessible via mobile phone and delivers education tailored to a <6th-grade reading level [67-69] via interactive learning activities that provide guidance on making healthy lifestyle changes in the context of common environmental barriers (eg, eating healthy on a budget and low-cost ways to manage stress). Supplemental health topics (eg, breastfeeding, infant health, and depression) are also available because our formative research and work by others suggested that pregnant and postpartum people across races are more likely to use digital health tools that offer credible, perinatal-specific health information beyond nutrition and exercise [70,71]. The mHealth app contains a goal-setting activity, facilitates 2-way participant-coach communication, displays smart scale data, and promotes adherence and engagement via dynamic in-app messages and email reminders (Figure 1). End-user testing of the English and Spanish versions of the app completed in preparation for the trial (the testing involved 3 English-speaking and 3-Spanish speaking parents and 2 bilingual home visitors) generated reactions to app design and images, usability, interactive functionality, cultural appropriateness, and effectiveness. Consistent feedback gathered (and addressed) included preferences for a brighter color palette, more images, less text and fewer numbers, more traditional Latinx food options, larger-sized body types, simpler graphics (ie, bar graph vs line graph), and a stronger representation of family (ie, households with multiple children). If cost is a barrier, the study subsidizes web-based access (eg, by providing data cards).

The *coach/coach manager interface* provides dynamic access to participant smart scale weights and app activity (ie, goals and free-text responses) as well as food and exercise data for those who choose to track these behaviors using the "electronic wellness journal" that syncs data to the interface. The interface additionally serves as a documentation and scheduling tool. A coach manager interface provides individual and aggregate summary data to facilitate regular participant oversight, ongoing support, and the management of coaches and intervention adherence monitoring throughout the study.

Usual Home Visiting Services Comparison

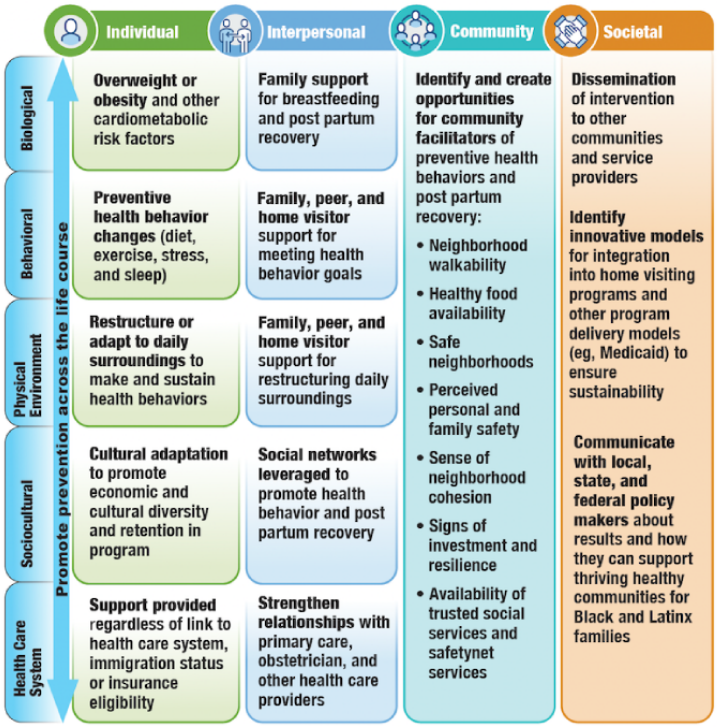
Participants randomly assigned to the comparison arm receive usual home visiting services per agency guidelines and requirements. In addition, we provide a brief, publicly available educational video on urgent maternal warning signs [72,73]. Private, staff-monitored Facebook groups are offered to disseminate information on healthy pregnancy and allow for community building and retention for both groups (usual home visiting services and H42-HV). Both groups are also provided county-specific resource lists with information on green spaces, food banks, mental health resources, medical centers, and intimate partner violence support. This resource list is available as an electronic map (using Google Maps) and a paper version.

National Institute on Minority Health and Health Disparities Research Framework Adaptation for the H42-HV Intervention

We adapted the National Institute on Minority Health and Health Disparities research framework [74] to depict the multilevel influences (individual, interpersonal, community, and societal levels) that embedding the remote intervention into early home visiting services has on health outcomes and disparities, including the social determinants of health (Figure 3). The H42-HV intervention impacts *individual-level* factors by promoting a healthy lifestyle in women with cardiovascular risk factors, regardless of insurance coverage or health literacy. While coaches provide education and strategies for making healthy changes (ie, adding fruits and vegetables to participants' diet), home visitors address context-specific barriers (eg, healthy food availability) and leverage context-specific assets (eg, local food banks) to increase success at achieving behavioral goals. At the *interpersonal level*, home visitors provide social support and connect participants with social support networks that promote a healthy lifestyle and provide tools to navigate family or peer norms, while health coaches teach participants effective communication skills to strengthen the support they receive from their existing network (eg, home visitors, health care providers, family members, and peers) and tailor this support toward making healthy changes. The H42-HV intervention addresses *community-* and *societal-level* influences by connecting participants with local resources and promoting

parent and infant use of health care services (eg, postpartum care and primary care). Ultimately, the study is designed to promote a holistic approach to reducing cardiometabolic health inequities among birthing people.

Figure 3. National Institute on Minority Health and Health Disparities research framework adaptation for the Healthy for Two–Home Visiting intervention.



Data Collection and Data Sources

Effectiveness Measures and Methods

Tables 1 and 2 summarize the methods of measurement and timing aimed at improving access and retention as well as minimizing participant burden (also refer to Figure 4). Early conversations with home visiting program leaders indicated that home visitors would not have time to collect study data; therefore, data collection procedures were designed to not involve home visitors. Data are collected through 4 methods: a cellular-enabled home smart scale, medical record review, web-based surveys via REDCap, and Medicaid claims data.

Table 1. Schedule of intervention effectiveness measures: electronic medical record review, smart scale, and Medicaid claims.

Measure	Pregnancy		Post partum			
	Baseline[a]	37 wk	Delivery[b]	2 mo	4 mo	6 mo
Maternal weight and height	Electronic medical record review	Smart scale	—[c]	Smart scale	Smart scale	Smart scale
Labor and delivery discharge summary from outside hospitals	—	—	Electronic medical record review	—	—	—
Infant weight and length from pediatric practices	—	—	Electronic medical record review	—	—	—
Maternal and infant health care use				Medicaid claims	Medicaid claims	Medicaid claims
Home visiting use and safety net services				Medicaid claims	Medicaid claims	Medicaid claims

[a]Baseline window: 20 to 33 wk of gestation.

[b]Delivery through 2 wk post partum.

[c]Not applicable.

Table 2. Schedule of intervention effectiveness measures: web-based surveys.

Measure	Pregnancy		Post partum		
	Baseline[a]	Delivery[b]	2 mo	4 mo	6 mo
Web-based surveys					
Demographics and medical history [75-78]	✓	✓[c]			
Dietary behaviors [79]	✓				✓
Physical activity [80]	✓		✓		✓
Depression and anxiety [81]	✓	✓	✓	✓	✓
Brief Perceived Stress Scale [82]	✓		✓	✓	✓
Brief Pittsburgh Sleep Quality Index [83]	✓		✓	✓	✓
Functional Social Support Questionnaire [84]	✓		✓		✓
Social determinants of health [76,78]	✓				
Everyday discrimination [85]	✓				
Tobacco, marijuana, and alcohol (PRAMS[d]) [86]	✓				✓
Pregnancy intention (PRAMS) [86]	✓				
Usual source of (maternal) care (PRAMS) [86]	✓				✓
Experiences with care (PRAMS) [86]		✓			
Infant care (PRAMS) [86]		✓	✓		
Postpartum visit attendance and support (PRAMS) [86]				✓	
Postpartum contraception (PRAMS) [86]				✓	✓
Breastfeeding intention and practices (PRAMS) [86,87]			✓	✓	✓
Use of community and safety net services: Supplemental Nutrition Program for Women, Infants, and Children (PRAMS) [86]			✓	✓	✓
Engagement with home visiting			✓	✓	✓
Safety survey		✓	✓	✓	✓

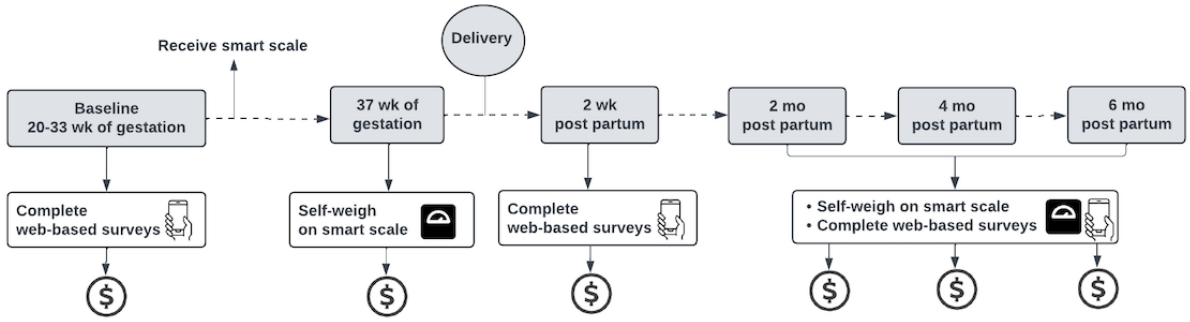
[a]Baseline window: 20 to 33 wk of gestation.

[b]Delivery through 2 wk post partum.

[c]Infant race and ethnicity collected at delivery.

[d]PRAMS: Pregnancy Risk Assessment and Monitoring System.

Figure 4. Data collection and retention.



Assessment and Verification of Maternal Weight Using a Smart Scale

Smart scale weights are collected at 4 time points: 37 weeks of gestation; and 2, 4, and 6 months post partum (Table 1). Participants are instructed to weigh themselves in light indoor clothes without shoes on their home smart scale (BodyTrace [66]). The smart scale transmits data to the study team via cellular connectivity (no Wi-Fi or cellular plan is required), which is ideal for rural client communities with intermittent Wi-Fi or those with reduced access to cellular data or inconsistent data plans. The BodyTrace smart scale was selected

because it demonstrates good concordance with in-person assessments [88,89] and has been used in several large weight management trials [90,91], including those with racially diverse populations with low incomes and literacy levels [92-94]. The scale is mailed to participants' homes after randomization, and brief SMS text reminders to weigh are sent at each study assessment time point (ie, "Time to step on your scale"). Staff monitor weight data transmitted to the study's REDCap server in real time and reach out to participants with no weight by the middle of each designated assessment "window," which ranges from –10 days to +10 days at designated study outcome assessment time points. Staff also monitor battery power and the strength of the cellular connection to assist participants with related issues, as needed. To mitigate the disruption that environmental factors (eg, potential for multiple users or scale displacement) can have on data quality, we programmed a dynamic weight cleaning procedure that requires participants to confirm questionable weights by responding to a 1-question survey sent via SMS text message. For intervention participants, this cleaning procedure ensures real-time accuracy of the weight graphs in the H42 mHealth app, as well as automated reminders, including in-app messages that prompt participants to weigh if a confirmed weight is not available after 7 days. After 14 days, coaches are notified to conduct personalized outreach to remind participants to weigh themselves.

Obtaining Medical Records and Abstracting Information on Prepregnancy Weight

Participants consent to pre- and postnatal medical record release for themselves and their infant from before pregnancy through 1 year post partum (Table 1). We use a secure electronic fax system (OpenText Fax; Open Text Corporation) to request medical records from prenatal clinics, offices, and hospitals. "Prepregnancy" weight is defined as the earliest measured weight obtained from medical records up to 18 weeks of gestation; when not available, we use self-reported weight. We also abstract height, parity, and comorbid conditions from medical records.

Web-Based Surveys

We used REDCap to build and design web-based surveys using standard instruments selected to minimize participant burden and enable completion at home (Table 2). Collectively, surveys take 10 to 20 minutes to complete, depending on the total number and length of those designated at each time point; staff-led telephone-assisted surveys are available, when preferred.

Demographics and Social Determinants of Health

Maternal and infant demographics and social determinants of health are collected using standard questions from the PhenX toolkit [78], the 2020 US Census Informational Questionnaire [75], and the Accountable Health Communities Health-Related Social Needs screening tool [77]. Additional common data elements, using standard and commonly used measures related to participant characteristics and social determinants of health, were incorporated, as required by the National Institutes of Health–Health Equity and Action Network for data harmonization at the National Institutes of Health Multiple Chronic Diseases Disparities Research Consortium [76]. Experiences with chronic, routine discrimination [95] are assessed using the 9-item Everyday Discrimination measure [85], which demonstrates good reliability (Cronbach α=0.88) and is shown to be a strong and consistent predictor of health and well-being [85].

Maternal Health Behaviors, Attitudes, and Experiences

Dietary intake is assessed as estimates of servings of fruits and vegetables, added sugars, whole grains, fiber, and calcium using the 26-item Dietary Screener Questionnaire [79], which demonstrates agreement with 24-hour dietary recalls [96]. Exercise frequency and intensity are measured using the 7-item International Physical Activity Questionnaire–Short Form, which has acceptable reliability (pooled ρ=0.76) and some agreement with the accelerometer standard (pooled ρ=0.30) in a diverse sample [80].

Mood is assessed using the 10-item Edinburgh Postpartum Depression Scale for postnatal depression, which illustrates moderately high validity (sensitivity=85%, specificity=77%) and split-half reliability (r=0.88) in the original sample of 60 mothers [81]; these results have been confirmed in other validation studies [97]. We measure stress using the 4-item Brief Perceived Stress Scale [98], which is a shortened version of the original 14-item scale [82] and has acceptable psychometric properties [99]. We assess sleep using the 6-item Brief Pittsburgh Sleep Quality Index [83], which shows good internal consistency (Cronbach α=0.79, McDonald ω=0.91) and adequate validity (sensitivity=76%, specificity=77%) in a large population-based sample [83]. Perceived social support is quantified using the 8-item Duke-UNC Functional Social Support Questionnaire [84], which has favorable test-retest reliability (r=0.50-0.85) and is significantly correlated with other social support measures [84].

Several questions from the standard and core measures of the Pregnancy Risk Assessment and Monitoring System (PRAMS) [86] assess pregnancy and breastfeeding intentions and practices, contraception, substance use (tobacco, marijuana, and alcohol), and experiences with or use of health care before and after birth.

Infant Health, Sources of Care, and Feeding Practices

Infant overall health, feeding, and sources of care are assessed using the PRAMS [86] and Infant Feeding Practices Survey [87]. The use of community and safety net programs (ie, Supplemental Nutrition Program for Women, Infants, and Children) is also measured using the PRAMS [86].

Engagement With Home Visiting Services

Engagement with home visiting services and the frequency of contacts with home visitors will be collected at all postpartum time points to assess the "dose" of home visiting during the study.

Intervention Satisfaction

Intervention participants complete a satisfaction survey at the end of the study using an adapted survey tool administered and reported on in previous trials [33,34].

Medicaid Claims Data

We will request Maryland Medicaid claims data for all consented participants with Medicaid to assess maternal and infant health care use outcomes (ie, attendance at prenatal care visits, postpartum visit, primary care visits, infant visits, and receipt of infant vaccines) via a data use agreement with the Maryland Department of Health (Table 2).

Implementation Process Measures and Methods

Overview

Measures to evaluate the implementation are based on the PRISM framework [45] and domains from the CFIR [46]. Table 3 outlines all implementation outcomes and measures.

Table 3. Implementation process measures and methods.

PRISM[a]+CFIR[b] domains	Implementation process measure	Data collection method (before, during, and after the trial)
Organizational perspectives	Home visiting program perceived usability, adaptability, and relative priority of the intervention	Surveys before and after program orientation; focus groups after the trial
Organizational characteristics (inner setting from the CFIR)	Home visiting program culture, management support and cooperation, systems, training, staffing, and incentives	Home visiting leader surveys before the trial
External environment (outer setting from the CFIR)	Home visiting program regulatory environment (policies and incentives); patient needs and resources	Home visiting leader surveys before the trial; county reports; census and county rankings database
Reach	Total number of clients enrolled out of those screened and eligible; total number of clients enrolled out of new pregnant clients enrolled in the home visiting program	Study recruitment and enrollment data; home visiting program leader surveys after the trial
Implementation (engaging, reflecting, and evaluating process from the CFIR)	Engagement of program leaders in implementation process; qualitative feedback on the progress and quality of the implementation	Coordinating council, formative interviews with home visiting program leaders, focus groups, and research team discussion and reflection throughout the trial
Adoption	Proportion of sites across the state that opt to participate in the study; adoption of training and recruitment procedures; level of involvement supporting intervention participants	Home visiting staff focus groups after the trial; review of study recruitment and enrollment data
Fidelity of the intervention (coach and participant)	Coach adherence to meeting guides and patient-centered approach; participant adherence to intervention components and perceived acceptability	Review of audio-recorded coach meetings during the trial; reports from data management systems; participant acceptability survey after completing the study

[a]PRISM: practical, robust implementation and sustainability model.

[b]CFIR: Consolidated Framework for Implementation Research.

Organizational Perspectives

To support state and program leader feedback gathered during the conceptualization phase of the study (refer to the Application of a Community-Engaged Approach subsection), home visitors' perspectives of the intervention were assessed via survey before and after a 1-hour study staff–led orientation (an overview of study goals, design, and referral procedures) that they received before the trial. They rated the importance of, and the need for, resources to address various health-related topics (eg, nutrition and exercise) with their clients before the training and after they rated intervention acceptability, appropriateness, and feasibility [100]. At the end of the study, we will conduct 2 focus groups with home visitors from participating programs to further explore the perceived usability, acceptability, and adoption of the intervention. Interview guides will be developed using the PRISM framework [45] and include questions assessing facilitators and barriers to implementation.

Organizational Characteristics (Inner Setting From the CFIR)

Features of home visiting programs through which the implementation process will proceed and features that may support or impede the programs' ability to successfully implement the intervention (eg, structure, enrollment, staffing, service modality, and curriculum) were assessed before the trial using a survey completed by home visiting program leaders.

External Environment (Outer Setting From the CFIR)

The county-level economic, political, and social contexts within which the home visiting programs reside and which may affect their ability to successfully implement the intervention (eg, social determinants of health, obesity rates, demographics, reimbursements, and health and wellness resources) will be assessed before the trial using a survey completed by home visiting program leaders and publicly available data from county reports, US Census Bureau data [75], and a county rankings database [101].

Study Reach

We will quantify study reach as (1) the total number of clients enrolled in the study out of new pregnant clients enrolled in home visiting during the enrollment period and (2) the total number of clients enrolled in the study out of those screened and eligible for the study.

Implementation (Engaging, Reflecting, and Evaluating)

We will measure implementation through a combined strategy of gathering feedback from home visiting programs about the progress and quality of the implementation and holding regular debriefings with personnel and team about progress and experience.

Adoption of Intervention

We will track the proportion of home visiting sites across the state that opt to participate in the study and assess the level of involvement in study procedures and the intervention via survey and home visitor focus groups after the trial.

Fidelity of the Intervention: Coach and Participant Adherence (During and After the Intervention)

We will examine intervention fidelity and its impact on the primary outcome using common procedures applied in multicomponent remote lifestyle intervention trials [102,103]. Health coach fidelity to a participant-centered approach and standard meeting components (eg, reviewing successes and progress as well as setting goals) will be measured using an iterative quality assurance process of sampling and reviewing audio-recorded coach meetings. We will track participant adherence to each component of the intervention (coach meetings, mHealth app, and smart scale use) and intervention acceptability using an end-of-study survey.

Retention Strategies for Participants

On the basis of our experience with recruiting and retaining pregnant women, we will use several methods to achieve high retention, including rapport building, sending birthday and birth cards, and using email and SMS text message reminders based on each participant's preferred method of contact. Participants will be provided gift cards after each data collection visit: US $10 at enrollment; US $10 at 37 weeks of gestation; US $15 at 2 weeks post partum; and US $20, US $25, and US $30 at 2, 4, and 6 months post partum, respectively (Figure 4). As participants will be engaged in home visiting and consider the program part of their care, we anticipate low risk for loss to follow-up.

Methods for Ongoing Home Visitor and Community Engagement

Home visitor engagement will involve monthly recruitment updates shared with sites and site supervisors, raffle incentives, ongoing training opportunities on topics of interest, and brief one-on-one "check-ins" between a study team member and home visitor "site champion" aimed at quickly mitigating concerns or struggles pertaining to study procedures. Community engagement throughout the trial will involve quarterly newsletters to all stakeholders (ie, coordinating council members and state-level leaders), including home visitor and community member "spotlights" and participant success stories. In addition, each home visiting site will receive an annual financial incentive.

Analytic Approach

Sample Size and Power Estimates

With 360 participants, our objective is to determine the minimum detectable difference (MDD) for the primary outcome of PPWR between the 2 study groups. Our assumptions are as follows: a 2-tailed type I error rate of 0.05, a type II error rate of 0.10, and ≥70% follow-up for the main outcome of PPWR at 6 months. On the basis of the past experience [33] and published literature, we anticipate <30% loss to follow-up for 6-month weight measurements, consequential to various forms of dropout (eg, lost to follow-up). With this dropout rate and the assumption that the dropout is consistent with missing at random, we expect to randomize 360 participants (n=180, 50% per arm) to retain an effective sample size of 252 participants (n=126, 50%/arm) for our primary outcome. SDs for the MDD evaluation were informed by previous studies of similar combined diet-exercise lifestyle interventions to limit weight gain in pregnancy and promote postpartum weight loss [26,41,104,105]. Under these considerations, the resulting MDDs range from 2.3 to 3.6 kg with corresponding SDs for PPWR of between 5.5 and 8.8 kg.

Main Analytic Model for the Primary Outcome of PPWR

Analysis will follow the intention-to-treat principle. The main analysis will assess the between-group difference in PPWR (the difference between earliest pregnancy weight and weight at 6 mo post partum) using a mixed effects model characterized by a mean model relating the outcome to the predictors and a variance-covariance model addressing variance of all available longitudinal weight outcomes and correlation between outcomes measured over time within individual. The predictors in the mean model will include a group indicator (0 for the comparison arm and 1 for H42-HV) as well as 3 binary indicators for 2-, 4-, and 6-month postpartum visits, respectively, with baseline visit as the reference, and the corresponding group-by-visit interaction terms, adjusting for study sites (region and primary language served) and baseline BMI category used for randomization stratification, as fixed effects. The regression coefficient of the group by 6-month postpartum weight interaction term will estimate the intervention effect on the primary outcome, that is, mean difference in PPWR at 6 months between the intervention and control groups. We will use an unstructured variance-covariance model to allow full flexibility on outcome variances and longitudinal correlations for the repeatedly measured weight data. A model-based 2-tailed *t* test will be used to evaluate the intervention effect and derive the associated 95% CI. The Kenward-Roger approximation will be used to calculate the *df* for the *t* test, with $P<.05$ considered statistically significant [106].

Data from all randomized participants will be used in this analysis, with missing data included using a software-specified missing indicator. The main analysis will assume that outcome data are missing at random and use an observed data likelihood approach implemented through the mixed effects regression model, where baseline characteristics associated with the probability of missing outcome data will be further adjusted for in the mean model. Sensitivity analysis through multiple

imputation of missing outcome data under plausible missing-not-at-random scenarios will be conducted to evaluate the robustness of the findings from the main analysis conducted under the missing-at-random assumption.

Secondary Outcomes and Additional Analyses

Secondary outcomes include maternal, infant, and organizational process outcomes. For secondary maternal outcomes, available data from all randomized individuals will be included. Between-group differences in GWG (defined as the difference between the weight at 37 weeks of gestation and prepregnancy weight) and infant weights will be assessed using the same mixed effects modeling approach as described for the primary outcome, with separate models for each outcome. Between-group differences in the binary outcomes of diet, exercise, breastfeeding, and women's wellness measures (depression, sleep, stress, and social support) will be described between the H42-HV and comparison arms using standard cut points for the scales and modeled using logistic regression model–based longitudinal models implemented through a generalized estimating equations approach [107]. The mean models will similarly use the group indicator, visit indicators, and the corresponding group-by-visit interaction terms, adjusting for the variable used to stratify the randomization. Robust variance estimates will be used for statistical inferences to derive 95% CIs for the population-average estimates and corresponding *P* values. Conforming to recommended maternal postpartum care use and well-baby care use over time will separately be modeled using a similar generalized estimating equations approach as described for the longitudinal binary outcomes.

Exploratory Analyses for the Heterogeneity of the Intervention Effect

We will explore for potential moderators of intervention effects by conducting subgroup analyses based on baseline survey data (race, ethnicity, home visiting program characteristics, baseline BMI category [overweight or obese], language spoken at home, low English proficiency, income, and education level) and examining effect modification by adding appropriate interaction terms to the primary mixed effects model. We do not expect the intervention effects to vary across subgroups, and we will interpret carefully any observed heterogeneity, or lack thereof, given the exploratory nature of these analyses.

Safety Surveillance and Monitoring

For active surveillance, a safety medical officer will oversee the postdelivery review of medical records, including labor and delivery notes and infant discharge summaries. We will administer safety surveys after delivery and at 2, 4, and 6 months post partum to enable tracking of all maternal and infant hospitalizations, emergency department visits, and labor and delivery triage evaluations (Table 2). We have developed protocols to alert the team and manage high levels of depressive symptoms or interpersonal violence (Table 2). The Johns Hopkins Institutional Review Board is required to review all serious safety events. In addition, the study has a sponsor-approved data safety and monitoring plan, and oversight from the Mid-Atlantic Center for Cardiometabolic Health Equity Data and Safety Monitoring Board that meets twice a year to review study progress, intervention adherence, and adverse events (mild, moderate, and severe).

Ethical Considerations

The protocol received initial approval from the Johns Hopkins Institutional Review Board in June 2022 (IRB00307430) and was determined to be minimal risk. Standard continuing reviews occur yearly; protocol amendments are also reviewed and subsequently updated in the ClinicalTrials.gov registry. During the informed consent process (refer to the Screening and Recruitment subsection), participants are made aware of their right to privacy and confidentiality and are informed that all health information is deidentified or stored on secure servers. They are also advised that they can withdraw from the study at any time without consequence from the research team and medical or home visiting services, and if this occurs, Johns Hopkins may use any data collected before withdrawal. Participants will be provided gift cards after each data collection visit (for details, refer to the Retention Strategies for Participants subsection). In addition, each home visiting site will receive an annual financial incentive.

Results

This study was funded in June 2021, and recruitment began in April 2023. As of November 2024, we enrolled 90 participants. Data collection to assess the intervention's effectiveness is expected to end in June 2026. Implementation evaluation is expected to conclude in December 2026.

Discussion

Anticipated Findings

We designed this hybrid type I effectiveness-implementation randomized controlled trial to test a remote lifestyle intervention for weight management during pregnancy and post partum in a community-based setting that serves individuals who identify as Latinx and non-Hispanic Black. The goal of this hybrid trial is to evaluate the effectiveness of a newly adapted remote lifestyle intervention (H42-HV) and effectively integrate the intervention into early home visiting services to reduce PPWR. We hypothesize that participants who receive the H42-HV intervention will have a lower mean difference in PPWR at 6 months than control group participants. This would add to the limited evidence supporting the effectiveness of counseling and lifestyle interventions during and after pregnancy in minimizing GWG [25-28] and reducing PPWR [29-32] among racial and ethnic minority groups [32,35]. Furthermore, because few counseling and lifestyle interventions for pregnant and postpartum people have been tested in community-based settings, the use of implementation science methods will enable the gathering of important data about the facilitators and barriers to implementing the intervention in the early home visiting setting and among this population considered vulnerable. Early home visiting programs hold promise to be an ideal setting to integrate lifestyle interventions because of their unique ability to address relevant social and environmental conditions impeding healthy behaviors (eg, access to healthy foods and transportation), as well as support and improve transitions to

postpartum care. We anticipate that our study findings will demonstrate feasibility comparable to that reported in another trial of a lifestyle intervention embedded into early home visiting [41,42]. Through the implementation science approach, we will also provide evidence to support policy translation, including the expansion of H42-HV delivery into other US states' home visiting programs, and into Medicaid Managed Care coaching and case management programs as Medicaid coverage expands into the postpartum period in more states [108].

Strengths and Limitations

A major strength of the trial's design is the community-engaged approach, which began during the grant conceptualization and preimplementation phases to inform project design. Community-engaged research approaches have increased dramatically in the last few decades and are linked with statistically positive outcomes and success in recruiting and retaining racially and ethnically diverse populations experiencing marginalization [109-111]. Community-engaged research has many benefits, including ensuring intervention appropriateness, acceptability, and applicability [112-115]; ensuring that study methods and intervention are properly adapted to the population of interest [114,116,117]; and promoting trust, transparency, and bidirectional learning between research teams and stakeholders [112,118,119]. Adopting this approach has already guided key research design decisions, including (1) limiting the primary role of home visitors to the recruitment of study participants to minimize impact on workflow, (2) enrolling participants during mid- to late pregnancy (20-33 wk) to align with client enrollment in home visiting programs, (3) defining the primary outcome as weight retention at 6 months post partum to allow time for increased support during the postpartum period, and (4) focusing study goals and messaging on achieving "overall health and wellness" versus a "healthy weight" to minimize the effects that weight bias internalization may have on recruitment and intervention acceptability. Using remote data collection procedures was another important design consideration (ie, smart scale and access to prenatal medical records), given the transportation barriers of home visiting clients living in rural locations and anticipated challenges they might have in reporting their height and weight to confirm eligibility—an issue that was confirmed soon after study launch. We anticipate that the continued involvement of our coordinating council as well as other methods of community engagement will drive future decisions about the interpretation of data and dissemination of findings.

The iterative process of end-user interviews that informed the design, features, and functionality of the H42 mHealth app was especially valuable for adapting and improving it, including methods for incorporating weight goals and progress (ie, simple, colorful graph versus weight change statistics) and translating the interactive goal-setting activity for Spanish-speaking participants. Comprehensive measures of adherence to coaching, the H42 mHealth app, and the smart scale are a major strength of the study, given the growing complexity of remote lifestyle intervention packages and the critical need to differentiate the effects of unique components [27]. Similarly, access to robust engagement metrics for distinct mHealth app features (ie, interactive goal setting, coach messaging, access to weight data, comprehension quizzes, and educational videos) may build upon the patterns of website engagement characterized by Power et al [120] in a sample of individuals with low-income status who identified as Latinx; of note, in this particular study, website engagement was a strong predictor of weight retention at 6 months post partum.

The design of our study has limitations that could impact the interpretation of the results. First, control participants will have access to a scale for data collection, and regular self-weighing is a key component of behavioral weight management [58]. From a health equity and ethical perspective, we decided that we would refrain from instructing control participants not to weigh themselves outside of data collection and, instead, statistically control for the number of measured weights across the groups. Nonetheless, given the enhanced level of engagement with self-weighing in the intervention group (ie, reminders, ability to view progress on the app, and feedback from the coach), we expect the frequency of weighing in the control group to be significantly lower, and frequency is the strongest known predictor of overall weight change [121]. Another limitation is our limited ability to formally measure and control for the varying levels of support that the home visitors offer clients throughout the trial, which may differentially impact behavior change (eg, addressing access to healthy food and discussing a healthy lifestyle). This lack of control precludes our ability to measure intervention effectiveness for a Latinx and non-Hispanic Black, English- and Spanish-speaking sample considered high risk outside of the context of home visiting. Although home visitors were intentionally removed from intervention delivery, early feedback conveyed a preference among some home visitors to be actively involved, specifically with the ability to access SMART goals (assuming clients' permission). The differences in home visitor training (ie, nurse vs paraprofessional), curriculum, and the intensity of home visiting models in the trial (ie, frequency of visits ranging from weekly to 2 visits total during the first 6 mo post partum) may also differentially impact client success. We expect qualitative data on intervention adoption captured in focus groups after the trial to enhance our understanding of the potential role home visitors play in moderating intervention effects and will leverage these insights for future trial designs and intervention adaptions.

Conclusions

There is a critical need to develop effective lifestyle interventions for pregnant and postpartum individuals who identify as Latinx and non-Hispanic Black and experience the greatest risk for adverse pregnancy outcomes. This study has the potential to provide a high-quality assessment of the effectiveness of a remote lifestyle intervention for a Latinx and non-Hispanic Black population considered high risk and highlight facilitators and barriers to its implementation in a grounded service strategy specifically geared toward improving maternal and infant health. We expect the study to yield important findings that aid in refining future lifestyle intervention approaches for pregnant and postpartum people, particularly those who identify as non-Hispanic Black and Latinx, and facilitate scalability in community-based settings,

ultimately improving maternal and infant long-term health and promoting health equity.

Acknowledgments

This trial was funded as 1 of 3 studies at the Mid-Atlantic Center for Cardiometabolic Health Equity funded through the National Institute on Minority Health and Health Disparities Centers for Multiple Chronic Diseases Associated with Health Disparities: Prevention, Treatment, and Management (RFA-MD-21-007) under the P50 mechanism.

Data Availability

The datasets generated and analyzed during this study will be available from the corresponding author on reasonable request.

Authors' Contributions

Conceptualization: KMB (lead), WLB (lead)
Data curation: LMM (lead), CDM (supporting)
Funding acquisition: KMB (lead), WLB (lead)
Investigation: KMB (lead), WLB (lead), LMM (supporting), CDM (supporting), LEA (supporting), JWC (supporting), NKJ (supporting), AS-U (supporting)
Methodology: KMB (lead), WLB (lead), LMM (supporting), CDM (supporting), JWC (supporting), NKJ (supporting), NYW (supporting)
Project administration: KMB (lead), WLB (lead), LMM (supporting)
Resources: AS-U (supporting)
Supervision: KMB (lead), WLB (lead), LMM (supporting), CDM (supporting), JWC (supporting), NKJ (supporting)
Writing (original draft): LMM (lead), KMB (supporting), WLB (supporting)
Writing (review and editing): LMM (lead), KMB (lead), WLB (lead), CDM (supporting), LEA, (supporting), JWC (supporting), NKJ (supporting), AS-U (supporting), KAC (supporting), NYW (supporting)

Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer review report from the National Institute on Minority Health and Health Disparities Special Emphasis Panel - National Institute on Minority Health and Health Disparities - Centers for Multiple Chronic Diseases Associated with Health Disparities: Prevention, Treatment, and Management (P50) ZMD1 MLS (A1) (National Institutes of Health, USA.
[PDF File (Adobe PDF File), 226 KB - resprot_v14i1e62847_app1.pdf]

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Abbreviations

CFIR: Consolidated Framework for Implementation Research
GWG: gestational weight gain
H42-HV: Healthy for Two–Home Visiting
MDD: minimum detectable difference
mHealth: mobile health
PPWR: postpartum weight retention
PRAMS: Pregnancy Risk Assessment and Monitoring System
PRISM: practical, robust implementation and sustainability model
REDCap: Research Electronic Data Capture
SMART: specific, measurable, achievable, relevant, and time-bound

Edited by T Leung, D Khajeei; submitted 13.06.24; this is a non–peer-reviewed article;accepted 25.10.24; published 07.01.25.

Please cite as:
Martin LM, McKinney CD, Escobar Acosta L, Coughlin JW, Jeffers NK, Solano-Umaña A, Carson KA, Wang NY, Bennett WL, Bower KM
Remote Lifestyle Intervention to Reduce Postpartum Weight Retention: Protocol for a Community-Engaged Hybrid Type I Effectiveness-Implementation Randomized Controlled Trial
JMIR Res Protoc 2025;14:e62847
URL: https://www.researchprotocols.org/2025/1/e62847
doi:10.2196/62847
PMID:

Protocol

Adaptive Just-in-Time Intervention to Reduce Everyday Stress Responses: Protocol for a Randomized Controlled Trial

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Abstract

Background: Personalized approaches to behavior change to improve mental and physical health outcomes are needed. Reducing the intensity, duration, and frequency of stress responses is a mechanism for interventions to improve health behaviors. We developed an ambulatory, dynamic stress measurement approach that can identify personalized stress responses in the moments and contexts in which they occur; we propose that intervening in these stress responses as they arise (ie, just in time; JIT) will result in positive impacts on health behaviors.

Objective: This study aims to (1) use an experimental medicine approach to evaluate the impact of a smartphone-delivered JIT stress management intervention on the frequency and intensity of person-specific stress responses (ie, stress reactivity, nonrecovery, and pileup); (2) evaluate the impact of the JIT intervention on the enactment of health behaviors in everyday life (physical activity and sleep); and (3) explore whether changes in stress responses mediate the interventions' effects on health behaviors.

Methods: In a 2-arm phase 2 clinical trial, we will enroll 210 adults in either a JIT stress management intervention or an active control condition. For 4 weeks, participants will complete 8 brief smartphone surveys each day and wear devices to assess sleep and physical activity. After a 1-week run-in period, participants will be randomized into the JIT intervention or an active control condition for 2 weeks. Participants in the JIT intervention will receive very brief stress management activities when reporting greater than typical stress responses, whereas control participants will receive no personalized stress management activities. Participants enrolled in both conditions will engage in self-monitoring for the entire study period and have access to a general

stress management education module. Self-report outcomes will be assessed again 1 month after the intervention. We will use mixed-effects models to evaluate differences in person-specific stress responses between the intervention and control groups. We will conduct parallel analyses to evaluate whether the intervention is associated with improvement in health behavior enactment (ie, sleep and physical activity). The Pennsylvania State University Institutional Review Board approved all study procedures (STUDY00012740).

Results: Initial participant recruitment for the trial was initiated on August 15, 2022, and enrollment was completed on June 9, 2023. A total of 213 participants were enrolled in this period. Data are currently being processed; analyses have not yet begun.

Conclusions: We anticipate that this research will contribute to advancing stress measurement, thereby enhancing understanding of health behavior change mechanisms and, more broadly, providing a conceptual roadmap to advance JIT interventions aimed at improving stress management and health behaviors.

Trial Registration: Clinicaltrials.gov NCT05502575; https://clinicaltrials.gov/study/NCT05502575

International Registered Report Identifier (IRRID): DERR1-10.2196/58985

(JMIR Res Protoc 2025;14:e58985) doi:10.2196/58985

KEYWORDS

stress; stress responses; stress management; just-in-time adaptive intervention; sleep; physical activity; behavior change; experimental medicine approach

Introduction

Background

Broadly defined stress processes (eg, chronic stress and allostatic load) are associated with an increased risk for poor mental and physical health outcomes [1]. Traditional research on this topic tends to focus on between-person assessment examining, for example, whether those with more major life events or more chronic stressors for relatively long periods have worse health. However, chronic stress is characterized by a series of repeated acute events, each including exposure to stressors and slow and delayed recovery from stressful events [2]. Thus, to effectively characterize and intervene in stress processes, a granular measurement of acute stress is needed that uses a personalized, within-person approach. In this case, the goal is to understand an individual's stress experience at a given moment compared to another moment (eg, their normal resting state). Such an approach captures the dynamic and temporal nature of the stress experience that occurs within an individual as they navigate their natural environment. Furthermore, this within-person approach to capturing stress experiences affords the opportunity to identify and intervene in such processes before, or at the onset of, their occurrence to attenuate the association between stress and poor health outcomes [3-5].

To help advance stress measurement approaches, we developed and refined methods for the self-report assessment needed to measure and characterize how individuals experience stress in their everyday lives in a way where each stress event can be adequately captured and studied [4,5]. We proposed that a stress event can be broken down into distinct components. Specifically, our approach focuses on assessing events that elicit immediate emotional and cognitive responses (ie, reactivity), the degree to which we adapt and recover (ie, recovery), and the temporal patterns of responding to and recovering from multiple stressors over time (ie, pileup). This assessment strategy took a within-person approach that permitted the repeated assessment of stress experiences close to their occurrence. It estimated how these stress response components (ie, reactivity, recovery, and pileup; RRP) unfold with time and in natural contexts. We demonstrated the utility of assessing these specific components of the stress responses (ie, RRPs) across 3 indicators (ie, negative affect, perseverative cognition, and subjective stress) to index "moments of risk," where such moments are specific to a person and context [6-8]. Furthermore, we were able to link specific stress response targets to health behaviors (ie, sleep and physical activity) both within and between individuals [9,10]. Given that these stress response components and indicators are related to the enactment of health behaviors in everyday life, we contend that they may be potent targets for intervention, and we aim to test this using the experimental medicine approach [11-13].

There is growing awareness and need for better personalized and precision medicine approaches in the behavioral sciences [14]. Advances in smartphone technology (ie, apps, location, and activity) and the widespread use of mobile and sensing devices have led to the development of ecological momentary interventions that use contextual information and self-report data to match intervention content to contextual needs and deliver that content in real time [3,15]. A just-in-time (JIT) intervention framework advances this approach using rule-based algorithms to deliver the right intervention at the right time based on prespecified triggers (eg, specific variable, context, or combination of variables and context).

We suggest that our stress response assay is well suited to inform the JIT and related interventions. First, our approach is highly personalized in deriving person-specific estimates of momentary or daily risk. We have chosen to not implement static threshold–based general rules applied across all individuals; for example, with the intervention content delivered when some predetermined threshold value is exceeded (eg, a score of ≥6 on a 7-point scale) or when individuals report being in a specific location deemed risky. Although intervention delivery using this method may still benefit the recipient, it does not fully allow for adaptation to the individual with time or across changing contexts. The approach proposed in this protocol, and in some of our previous work [4,5], goes beyond using group or

sample-level fixed-risk estimators, providing an adaptive and individualized framework to identify moments of maladaptive stress responses across several key indicators specific to the person. Second, we have developed, tested, and refined an intervention algorithm that uses our stress assay to process real-time information to identify and provide personalized intervention content as stress targets arise. This approach includes providing intervention content matched to general availability and the intensity and frequency of the individual's experience. We propose that the implementation of this stress assay and the JIT intervention framework has the potential to inform approaches to individualized stress management, intervention design, and implementation science more broadly.

Aims

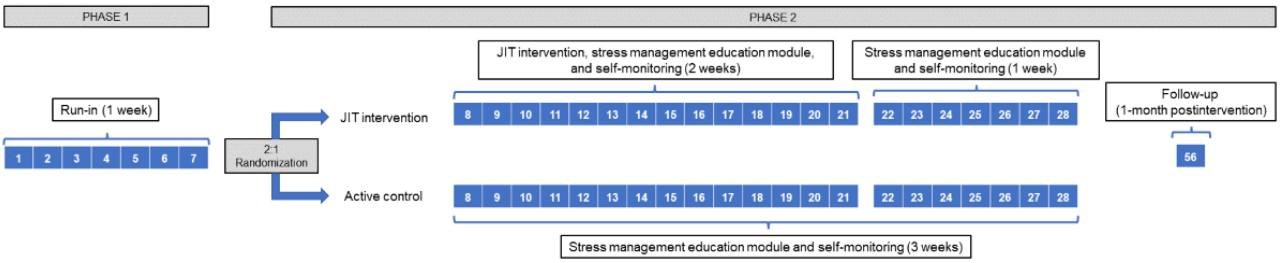
This study aims to determine the effectiveness of a JIT stress management intervention, delivered via a study smartphone, on the outcomes of stress responses, sleep, and physical activity. This study will leverage our optimized stress assay to identify moments of risk and deliver empirically derived multimodal JIT intervention content in everyday life, with the aim of modifying stress response components (ie, RRPs) across multiple indicators (ie, negative affect, preservative cognition, and subjective stress) to subsequently produce positive change in daily physical activity and night sleep. Using the experimental medicine approach within the context of a phase 2 clinical trial, our primary aim is to evaluate the impact of a 2-week smartphone-delivered JIT intervention (relative to an active control consisting of self-monitoring and stress management education) on the frequency and intensity of stress responses (RRPs), as measured by (person-specific) negative affect, perseverative cognition, and subjective stress. Our secondary aim is to evaluate the impact of the JIT intervention on the enactment of health behaviors in everyday life (ie, daily physical activity and night sleep). Our third aim is to explore whether the interventions' effects on health behaviors are mediated by changes in our target mechanism (RRPs).

Methods

Project Overview and Trial Design

This study is a 2-arm phase 2 clinical trial (ClinicalTrials.gov NCT05502575). The study has 2 phases (Figure 1), including a 1-week baseline eligibility "run-in" period (phase 1), followed by a 2-week randomized controlled trial (phase 2) for those eligible after phase 1, with a 1-week observational interval following the intervention.

Figure 1. Study design. JIT: just in time.



Ethical Considerations

The Pennsylvania State University Institutional Review Board approved all study procedures (STUDY00012740). All participants provided informed consent. All study data are deidentified and encrypted. Participants were compensated equitably for participation according to what study phases and components they completed, as detailed in the Procedures section.

Phase 1

Phase 1 of this study serves 3 primary purposes. First, it is a data-capture period that enables us to collect individual baseline data on each participant to be used to inform the JIT intervention algorithm in phase 2. Second, it allows us to screen for participant compliance with the protocol and ensure that those enrolled in phase 2 meet minimum standards for data completeness (ie, >70%). Third, this period allows us to exclude participants who do not regularly report stress during everyday life and thus may not be impacted by our intervention.

Phase 2

Phase 2 is the clinical trial portion of the study and will serve as the between-group test of our JIT intervention on night sleep and physical activity. This study phase will be initiated immediately following phase 1 and is 3 weeks long. Participants who are eligible for phase 2 will be randomized into one of two conditions as follows: (1) JIT intervention (ie, JIT stress management, self-monitoring, and web-based stress education module) or (2) active control (ie, self-monitoring and web-based stress education module). The first 2 weeks of phase 2 are the active intervention period, while the final week is a self-monitoring period.

Participants

To examine the impact of our intervention on our primary outcomes without the influence of age-related stressors or increased probability of health comorbidities that could impact our measures of sleep and physical activity, our target population will be generally healthy middle-aged adults. Specifically, we will recruit English-speaking men and women aged 35 to 65 years who report good general health and are free of physical limitations from the mid-Atlantic region of the United States.

We will exclude people who report (1) residing in the same household as current or former participants (to prevent any contamination of the intervention or unblinding of condition allocation); (2) an inability to answer smartphone survey SMS text messages due to restrictions or policies in the workplace; (3) a diagnosis of a mental health condition that required a

medication adjustment or hospitalization within the last 3 months; (4) being a primary caretaker for a parent, child, and family member who is severely disabled; (5) employment that requires shift work as this will result in abnormal sleep patterns; (6) a diagnosis of sleep apnea, use of a continuous positive airway pressure machine, or score above threshold on STOP-BANG; (7) the use of physician-prescribed pharmaceutical sleep aids or over-the-counter sleep aids for ≥3 days per week; (8) an inability to be physically active or who have medical contradictions for physical activity; or (9) physical exercise of ≥200 minutes per week at a moderate or vigorous intensity or ≥10 hours of walking per week as this raises the possibility of ceiling effects on activity.

Recruitment and Screening

Participants will be recruited through advertisements posted in the local communities (eg, community centers, grocery stores, libraries, and cafés), online channels (eg, social media and study recruitment websites), and mailed flyers. Interested participants can contact the study team via phone or email and will be given a brief study overview. Participants can also access study information and preliminary web-based screening forms using a link on the recruitment materials. Individuals interested in participating will be screened to determine eligibility and scheduled for an introductory training session if eligible. All screening and scheduling will be conducted via phone using a script.

Randomization

Randomization for this study will occur upon enrollment into phase 2 using discrete codes entered into the smartphone app by a research assistant blind to study goals. Participants will be allocated on a 2:1 ratio that favors the JIT intervention condition to provide a sample size large enough to support our planned analyses. To balance participant characteristics within the study conditions, participants will be equally randomized across 3 age categories (including those aged 35 to 44, 45 to 54, and 55 to 65 years) and by sex (male and female). Masking of the participant group identities from the training personnel, data collectors, and analysts will be used. Group assignments will be unmasked for analysis when the trial is complete and after all data have been entered.

Sample Size

Our initial power calculations suggest that our study target for participants enrolled in phase 2 should be 210 (n=140, 66.7% assigned to the JIT intervention condition and n=70, 33.3% assigned to the active control condition). In our previous work with a similar assessment schedule, we observed compliance rates of >70% on the momentary surveys and >80% on the device wear time across 2 weeks in 95.2% (120/126) of the participants (unpublished data). Of those participants, the lowest quartile reported approximately 3 stressor events across 2 weeks. Thus, we estimate that approximately 15% of participants enrolled in phase 1 will not qualify for phase 2 due to no reported stressors or low compliance rates with study procedures. It is also likely that some participants may choose not to continue participation in phase 2 even if they are eligible due to the intensive assessment schedule. We estimate that refusal will account for 25%, and an additional 10% of those participants may either drop out during phase 1 or become ineligible. Thus, we estimate that up to 50% of the participants enrolled in phase 1 may not continue to phase 2. Therefore, we expect to recruit and enroll approximately 450 participants in phase 1 to reach our target of 210 participants in phase 2.

Equipment

Study Smartphone

All study participants will be provided with an Android LG Rebel 3 smartphone. The smartphones will be preloaded with the MovisensXS app (Moviesens GmbH [16]), a secure assessment app that delivers, collects, and uploads the study smartphone surveys to a secure server. Devices will also be preloaded with the stress management intervention content. Each phone will have an active data plan and Wi-Fi capability to allow instantaneous survey uploads, intervention delivery, and access to the web-based stress education modules. Participants will only have access to the smartphone functions relevant to the study procedures, and all other smartphone capabilities will be locked.

Device-Assessed Sleep

Objective sleep outcomes will be collected using the Actiwatch Spectrum Plus (Philips Respironics [17]). Participants will be asked to wear the water-resistant Actiwatch on their nondominant wrist for the study's duration, only removing the device when bathing or swimming. This device measures wrist movement time series using the digital integration method and will be configured to collect activity data at 32 Hz. At study completion, data from the Actiwatch will be processed to detect off-wrist periods and downloaded in 15-second epoch files using the Respironics Actiware software (version 6.0.9; Philips Respironics).

Device-Assessed Physical Activity

Participants will be asked to continuously wear a water-resistant ActivPAL4 activity monitor (PAL Technologies [18]) for the duration of the study. The ActivPAL4 monitor will be adhered to the midline of either thigh, halfway between the knee and hip, with adhesive tape. Participants will be instructed to remove the device only if bathing or swimming and will not be required to charge the device. This device uses an inclinometer and accelerometer to measure posture and activity intensity to quantify the time spent sitting, lying, standing, or stepping. Activity data will be collected at 20 Hz, with device data downloaded and processed using the PALbatch software (version 8.10.11.54; PAL Technologies).

Procedures

Phase 1 (Run-In Period)

Phase 1 of this study is 1 week in duration. Participants will attend a 90-minute introductory training session with a research assistant. During this visit, participants will take part in an informed consent procedure. They will be notified that they may be invited to another longer study after they have completed the 1-week study. However, no further information about the study or eligibility criteria for participation will be provided.

After informed consent is obtained, participants will participate in a study protocol training session to learn how to use the study smartphone to answer surveys. Each participant will be able to practice the surveys with a research assistant to ensure that they understand the survey items and how to operate the smartphone. Participants will also receive instruction on properly adhering and caring for the wrist-worn actigraphy device and the physical activity monitor. Finally, they will be asked to complete a demographics survey and baseline questionnaires. Each participant will receive a quick reference participant booklet that reviews relevant survey and device information.

During the 1-week study period, participants will be asked to complete 8 brief smartphone surveys per day that are delivered to the study smartphone, including 1 survey upon waking in the morning, 6 surveys delivered randomly throughout the day between 8 AM and 9 PM, and 1 survey at the end of the day before going to sleep. Participants will continuously wear the actigraphy and physical activity devices for the entire week. At the end of the 1-week study period, participants will attend a second session to return their devices and receive compensation (up to US $100). At this time, research assistants will assess survey and device data for compliance and completeness to determine whether the participant meets the criteria for eligibility into phase 2.

Eligibility for Phase 2

Survey data from phase 1 of the study will be used to inform the delivery of the JIT intervention in phase 2. Therefore, it is essential for participants who enter phase 2 to meet the minimum criteria for complete data on which to apply our intervention rules. For this reason, we will assess participant compliance with the study procedures and data completeness before inviting participants into phase 2. Specifically, participants who complete phase 1 will be eligible for phase 2 if they (1) return all study devices, (2) report at least 1 stressor in their surveys during the 1-week run-in period, (3) meet an acceptable rating threshold for survey compliance (ie, >70%), and (4) have valid accelerometry data for at least 5 nights during the 1-week study period. Given that these compliance checks will be conducted during a brief session, the physical activity data will not be assessed for completeness as it requires considerable time to download and review.

Once all devices are obtained and compliance checks are done, participants will be compensated according to completed study procedures. At the time of compensation, each participant will either be dismissed or invited to participate in phase 2 of the study. Those deemed eligible to participate in phase 2 will receive a brief overview of study procedures. They will participate in the consent procedure for phase 2 and a refresher training session if interested. If they are not interested, they will be dismissed.

Phase 2 (Clinical Trial)

Phase 2 will be initiated immediately following phase 1. The study procedures for phase 2 are similar to phase 1 (ie, 8 smartphone surveys per day and wearing study devices) but also involve randomization into either the JIT intervention condition or the active control condition. Participants will undergo another informed consent procedure and a brief review on using the study smartphones and how to wear and care for the study devices. All participants will be notified during the session that they will have access to web-based stress management education modules on the home screen of their smartphone (refer to Active Control Condition section); they may also receive additional prompts delivered to their smartphone and will be asked to follow all instructions provided to them to the best of their ability.

Given that both the participants and researchers will be blind to condition allocation, no training specific to interacting with the JIT intervention materials will be provided to participants. Importantly, no specialized training or instruction is required to participate in the intervention condition as all necessary instructions will be provided on the device when the intervention content is delivered. We adopt this approach as it may facilitate the scaling up of intervention delivery in the future (eg, by not requiring in-person or online training). After the phase 2 training session, participants will attach their study devices and continue to answer surveys delivered across the 3-week study period.

For the first 2 weeks of the 3-week study period, participants randomized into the JIT intervention condition will complete the 8 smartphone surveys per day, wear the 2 study devices continuously, and receive multimedia JIT intervention content to their smartphone during moments and days identified as appropriate for intervention (Figures 2 and 3). Participants randomized into the active control condition will continue to complete 8 smartphone surveys daily and continuously wear the 2 study devices. However, they will not receive any personalized stress management content. Participants in both conditions will have access to web-based stress management education information regarding the causes, consequences, and remediation of stress. This information was developed and curated by stress experts on our team (JMS, MJZ, and JAJ; ie, representing an informational standard of care) and will be available on study smartphones for the entire 3-week study period.

Figure 2. Just-in-time intervention algorithm. EOD: end of day. NA: negative affect; PC: perseverative cognition; RRP: reactivity, recovery, and pileup; SS: subjective stress.

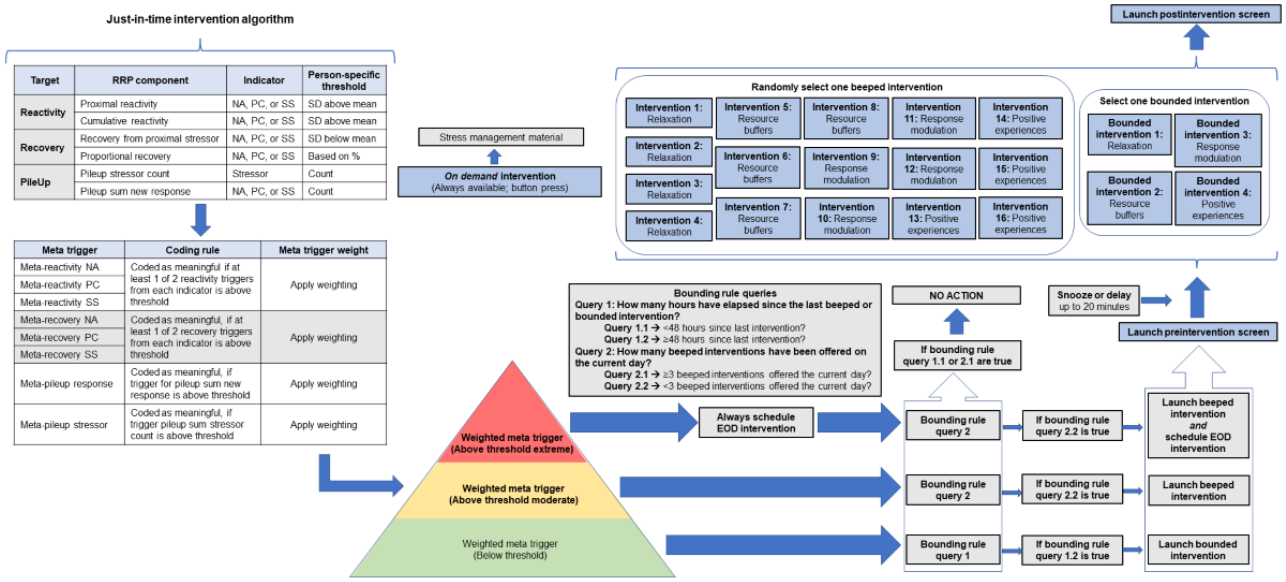
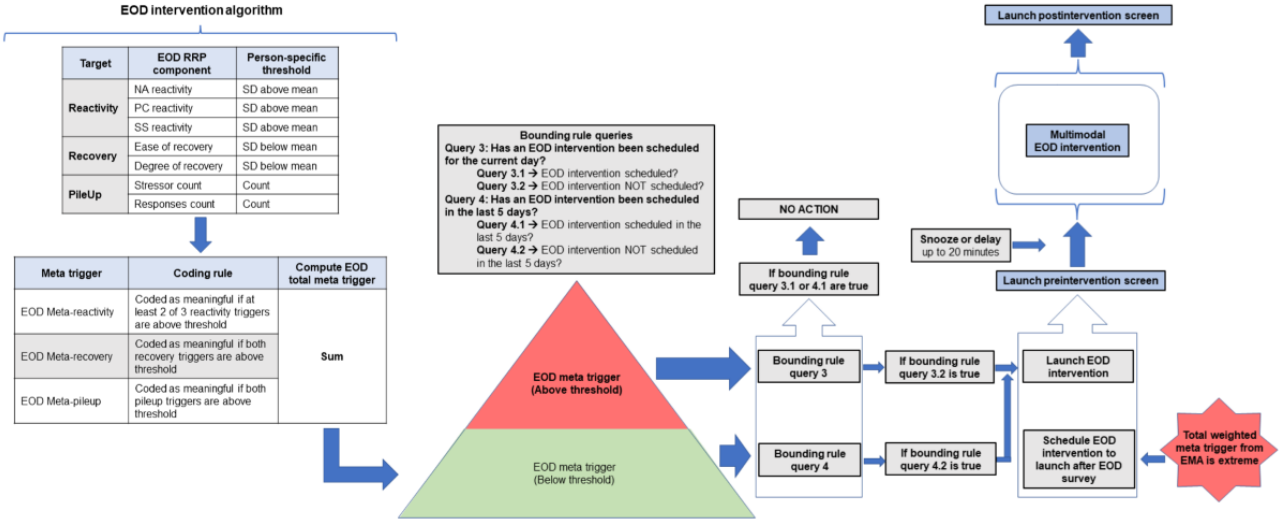


Figure 3. End-of-day (EOD) intervention algorithm. EMA: ecological momentary assessment; NA: negative affect; PC: perseverative cognition; RRP: reactivity, recovery, pileup; SS: subjective stress.



During the final week of the 3-week study period, the delivery of the JIT intervention content will cease (access to the web-based stress management education module will continue), and participants in both conditions will continue to engage in self-monitoring only. This final week of self-monitoring will provide information about the short-term impact of the JIT intervention and the immediate effects of tapering JIT intervention content. It will also evaluate whether any effects persist in whole or in part once the JIT intervention ceases. At the end of the 3-week study period, participants will attend a final session to return their devices and debrief about the study. A research assistant will assess participant compliance with the study procedures, and participants will receive their earned compensation of up to US $300 for phase 2.

Follow-Up

One month after the completion of phase 2, participants will be invited via email to complete a web-based follow-up self-report survey to assess changes in stress, sleep, and physical activity with measures capturing key study constructs. Participants will have 1 week to complete this survey to receive US $15 compensation.

Measures

Demographics

At baseline, participants will provide information on the following demographic characteristics: sex, age, race, ethnicity, education level, current work status, household income, subjective social status, marital status, number of adults and children in the home, and height and weight (ie, BMI). We will also inquire about active gymnasium memberships and the use of wearables and smartphone apps for sleep and physical activity.

Baseline and Follow-Up Measures

The measures selected for this study are intended to capture a broad range of constructs that may impact stress and stress

responses in everyday life, including personality, mood and affect, tendencies for ruminative and perseverative thinking styles, social support, and current stress. These person-level factors will help characterize our sample and may serve as potential explanatory variables for treatment response heterogeneity. We are also capturing information on current health status and preintervention and follow-up measures of self-reported sleep behaviors and sleep disturbance, physical activity behaviors, and physical activity intention or automaticity. The measures being assessed in this study and their assessment schedule are summarized in Table 1.

Table 1. Study measures.

Construct and scale name	Baseline	Follow-up
Health status (SF-36[a] [19])	✓	✓
Social support (Social Support Questionnaire [20])	✓	✓
Personality		
The Satisfaction with Life Scale [21]	✓	
Life Orientation Test-revised [22]	✓	
Big Five Inventory [23]	✓	
Rosenberg Self-Esteem Scale [24]	✓	
Mood and affect		
Positive and Negative Affect Scale [25]	✓	✓
Toronto Alexithymia Scale [26]	✓	
Perseverative cognition		
Recent Perseverative Cognitions	✓	✓
Perseverative Thinking Questionnaire [27]	✓	
Rumination-Reflection Questionnaire (Rumination subscale) [28]	✓	
Stress		
Recent stress	✓	✓
Current stress	✓	✓
Stress mindset [29]	✓	✓
Impact of Events Scale [30]	✓	✓
Perceived Stress Scale [31]	✓	✓
Sleep		
Insomnia Severity Index [32]	✓	✓
Pittsburgh Sleep Quality Index [33]	✓	✓
Physical activity		
International Physical Activity Questionnaire [34]	✓	✓
Physical activity intentions	✓	✓
Generic Multifaceted Automaticity Scale [35]	✓	✓
Acceptability (General acceptability)		✓

[a]SF-36: 36-Item Short Form Survey Instrument.

Smartphone Surveys

Overview

The smartphone surveys in this study capture momentary and global ratings of stressful events, subjective stress, positive and negative affect, perseverative cognitions, and health behaviors as participants go about their daily lives. There are 2 types of smartphone surveys in this study, including those that are self-launched by the participant by button press within the smartphone app (ie, morning and evening surveys) and those that are automatically delivered to the participant at semirandom intervals throughout the day (ie, beeped surveys). The self-launched surveys serve as broader retrospective assessments of these outcomes across the day. In contrast, the beeped surveys are meant to capture more proximal assessments of these outcomes in the contexts in which they occur (at the moment). The information collected in the smartphone surveys will be used to derive our indicators of stress in real time and inform the delivery of JIT intervention content (Figures 2 and 3).

Morning Survey

Participants will be asked to launch and complete the morning survey each day within 30 minutes of waking. This survey will assess the duration and quality of the previous night's sleep, current stress, affect, perseverative cognitions, plans for physical activity, and expectations for the day ahead.

Beeped Surveys

The beeped surveys will be automatically delivered to participants at 6 random times each day between 8 AM and 9 PM during the study period and are scheduled at semirandom intervals (1 to 4 hours apart; typically 2.5 hours apart) to capture most waking hours. These brief surveys assess the participant's current location, activities, social interactions, recent stressors, affect, perseverative cognitions, and physical activity (duration and intensity). Participants can delay (up to 15 minutes) or dismiss any survey if they cannot complete it at the indicated time.

Evening Survey

Participants will be asked to complete the evening survey each night before going to bed and instructed to think about their entire day (ie, from waking up) when completing the survey. This survey assesses stressful experiences and reactions to them; overall day-level affect and perseverative cognitions; physical activity (duration and intensity); consumption of caffeine, nicotine, and alcohol; use of backlit devices before going to bed; and daytime nap duration.

Objective Sleep

Two research staff (who have been satisfactorily trained on scoring sleep data by a sleep expert on our team) will independently score downloaded data from the sleep watch. Sleep intervals and relevant sleep outcomes will be derived using a previously validated algorithm [36]. Outcomes will include total sleep time, wake after sleep onset, sleep efficiency, and nap count or frequency and duration. Total sleep time will be calculated by the number of minutes between sleep onset and awakening. Wake after sleep onset is the total time spent being awake between sleep onset and awakening. Finally, sleep efficiency will be calculated as the proportion of actual sleep from sleep onset to awakening relative to the total sleep duration interval (%). Naps will be delineated as other sleep periods >30 minutes in length that occur outside of the main nighttime sleep period.

Objective Physical Activity

The physical activity data will be aggregated into 1-minute epochs. Using the sleep and wake times from the sleep data, all sleep periods will be excluded in the subsequent data aggregation process. Furthermore, any continuous sitting or standing events that are >5 consecutive hours will be classified as nonwear and will also be excluded. The remaining valid wake period will be classified into either time spent sedentary, standing, or stepping. Time spent stepping will further be classified into time spent in light physical activity or moderate to vigorous physical activity using the 100 steps per minute cut point [37]. Other relevant objective physical activity outcome variables will include step count and number of sit-to-stand transitions. The physical activity data will be further aggregated depending on the level of analysis as necessary (eg, hourly, daily, and person-level summary).

JIT Intervention

General Approach

In line with the principles of the JIT intervention approach, our goal was to develop empirically supported stress management content that is delivered during particularly stressful moments. It uses a nudge framework [38] to help a person reorient to a nonstress state via improved affect and reduced perseverative and maladaptive cognitions. More broadly, each nudge aims to help build a diverse toolkit of stress management skills that can be implemented in everyday life. Furthermore, this allows us to implement a personalized approach to intervention delivery using real-time information specific to the individual at a given moment to deliver content at moments of presumptive risk or need [39].

Intervention Content

The development and testing of our intervention content have been described previously [40]. Briefly, we developed our intervention content within 4 broad categories: relaxation, response modulation, positive experiences, and resource buffers.

Relaxation

These techniques aim to shift the body from a state of elevated or negative arousal to a relaxed or neutral state. Participants could do controlled breathing, deep breathing, progressive muscle relaxation, or an object-focused meditation.

Response Modulation

These techniques aim to promote self-regulatory behavior, in particular, to manage emotions, promote efforts to change thoughts and associated emotions to a more positive meaning, reduce impulsive behavior, and focus attention away from emotion-eliciting situations or thoughts. Participants could perform a reappraisal task to learn how to rethink negative situations, an attentional deployment task to train them to focus on positive stimuli, a third-party observer task that asks them to imagine how an outsider would view their stress, or an affect labeling task to encourage the ability to use words to self-describe negative emotional events.

Positive Experiences

This category aims to facilitate engagement in activities that can induce positive mental states. Participants could imagine saying positive statements to themselves, reacting to positive imagery, engaging in a gratitude exercise, or a reminiscing task that engages them to relive a positive event in their lives.

Resource Buffers

This category aims to increase the quality of life at the moment to enhance function and resilience. Participants could engage in a self-affirmation task to embrace those facets of their life that are most positive, a self-efficacy task to encourage them to find moments they have successfully dealt with life events, a social comparison task that allows them to learn from others who have successfully dealt with stress in their lives, or a best

possible self activity (imagining an idealized version of themselves and how they might achieve that self).

Intervention Types

Overview

The intervention content was developed to be appropriate for everyday life, including the consideration of general availability to engage with the intervention content. Therefore, we developed 2 intervention types of differing lengths and time of day availability, and all content was intended to be displayed to the participant on a smartphone. Each activity is intended for the participant to do independently, not requiring interaction with others.

Microinterventions

These very brief interventions (ie, microinterventions) are no more than 1 to 2 minutes in duration. This suite of microintervention content includes 16 brief videos, including 4 microinterventions across each of the 4 categories described above. For any given participant randomized into the JIT condition, when an intervention moment is identified (refer to Intervention Delivery section), 1 of the 16 microinterventions will be randomly selected from the suite of videos and presented to them on the smartphone. To maximize engagement and increase the potential for exposure to the different skills and activities, each time an intervention is delivered, it will not be placed back in the pool of available videos for potential delivery until all 16 videos have been used.

Once a microintervention is initiated, participants will receive an audible alert from the phone, and once activated, they will be notified that their stress levels appear elevated and that a recommended intervention is available to help reduce their stress. Next, they will receive a description of the activity they will engage in and how to be prepared to do it most effectively. They will then initiate the intervention video on the smartphone and follow the guided instructions. Each activity is designed so that previous training is unnecessary, but continued engagement may increase one's enjoyment and ease in doing the activity. At the end of each intervention, we will ask the participant to consider what worked with the intervention and plan how to use it in a future moment of stress. To this end, participants must consider when they are stressed and thus engage in some self-monitoring of their behaviors. Furthermore, by encouraging participants to use the activity on their own, they may be more likely to practice and improve their skills.

End-of-Day Intervention

We also wanted to provide a longer, more comprehensive intervention that covered the various domains of our broader intervention approach while providing an opportunity for more focused skill-building. This 20-minute singular intervention will be delivered in the evening when people may have more time to engage in the focused activity. It comprises multimodal components that cover several broad domains and represents a progression of many of the techniques and categories noted above. The goal is to guide an individual through more extensive training to reduce stress via improved affect and reduced perseverative cognitions. It is intended to be repeated to build general skills in the broad domains it covers. Similar to what was outlined previously, participants will receive stressor-focused framing before and after the intervention.

Intervention Delivery

As described earlier, in our previous work, we developed a stress assay that used self-reported survey data on different stress response indicators (ie, negative affect, perseverative cognitions, and subjective stress) and several stress targets (ie, RRPs) to be able to derive person-specific means and SDs [4,5]. Using this information, we were able to establish person-specific thresholds that would indicate meaningful derivations from an individual's norm (ie, identifying when they are stressed), as well as moments or days that were associated with poor health behavior enactment (eg, sleep and physical activity [9,10]). In this study, we aim to use this assay to identify "moments of risk" and intervene "just in time" to prevent downstream impacts on our health behaviors of interest (ie, sleep and physical activity). To provide intervention content at these moments of elevated stress while also maximizing the probability of participant engagement with the intervention content, we developed several pragmatic principles and boundaries to guide our intervention delivery. We refer to these general principles and rules as our intervention algorithms. These algorithms, when paired with the smartphone survey data in real time (ie, uploaded from the smartphone to the study server via mobile data plan), allow us to process the participant's survey data, aggregate the information across moments and days, provide a solution (ie, trigger) for whether or not intervention content should be delivered to the participant at that moment, and subsequently deliver the content to the participant, all in near real time.

To provide us with the greatest opportunity to interfere with current or ongoing stress responses and to maximize the probability of availability, we decided that interventions would only be delivered immediately following the completion of a survey (beeped or evening). This ensures that the participant is near their study smartphone should an intervention be delivered. It also allows us to intervene in active or ongoing stress responses in the contexts in which they occur. Although this approach has some limitations, such as requiring the individual to have the mental resources to engage with the intervention during periods of elevated stress, it was chosen in an attempt to optimize intervention impact and participant engagement. This approach also provides a natural connection between this study's intervention and survey types.

We have created 2 overlapping intervention algorithms to match intervention types (ie, microinterventions and end-of-day intervention) to survey data (ie, beeped and evening) while accounting for participant availability and burden. We developed the JIT intervention algorithm (Figure 2) to process information from the beeped surveys and trigger brief microinterventions during the day. Then, we developed the end-of-day intervention algorithm (Figure 3) to process information from the evening survey and trigger the longer end-of-day intervention. These algorithms, when combined, allow us to leverage our stress assay to detect moments of elevated stress responses in individuals at both the moment and day level, providing brief interventions in the moment or longer and more focused

interventions at the end of the day, when there are generally fewer daily demands on an individual.

In broad terms, the intervention algorithms use survey data from phase 1 to derive person-specific thresholds for each participant to inform intervention delivery in phase 2. This approach highlights the importance of selecting highly adherent participants to continue to phase 2 of the study. Once enrolled in phase 2, person-specific thresholds will be continuously updated as surveys are completed and intervention content is delivered. When survey data are collected from participants throughout the day and in the evening, it will be automatically uploaded and processed in the algorithm in real time to determine whether a participant's state indicates elevated stress levels. The algorithm will access all previous responses preceding that specific moment and the person-specific thresholds to do this. This information will then be combined with the current survey data to determine whether there is a meaningful deviation from an individual's norm. Each meaningful score will be weighted and combined with other meaningful scores for that specific moment to derive a weighted summary risk score. Each moment's risk level will then be evaluated based on the weighted summary risk score. Depending on this score, an intervention may be delivered to a participant at that moment, and, in some cases, a longer intervention may also be scheduled for delivery at the end of the day. This process will be repeated continuously for each participant as survey data are uploaded.

As an initial attempt to manage participant expectations and burden in this study, we incorporated a set of rules that will govern the upper and lower limits of intervention delivery (ie, ensure both a minimum and maximum frequency) and serve 2 purposes. First, our lower bound rules ensure that at least some intervention material is pushed out to each participant who is randomized into the JIT intervention condition, even in the absence of person-specific elevated stress. This includes providing a microintervention at least every 48 hours, regardless of whether elevated stress levels triggered an intervention, and an end-of-day intervention at least once every 5 days. We think this approach will keep participants engaged while providing a minimum "dose" of intervention content. We are also aware that participants in this study may experience stress below our intervention threshold (especially as their time and exposure to intervention content progresses) or that we may miss some stress responses or events with our survey schedule. Therefore, providing some minimum level of intervention content could provide the skills or resources to maintain the treatment effect, prevent future stress responses, or buffer any ongoing subthreshold stress. Second, the upper bounds of our intervention delivery will prevent us from overwhelming participants should they experience a bout of frequent or intense stress. To prevent undue participation burden related to engaging in microintervention content, we will limit microinterventions to a maximum of 3 on any given day (between 8 AM and 9 PM). We will provide the option to dismiss or delay any intervention for up to 20 minutes. We will have access to the uptake of all intervention content, including the date and time it was delivered and initiated by the participant, its duration, and the completion time.

Active Control Condition (Self-Monitoring and Stress Management Education)

In this study, participants enrolled in the active control condition will engage in self-monitoring for the duration of phase 2. Although there is some evidence that self-monitoring on its own might be a strategy for reducing negative affect and perseverative cognition [41], we wanted to provide a more stringent test of the "just in time" aspect of our stress management intervention. Therefore, we decided to bolster our comparison condition by providing access to a stress management education module comparable to any usual care stress management resource that an individual could access if needed. With this in mind, we developed 8 brief readings and tips that focused on stress education and the impact of stress in everyday life and adapted these materials into a web-based reading or reference module [40]. All participants enrolled in phase 2 of the study will have access to this module on the home screen of their study smartphone. If the module link is activated, they will be provided with a summary of the purpose of the module, followed by a list of 8 topics they can choose. Each module will take about 2 minutes to read and is followed by a brief, generic stress management tip that can be incorporated into everyday life. The stress management tips were derived from the same 4 categories outlined earlier, with 2 activities from each of the 4 categories included in the module. Participants will have access to this module 24 hours per day for the entirety of phase 2 and can access the readings as often as they want. User statistics will be collected each time a participant accesses the module, including the topics accessed, the number of times the module is accessed per day across the study, and a singular item about acceptability.

Proposed Analyses and Analytical Approach

All collected data will be subjected to a rigorous data-cleaning procedure to identify invalid data points (eg, out-of-range, implausible, and outlier variables will be scrutinized). General descriptive statistics (ie, mean, median, percentages, and SD) will be used to characterize the study sample. To evaluate the effect of the smartphone-delivered JIT intervention on RRP (specific aim 1), we will use mixed-effects models to evaluate any significant differences in RRP scores between the 2 study groups (ie, intervention group vs control group). In addition to the main effect differences between the 2 groups, we are interested in the potential cumulative effect of receiving multiple interventions across the 2-week study duration (testing a "dose" effect of the microinterventions) or whether potential benefits do not occur immediately but rather develop during the intervention period (eg, if it takes some time for the JIT intervention to lower stress responses). To evaluate this latter effect, we will test the group-by-time interaction effect in a multilevel (eg, momentary RRP nested within days, days nested within person, and person nested in group) mixed effect model. Analyses will be conducted using the SAS statistical program (version 9.4; SAS Institute Inc).

For our second aim, evaluating whether the intervention is associated with improved health behavior levels (ie, sleep and physical activity), we will use the same approach described for our first aim. That is, we will evaluate the overall treatment

effect and how this effect changes with time. Unique in this evaluation, we will test these relationships using continuous outcome (ie, the amount of time spent on these health behaviors) as well as the likelihood of meeting the threshold for recommended levels of physical activity (≥150 minutes of moderate to vigorous physical activity/week) and sleep (>7 hours/night). That is, we are interested in finding out whether participants who receive the innovative JIT intervention were more likely to meet recommended levels of physical activity or sleep.

Finally, we will test whether changes in RRPs mediate the group-level effects of the intervention on health behaviors. In other words, we want to evaluate whether any benefits observed in health behaviors are due to the changes in stress responses (RRPs). All evaluations will be conducted using an intent-to-treat analysis, with imputation conducted for missing data as appropriate, and a per-protocol (completers) analysis. Given the large number of analyses planned, we will evaluate and implement appropriate methods to reduce the likelihood of false positives (eg, false discovery corrections). Theoretically informed but more exploratory analyses will be conducted to examine if there are individual difference moderators of observed effects.

Results

Participant recruitment for the trial was initiated on August 15, 2022. Initial enrollment was completed by June 9, 2023, with 213 participants enrolled. Each of the multiple data sources (eg, ecological momentary assessment survey reports, physical activity, and sleep) is being cleaned and processed for use. Study analyses have not yet begun.

Discussion

Principal Findings

In this trial, we will evaluate the effectiveness of a JIT stress management intervention, delivered via a study smartphone, on the outcomes of stress responses, sleep, and physical activity. We hypothesize that those receiving the JIT intervention and standard stress management material will show better stress response processes, greater engagement in physical activity, and better sleep than those receiving only standard stress management material.

This study will provide valuable insight into the potential utility of characterizing, in a personalized manner, components of everyday stress responses and using individualized moment and day-level risk indicators to deliver JIT stress management microinterventions (relative to generic stress management educational materials coupled with intensive self-monitoring). The JIT stress management microintervention condition is predicted to enhance stress response (ie, reduced reactivity, better recovery, and less pileup) across multiple indicators (subjective stress, affect, and cognitions) relative to the control condition. In turn, it is thought that enhanced stress response processes will allow individuals to successfully engage in more positive health behaviors; namely, the group receiving the JIT intervention will exhibit more physical activity, less sedentary time, and improved sleep.

Our stress response components (RRPs) have been developed based on preliminary work and theoretical considerations; however, it is important to note that both their specific implementation (eg, the level at which momentary risk is presumed) and how they are used to trigger JIT microintervention can be readily adapted. Thus, this study is not intended to serve to finalize or concretize the specific implementation of this approach or the intervention itself (eg, the triggering algorithm and microintervention content); rather, it is meant to serve as a foundational proof-of-concept demonstration of this approach that can (and should) be adapted, refined, and tailored by others to specific samples, contexts, and research or clinical questions. It may also be fruitful to consider matching microintervention content to the nature or type of stressor experienced and the context (eg, location and social features) in which it was experienced.

This trial requires a high level of engagement by participants. Although there is the presumptive benefit of receiving stress management to enhance motivation and no side effects as might be experienced in a pharmaceutical trial, there is the requirement of actively responding to multiple brief surveys each day for a lengthy period. Clearly, this raises the possibility of self-selection, biasing the type of person who ultimately enrolls in the study. If the results of this trial indicate positive benefits for our primary outcomes, participant burden will have to be carefully considered moving forward to address issues related to generalizability and potential for dissemination.

Several other domains represent exciting future directions for this line of work to continue to refine, extend, and enhance the JIT microintervention approach we have developed. For example, developing and implementing additional stress target measurement indicators (eg, physiology and positive affect) for inclusion in the stress assay should be possible. Similarly, this work can be extended to encompass various health behaviors at different temporal scales. This stress assay can be used for intervention in "intensive" ways and integrated into more standard intervention formats (eg, face-to-face). For example, it can generate a highly reliable between-person risk indicator for risk stratification; moreover, our assay will provide risk components to allow personalized (precision) approaches to (standard) intervention. The time-varying nature of the stress assay would also allow for the development and implementation of not only JIT but also adaptive interventions, ones that "learn" what is effective for each individual and deliver what is most helpful for that individual at that moment (or stressful moments anticipated to occur in the near future).

Conclusions

This trial evaluates the effects of a novel, personalized JIT stress management intervention on everyday stress responses and the enactment of physical activity and sleep behaviors. Overall, we hypothesize that we will see the benefits of intervention over our active control condition and hope that this stress assay and adaptive JIT intervention approach will prove a valuable assessment and intervention tool for measuring and treating stress and stress-related disorders.

Acknowledgments

This study is supported by the National Institutes of Health Science of Behavior Change Common Fund Program through awards given by the National Institutes of Aging (grants UH2-AG052167 and UH3-AG052167).

Data Availability

The datasets generated during and analyzed during this study are not yet publicly available while data analysis is ongoing but are available from the corresponding author on reasonable request.

Authors' Contributions

The study was conceptualized by MJZ, MJS, DMA, OMB, DEC, RSS, SBS, CNS, PAG, and JMS. The stress assay was developed by MJZ, MJS, DMA, OMB, DEC, DM-C, JK, RSS, SBS, MJLT, and JMS, and the intervention content was developed by JAJ, MJZ, DEC, CNS, EMR, PAG, and JMS. The intervention algorithm was developed by JAJ, MJZ, MJS, DMA, DM-C, JK, RSS, SBS, MJLT, and JMS. The trial implementation was performed by JAJ, EMR, NLS, and JMS. All authors reviewed and approved the manuscript before submission.

Conflicts of Interest

Outside of this work, OMB received subcontract grants to The Pennsylvania State University from Proactive Life LLC (formerly Mobile Sleep Technologies) doing business as SleepSpace (NSF/STTR #1622766, NIH/NIA SBIR R43-AG056250, R44-AG056250).

Multimedia Appendix 1
Peer review report from the Science of Behavior Change Common Fund Program - National Institutes of Aging (National Institutes of Health, USA).
[PDF File (Adobe PDF File), 99 KB - resprot_v14i1e58985_app1.pdf]

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Abbreviations

JIT: just-in-time
RRP: reactivity, recovery, and pileup

Edited by T Leung, D Khajeei; submitted 29.03.24; this is a non–peer-reviewed article;accepted 04.11.24; published 22.01.25.

Please cite as:
Johnson JA, Zawadzki MJ, Sliwinski MJ, Almeida DM, Buxton OM, Conroy DE, Marcusson-Clavertz D, Kim J, Stawski RS, Scott SB, Sciamanna CN, Green PA, Repka EM, Toledo MJL, Sturges NL, Smyth JM
Adaptive Just-in-Time Intervention to Reduce Everyday Stress Responses: Protocol for a Randomized Controlled Trial
JMIR Res Protoc 2025;14:e58985
URL: https://www.researchprotocols.org/2025/1/e58985
doi:10.2196/58985
PMID:

Protocol

Comparative- and Cost-Effectiveness Research Determining the Optimal Intervention for Advancing Transgender Women With HIV to Full Viral Suppression (Text Me, Alexis!): Protocol for a Randomized Controlled Trial

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Abstract

Background: Many transgender women with HIV achieve suboptimal advancement through the HIV Care Continuum, including poor HIV health care usage, retention in HIV medical care, and rates of viral suppression. These issues are exacerbated by comorbid conditions, such as substance use disorder, which is also associated with reduced quality of life, increased overdose deaths, usage of high-cost health care services, engagement in a street economy, and cycles of incarceration. Thus, it is critical that efforts to End the HIV Epidemic include effective interventions to link and retain transgender women in HIV care through full viral suppression.

Objective: This study builds on the promising findings from our two Health Resources and Services Administration-funded demonstration projects, The Alexis Project and Text Me, Girl!, which used peer health navigation (PHN) and SMS text messaging, respectively, for advancing transgender women with HIV to full viral suppression. Though the effectiveness of both interventions has been established, their comparative effectiveness, required resources or costs, cost-effectiveness, and heterogeneous effects on subgroups, including those with substance use disorder, have not been evaluated. Given the many negative personal and public health consequences of untreated or undertreated HIV, and that HIV services for transgender women are frequently delivered in resource-limited, community-based settings, a comprehensive economic evaluation is critical to inform decisions of stakeholders, such as providers, insurers, and policy makers.

Methods: Text Me, Alexis! is a 3-arm randomized controlled trial. Participants (N=195) will be randomized (1:1:1) into: PHN alone (n=65), SMS text messaging alone (n=65), or PHN+SMS text messaging (n=65). Using the same time points as the Health Resources and Services Administration demonstration projects, the repeated-measures design will assess participants at baseline, 3, 6, 12, and 18 months post randomization. Over the course of the 90 days, participants in the PHN arm will receive unlimited navigation sessions; participants in the SMS text messaging arm will receive 270 theory-based SMS text messages (3 messages daily) that are targeted, tailored, and personalized specifically for transgender women with HIV; and participants in the PHN+SMS text messaging arm will receive a combined PHN and SMS text message intervention. The desired outcome of Text Me, Alexis! is viral suppression and cost-effectiveness.

Results: Recruitment began on April 10, 2024, and the first participant was enrolled on April 11, 2024. Data collection is expected to be completed in July 2027. Primary outcome analyses will begin immediately following the conclusion of the follow-up evaluations.

Conclusions: Transgender women are a high-priority population for reaching End the HIV Epidemic goals. Findings have the potential to improve individual and population health outcomes by generating significant improvements in viral suppression among transgender women and guiding service provision and public policy.

International Registered Report Identifier (IRRID): DERR1-10.2196/65313

(JMIR Res Protoc 2025;14:e65313) doi:10.2196/65313

KEYWORDS

HIV/AIDS; transgender women; SMS text messaging; peer health navigation; HIV Care Continuum

Introduction

Background

Current national data suggests that over 14% of transgender women in the United States are currently living with HIV [1], a rate at least 30 times higher than that observed in the general population aged 13 years and older (0.44%) [2]. National data on transgender women with HIV demonstrate lower rates of linkage to HIV care, retention in care, antiretroviral therapy (ART) uptake, ART adherence, and viral suppression than cisgender men and women [3,4]. Thus, any concerted effort to End the HIV Epidemic must include effective interventions to link and retain transgender women in HIV care through durable viral suppression [5,6]. The HIV prevalence rate of transgender women in Los Angeles County (LAC) exceeds national prevalence estimates, with an estimated 33% of transgender women with HIV, of whom only 58% achieved sustained viral suppression in 2022 [7]. As such, transgender women have been identified as a high-priority population, and LAC as a priority county for Ending the HIV Epidemic [6-8].

Transgender women in the United States experience numerous barriers to retention in HIV care, ART adherence, and viral suppression, including structural determinants of health, such as poverty and housing instability [9,10]; lack of access to health insurance [11]; transphobic stigma and discrimination from providers, including HIV specialists [11-13]; and disproportionate rates of individual-level health disparities including lack of perceived support [14], experiences of violence [15], cycles of incarceration [10,16], and untreated or undertreated substance use disorders (SUD) and mental health disorders, which are highly comorbid [17,18]. A 17-year comparison study in LAC demonstrated that these conditions have worsened among transgender women, with decreased levels of income and housing stability, increased incidents of physical harassment and abuse, and increased rates of HIV and sexually transmitted infections [19].

Evidence demonstrates that transgender women who are successfully linked and retained in HIV care go on to achieve rates of viral suppression similar to that of cisgender men and women, confirming linkage and retention to HIV care as critical intervention outcomes [20,21]. Among transgender women, access to gender-affirming resources and care [6,13], greater medication self-efficacy [22], and tailored HIV messaging (eg, addressing fears of ART or hormone drug-drug interactions) [23-25] are all associated with higher odds of ART uptake and adherence.

As an intervention modality, peer health navigation (PHN) is considered generally well-suited for application among transgender women, as it can be tailored to each participant's needs, and is premised on increasing participants' self-efficacy [20,26,27]. Interventions including PHN have been shown to be efficacious in improving rates of HIV care engagement, ART adherence, and viral suppression among transgender women [28-30]. However, due to the intensity of PHN, some transgender women may prefer a lower-intensity intervention such as SMS text messaging to deliver gender-affirming, transspecific SMS text messages, which are based on theories to improve self-efficacy and avoid or reduce health risks. SMS text messaging is a viable option since telehealth and technology-based interventions have demonstrated both acceptability and effectiveness among transgender women [23,28,29,31,32].

The promising findings gleaned from our team's two Health Resources and Services Administration-funded Special Projects of National Significance demonstration projects guided the Text Me, Alexis! randomized controlled trial design. Reback et al [33] demonstrated that increased attendance to PHN sessions was associated with significant and sustained (ie, through 18 months) achievement of both behavioral (coefficient range 0.12-0.38) and biomedical (coefficient=0.10) HIV milestones (all $P \leq .01$); 85% were linked to HIV care, and 83% of the participants that enrolled detectable and achieved a 1 log viral load reduction went on to achieve viral suppression [28]. Additionally, Reback et al [24] produced significant and sustained (ie, through 18 months) overall increases in ART uptake, self-reported ART adherence as "excellent," and achievement of an undetectable viral load defined as 200 copies/mL (49% vs 77%, 5% vs 38%, 35% vs 52%, all $P \leq .001$) [25]. The Alexis Project has been included in the Substance Abuse and Mental Health Services Administration's intervention guide for persons with substance use and mental health disorders, and Text Me, Girl! has been included in the Ryan White HIV/AIDS Best Practices Compilation. Thus, the appropriate next step was Text Me, Alexis!, the randomized controlled trial to simultaneously assess the relative efficacy of these interventions, and their respective costs and benefits to determine their efficiency and inform widescale implementation.

An economic evaluation was included to inform "real-world" resource allocation decisions faced by relevant stakeholders. Economic value (ie, the extent to which a stakeholder's resources are efficiently allocated) is a fundamental concern for any intervention targeting transgender women with HIV, given the number of persons in need and the fact that services for transgender women are frequently delivered in resource-limited, community-based settings [3,19,20].

Primary and Secondary Aims

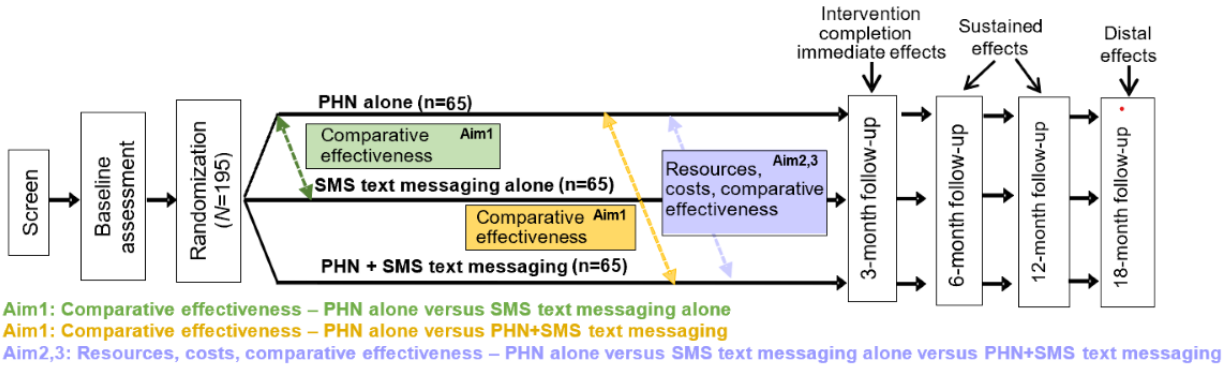
The primary aim of the Text Me, Alexis! study is to determine the comparative effectiveness of PHN alone, SMS text messages alone, and PHN+SMS text messaging combined with the goal of viral suppression and cost-effectiveness, and to identify the resources (eg, time and materials) required to prepare for, implement, and sustain each intervention, and estimate the associated costs. Further, the study will conduct a comprehensive cost-effectiveness analysis to determine the relative value of each intervention from the health care–sector, state policy makers, and societal perspectives. The secondary aim of the study is to determine heterogeneous intervention effects of PHN alone, SMS text messaging alone, and PHN+SMS text messaging due to social and structural determinants of health (eg, poverty, housing insecurity, food scarcity, educational attainment, and lack of insurance) and differing individual-level characteristics (eg, racial or ethnic identity, age, SUD—by type, and time since HIV diagnosis) among transgender women with HIV.

Methods

Study Design

Following screening, informed consent, and baseline assessment, participants (N=195) are randomized (1:1:1) into: PHN alone (n=65), SMS text messaging alone (n=65), or combined PHN+SMS text messaging (n=65). The 3-arm repeated-measures design will assess participants at baseline, 3 (immediate effects), 6, 12 (sustained effects), and 18 (distal effects) months post randomization to determine the relative effectiveness of the interventions, including heterogeneous treatment effects across subgroups and over time, the implementation and sustainment costs of each intervention, and their cost-effectiveness relative to one another. The study uses an "intent-to-treat" design whereby all assessments are administered to all participants regardless of their level of participation or retention in the study (Figure 1).

Figure 1. Comparative-effectiveness and cost-effectiveness design. PHN: peer health navigation.

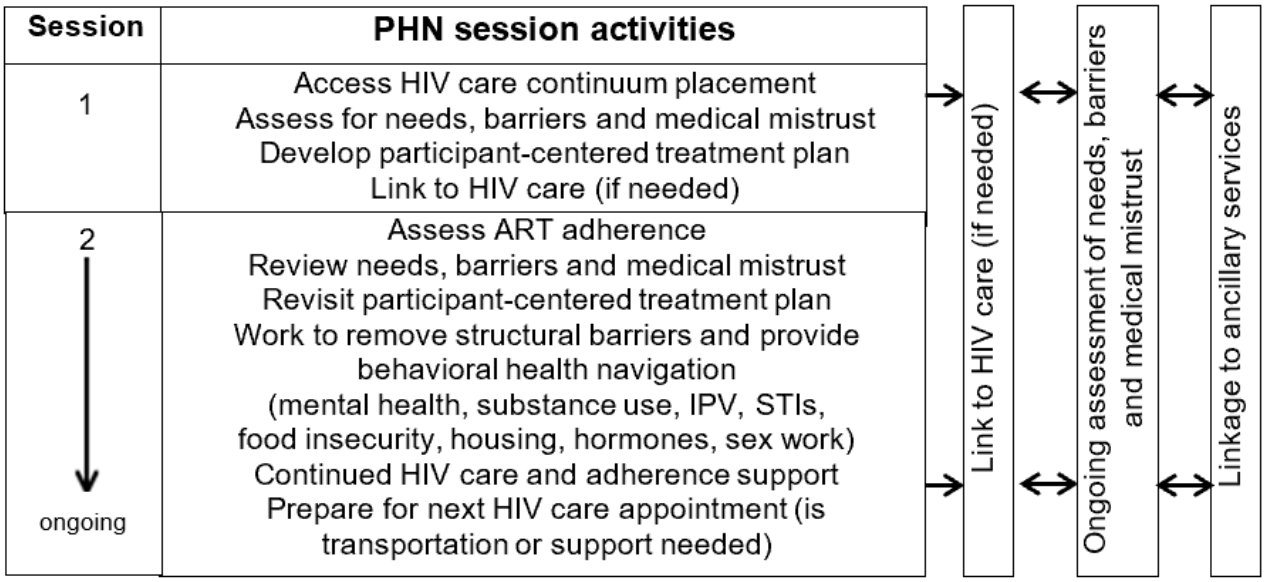


Study Arms

PHN

PHN is based on the theoretical foundation of social cognitive theory (SCT). Participant-centered PHN helps to (1) identify barriers to HIV care, (2) identify and link participants to needed auxiliary services, and (3) increase participants' self-efficacy in working with HIV care providers and other social service and treatment facilities. PHNs do not provide counseling or psychotherapy; they work with each participant to successfully navigate complicated health care and social service systems. The PHN intervention uses an individualized, participant-centered treatment plan with the goals of removing multiple and complex barriers that can impede linkage to and retention in HIV care and medication adherence to achieve virological suppression. Each participant works with a PHN to develop a participant-centered treatment plan and get linked to HIV care or other needed auxiliary physical, mental health, and psychosocial services (eg, hormone therapy, dental care, hepatitis testing or care, SUD treatment, mental health treatment, legal services, and job training or development; Figure 2). A priority of the first session is to schedule an HIV care appointment for the participant if needed. The PHN also works with each participant to establish HIV self-efficacy regarding her treatment plan. To establish an immediate connection, participants are introduced to a PHN immediately following randomization. PHN sessions are unlimited for 90 days.

Figure 2. PHN intervention delivery system. ART: antiretroviral therapy; IPV: intimate partner violence; PHN: peer health navigation; STI: sexually transmitted infection.



SMS Text Messaging

The SMS text messages are based on, and equally distributed across, three theories: social support theory (SST) [34-36], social cognitive theory [37,38], and health belief model (HBM) [39]. Table 1 illustrates how the SMS text message library was developed to have a theoretical foundation and be transculturally responsive. Participants receive three daily, theory-based SMS text messages for 90 days (270 unique scripted messages); participants do not receive the same scripted SMS text message twice. SMS text messages are evenly arrayed across: (1) HIV Care Continuum (HIV positivity/physical and emotional health, linkage/retention in HIV Care, and ART adherence/viral load suppression); and (2) theoretical foundation (SST, HBM, or SCT; Table 2).

SMS text messages are transmitted through gradual automation administration daily, including weekends, in real time, within a 10-hour period, and every 5 hours. Optimum hours were determined to be noon, 5 PM, and 10 PM, though participants may personalize the schedule to any 10-hour period and can choose to have the messages delivered through their cell phone or email. Both dosing (ie, three messages per day) and timeframe (ie, 10 hours) were determined during our prior SMS text messaging studies [23,25]. The intervention was designed to be cost-efficient, sustainable, and easily scaled by health clinics or community agencies. The automated SMS text message delivery system was developed by Dimagi [40]. Participants are asked to notify a research assistant immediately if they lose their cell phone or change their phone number or email address.

Table 1. Sample Text Me, Girl! SMS text messages: displays theoretical foundation, HIV Care Continuum placement, and adaptation from a general message to a transspecific message.

Theoretical foundation	HIV Care Continuum	General message	Transspecific message
Social support theory	HIV positivity/physical and emotional health	Take care of yourself	Trans pride is taking care of yourself
Health belief model	Linkage/retention in HIV care	See your doctor	Protect your trans beautiful body, see your doctor
Social cognitive theory	ART[a] medication adherence	Take your meds	Take your meds, girl! You can do it!

[a]ART: antiretroviral therapy.

Table 2. SMS text message content by theoretical foundation.

	HIV Care Continuum			Total
	HIV positivity/physical and emotional health	Linkage/retention in HIV care	ART[a] adherence/viral load suppression	
Theoretical foundation				
Social support theory	30	30	30	90
Health belief model	30	30	30	90
Social cognitive theory	30	30	30	90
Total	90	90	90	270

[a]ART: antiretroviral therapy.

PHN+SMS Text Messaging (Combined)

Participants in the PHN+SMS text messaging arm receive the same PHN and SMS text messaging interventions described above, but in concert to determine the effectiveness of the combined intervention when compared to PHN or SMS text messaging alone.

Theoretical Mechanisms of Behavioral Change

The theoretical foundations of the interventions serve as mechanisms of behavior change, increasing advancement through the HIV Care Continuum and maximizing potential public health impacts.

SST

According to SST, social support encompasses instrumental, emotional, and informational assistance. These forms of social support have been shown to mediate the relationship between stressful events and health outcomes [34-36].

HBM

HBM asserts that believing specific health behaviors can reduce threats to health predicts one's likelihood of engaging in protective health behaviors. The HBM is most effective when informative messages are culturally appropriate to the target population [39].

SCT

SCT posits interactive causal relationships among personal determinants, behavior, and environmental influences [37,38], and is designed to improve participant self-efficacy. Effective HIV care interventions must increase individuals' self-efficacy and guide them in developing self-regulation skills, offer practice and feedback opportunities, and engage resources to maintain health-promoting behavior change.

Participants

Inclusion criteria are (1) identifying as a transgender woman; (2) being 18 years or older; (3) having a verified HIV-positive serostatus; (3) not currently in HIV care, or had not had an HIV care visit in the previous 6 months, or had a viral load of ≥200 copies/mL on her last laboratory test result, or not currently prescribed ART, or prescribed ART but does not rate her ability to take all her medications as "excellent"; and (4) ability to receive daily SMS text messages on either a personal cell phone or via an email account. Potential participants must be able and willing to provide informed consent and comply with study requirements. Individuals are excluded if they do not meet all eligibility criteria.

Recruitment and Enrollment

Six recruitment strategies are used to ensure a diversity of participants are enrolled. (1) Web-based: banner ads and digital flyers will be placed through geo-mapping on appropriate websites and social media platforms and are optimized for mobile platforms at 300×250 pixels. (2) Print media: local ads will be placed in print media for transgender women. (3) Outreach: 2 research assistants conduct outreach in identified areas where transgender women congregate. Optimal sites, days, and times have been identified, including bars or clubs, motels, parks, boulevards, street corners, mini markets, boutiques, wig shops, electrolysis offices, salons, and lingerie stores. Outreach locations are continually modified through ongoing community mapping and input from the Community Advisory Board. (4) Poster advertisement and club cards: posters are placed throughout the research site and community collaborating sites to inform potential participants how to receive further information. Club cards will be distributed at dance clubs, bars, and transspecific events. (5) In-reach: potential participants often drop into the research site to inquire about services or to receive a daily hot meal. (6) Long-chain referral: current study participants are asked to recruit a maximum of three potential new participants. All recruitment and promotional activities are discussed at Community Advisory Board meetings.

Potential participants who inquire about the study are scheduled for intake within 48 hours. At intake, potential participants are screened for eligibility, complete the informed consent process, and take an informed consent quiz to verify their understanding of study procedures. At baseline, potential participants complete the baseline assessment, collect biospecimens, and are randomized to an intervention arm. Potential participants are considered enrolled and given a study ID number following randomization.

Randomization

Stratified block randomization with random block sizes is used to assign participants to each of the 3 study arms. To ensure balance with respect to certain covariates, participants are grouped by three stratification factors: (1) age (<35 and ≥35

years), (2) race or ethnicities (Latinx, all other race or ethnicities), and (3) HIV Care Continuum placement (linked, not linked to HIV care). Block randomization helps ensure balance in the number of participants assigned to each arm, while random block sizes make the sequence of assignments less predictable to research staff.

Measures

All data will be collected on an audio computer-assisted self-interview administered via the Qualtrics system. The following describes the measures used to address the study's specific aims.

Diagnostic and Statistical Manual of Mental Disorders (Fifth Edition)

The *DSM-5* (*Diagnostic and Statistical Manual of Mental Disorders* [Fifth Edition]) diagnostic items are necessary to make a determination of mild, moderate, or severe SUD. These findings are used to describe the sample characteristics and to determine the extent and effects of these individual-level health disparities as barriers to advancement along the HIV Care Continuum.

HIV Health Assessment

The assessment records demographics (eg, sexual identity, age, and race or ethnicity), educational attainment, housing status, access to insurance, HIV treatment status (including the position in the HIV Care Continuum), HIV medication status (including medication type and dose), and self-reported ART adherence.

The Los Angeles Transgender Health Survey

The instrument consists of seven modules: screening, sociodemographic characteristics, health care access and medical history, sexual behaviors (at all stages of gender transition), drug and alcohol use, legal and psychosocial issues, and HIV prevention.

Substance Use Frequency

This brief assessment assesses substance use, injection drug use, and injection protocols in the past 30 days.

HIV Treatment Adherence Self-Efficacy Scale

The HIV Treatment Adherence Self-Efficacy Scale (HIV-ASES) consists of 12 items assessing participants' self-efficacy to adhere to their HIV medication regimen, to measure behavior change associated with SCT [41].

HIV Treatment Optimism Scale

The HIV Treatment Optimism Scale is a 19-item scale associated with components of the HBM (perceived susceptibility to disease, perceived severity of the disease, perceived benefits of preventive behavior, and barriers to preventive behavior) [42].

Inventory of Socially Supportive Behaviors

The Inventory of Socially Supportive Behaviors (ISSB) is a 40-item scale measuring instrumental, emotional, and informational dimensions of SST [36,43].

Rapid HIV Antibody Test

Potential participants are administered a rapid HIV antibody test (INSTI HIV 1/HIV 2) during the screening process to verify HIV-positive status. Participants who show documentation of HIV-positive serostatus (eg, laboratory results, ART prescription) are not given an HIV antibody test.

Urine Drug Screen

Urine samples are tested using a 5-panel urine dip card [44], with drug detection cut-off values at: amphetamines (1000 ng/mL), cocaine (300 ng/mL), opiates (300 ng/mL), methamphetamines (500 ng/mL), and tetrahydrocannabinol (50 ng/mL). Valid samples are indicated by the temperature of the sample (33 °C to 36 °C) [44].

Viral Load Test

Participants receive a viral load test at each time point to assess virologic suppression or control as indicated by an undetectable HIV-1 level on the Aptima HIV-1 Quant Dx assay, which is the lower limit of quantification of ≤30 copies/mL [45]. Participants who access their electronic health records and provide viral load results within 14 days of the assessment are not reassessed with viral load testing performed as part of the study.

Drug Abuse Treatment Cost Analysis Program

The Drug Abuse Treatment Cost Analysis Program is a standardized, customizable tool designed to help identify intervention resources across diverse settings for the purposes of estimating the implementation and sustainment costs associated with the intervention [46].

Nonstudy Medical and Other Services

The usage of health care services by participants is self-reported using a time-anchoring methodology via the Nonstudy Medical and Other Services form [47-49]. Health care services will include nonstudy: HIV care, inpatient, outpatient, and emergency department services; SUD treatment medications; residential and outpatient SUD treatment days; hospital SUD detoxification days; and mental health treatment visits. This information is measured for the 90 days prior to baseline, then "since the last assessment." The use of nonmedical and other resources required for the economic evaluation from state policy maker and societal perspectives (eg, criminal-legal, labor productivity, and travel time to medical care) is also self-reported and collected via the Nonstudy Medical and Other Services form.

Patient-Reported Outcomes Measurement Information System-Preference

The PROMIS (Patient-Reported Outcomes Measurement Information System)-Preference (PROPr) measures a participant's health-related quality-of-life across the following PROMIS domains: cognitive function abilities, depression, anxiety, fatigue, pain interference, pain intensity, physical function, sleep disturbance, and ability to participate in social roles and activities [50-52]. The PROPr is also capable of generating a health utility index value, based on the participant's scores for each domain, that represents the general US

population's preference for the respondent's current health state. PROPr has 5 levels for each domain, ranging from "no problems" to "extreme problems." The health-utility value produced by PROPr can range from –0.022 to 1, where 0 represents death, 1 represents perfect health, and values below 0 represent states perceived to be worse than death. The health-utility value is used to calculate quality-adjusted life-years (QALYs) [50,53].

Statistical Analyses

Aim 1

The primary outcome of HIV care will be viral suppression (defined as less than 200 copies/mL). Secondary outcomes include the HIV-ASES, the HIV Treatment Optimism Scale, the ISSB, and urine drug screen results (test results for each of the 5 substances identified in the urine drug screen will be treated as different indicators). These outcome variables will be assessed at baseline and 3, 6, 12, and 18 months post enrollment. The resulting dependent variables will fall into one of two categories: (1) dichotomous variables (primary outcome: virologic suppression, and secondary outcome: urine drug screen results), assumed to follow a binomial distribution; or (2) continuous random variables (secondary outcomes: HIV-ASES, HIV Treatment Optimism Scale, ISSB scores), assumed to follow a normal distribution. All distributional assumptions will be evaluated prior to the conduct of analyses, and statistical methods chosen accordingly. Each of these dependent variables will be separately regressed on treatment condition (PHN alone vs SMS text messaging alone vs PHN+SMS text messaging), a set of baseline covariates (individual-level demographic characteristics), and time-varying covariates (social and structural determinants of health), using hierarchical linear regression where responses at each time point are nested within individuals. All analyses will be conducted on available study-related data from all participants, regardless of whether or when they drop out of treatment. The effect of interest will be a time × treatment condition interaction effect which will estimate the differential course and impact of the three intervention modalities over the follow-up period.

A generalized linear mixed model (GLMM) [54-56] will be used to conduct analyses of all outcomes following an intent-to-treat approach. The GLMM is an ideal statistical procedure for analyzing a broad class of longitudinal outcomes, including costs. As described above, key indicators of HIV care will be regressed on treatment conditions and a series of baseline and time-varying covariates. Treatment condition will be used to predict the slope of time, creating a time × treatment interaction term that is the effect of interest in the proposed study. We will also report on the relationships between time-varying covariates and the outcome measures, including time-shifted analyses where the value of the covariate at a previous timepoint is used to predict the outcome measure at a subsequent timepoint. Hypothesis testing for any given outcome will involve fitting the statistical model of interest and testing the effect of interest, as well as all other estimable effects in the model. We will use an iterative model-building approach where the simplest model is fit to the data first, and additional explanatory factors are added iteratively, in order of theoretical importance. Likelihood ratio tests are used to determine if the more complicated of the 2 models is a significant improvement over the simpler model. Variables of interest such as those specified in Aim 1 will always be included in the final model as the statistical tests of those parameter estimates (be they significant or nonsignificant) are of primary interest to this study.

Aims 2 and 3

The economic analyses will follow well-established guidelines [57-59]. The study will incorporate all resources or costs associated with the PHN, SMS text messaging, and PHN+SMS text messaging interventions from the health care sector, state policy maker, and societal perspectives [58-60]. The health care sector perspective includes all formal medical costs incurred by the system on behalf of participants, including the cost of the intervention, and participant out-of-pocket costs. The state policy maker perspective is crucial to informing resource allocation decisions on behalf of the public, who is primarily responsible for funding health care among this underserved population, given data indicating that most transgender women are either public health care insurance beneficiaries or uninsured [11,19]; moreover, the direct costs associated with criminal-legal resources, social safety-net programs, etc are paid for using public funds. In addition to the resources or costs included in the state policy maker perspective, the societal perspective accounts for those associated with untreated or undertreated HIV and comorbid conditions, such as premature mortality, reduced labor productivity, and those incurred by victims of crime [61,62].

The resources required to implement and sustain each intervention in a "real-world" setting (Aim 2) will be estimated using a detailed microcosting analysis, guided by a tailored version of the Drug Abuse Treatment Cost Analysis Program. The microcosting analysis will consist of gathering relevant administrative data and conducting semistructured interviews with site personnel in order to capture quantitative data regarding the resources (time and materials) used to deliver the interventions. The intervention implementation phase is considered to be the time period from conception (including planning activities) until the "steady state." Resources will be categorized as "fixed start-up" (incurred once), "time-dependent" (recurring, but does not vary with the number of participants), and "variable" (used every time a participant is served). The site visits and initial interviews will be conducted early in the study (~6 months following the first randomization). Follow-up interviews will be conducted virtually upon the study reaching a "steady state" (~12 months following the initial interview), to identify the time-dependent and variable resources required to sustain the intervention. "Steady state" will be determined with the assistance of site personnel. Implementation and sustainment costs will be estimated by assigning nationally representative price weights to the identified resources [58]. Research-specific costs will be excluded.

After estimating the implementation and sustainment costs associated with each intervention (PHN, SMS text messaging, and PHN+SMS text messaging), the relative value of each will be estimated according to the stakeholder perspective. This

process entails capturing all relevant resources used by participants in each arm, assigning nationally representative price weights to them, estimating the predicted mean costs, and testing for differences between resource categories. Estimating the incremental costs between arms according to resource category allows for a careful evaluation of the downstream savings resulting from improvements in HIV care and reductions in related risk behaviors. These include savings resulting from reduced usage of high-cost health care (eg, emergency department visits and inpatient stays) and criminal-legal resources, as well as increased labor and other forms of productivity. Price weights will be derived from sources reflecting national "real-world" costs faced by state policy makers and society.

The primary outcome of the cost-effectiveness analysis (Aim 3) will be the incremental cost-effectiveness ratio (ICER), which will be calculated as the incremental, predicted-mean cost of a given intervention relative to an alternative, divided by the incremental predicted-mean effectiveness of the 2 interventions. The primary measure of effectiveness for the economic evaluation will be QALYs. The secondary measure of effectiveness will be advancement along the HIV Care Continuum. The QALY is a measure that combines the health-related quality-of-life associated with an individual's health state and the time spent in that state and is recommended as the primary effectiveness measure in economic evaluation studies due to its ability to be compared across interventions and disorders [58,63]. In addition, generally accepted thresholds for defining value have been established for QALYs, unlike clinical measures [64,65]. The HIV Care Continuum is an important and widely accepted model or tool for assessing HIV care outcomes at both an individual and a public health level; thus, the additional cost required to achieve a one-step increase along the HIV Care Continuum for the average transgender woman with HIV will be a critically important clinical and policy-relevant measure. Two ICERs (one for each effectiveness measure) will be calculated for each stakeholder perspective at both 3 months (intervention completion; immediate effects) and 18 months (distal effects).

To help address censored data, we will model the person period and estimate all regressions using a multivariable GLMM. Separate regressions will be estimated to predict the mean value for each resource category, at each time period, by study arm. The statistical method of recycled predictions will be used to obtain the final predicted mean values [58]. Similarly, individual regressions will be used to predict the health utility index value and HIV Care Continuum steps gained for each participant, at each time point. QALYs gained will be estimated using the predicted health utility values and the area under the curve methodology [58]. The most appropriate distributional and link functions for each GLMM regression will be chosen according to the fit of the observed data [58].

To account for sampling uncertainty in point estimates, the *P* values and SEs will be estimated using nonparametric bootstrapping techniques within the multivariable framework combined with methods to address missing data based on recommended approaches [66]. All monetary values will be adjusted for inflation, and all measurements obtained beyond 12 months of baseline will be discounted for time preference using the recommended rate of 3% [58,65].

The most cost-effective strategy for each outcome measure (QALYs; HIV Care Continuum placement) will be determined using the rules of strong and extended dominance. Parametric methods based on parameters obtained from bootstrapping will be used to estimate cost-effectiveness acceptability curves for each ICER, which illustrate the probability that an intervention is cost-effective for different value thresholds [57].

Power Analysis

A simulation approach was used to conduct the power analysis and determine that N=195 (65 per arm) was an appropriate sample size to detect the effect of each intervention on our primary outcome, and the likelihood of virologic suppression over time [67]. Power by simulation is more flexible than traditional approaches because it can estimate power under a wide variety of circumstances, including when these assumptions are not met.

Ethical Considerations

All study procedures are approved by the Western Institutional Review Board (Study #1352118; Institutional Review Board Tracking #20231531). This trial has been registered at ClinicalTrials.gov under the number NCT06408350. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study.

Results

Recruitment began on April 10, 2024, and the first participant was enrolled on April 11, 2024. Recruitment spans approximately 33 months; enrollment goals are approximately 6 enrolled participants per month. Data collection, including all follow-up assessments, is expected to be completed in July 2027.

Discussion

Principal Findings

Many transgender women have suboptimal advancement through the HIV Care Continuum, including poor HIV health care usage, retention in HIV medical care, and rates of viral suppression; moreover, these issues are exacerbated by comorbid conditions such as SUDs. The Text Me, Alexis! study is a comparative-effectiveness research trial with a comprehensive economic evaluation that builds upon the promising findings of two Health Resources and Services Administration-funded demonstration projects in order to identify the optimal intervention for advancing transgender women with HIV to full viral suppression. Though the effectiveness of the demonstration projects has been established, their comparative effectiveness, required resources or costs, cost-effectiveness, and heterogeneous effects on subgroups, including those with SUDs, have not been evaluated.

Challenges

There are several challenges to the Text Me, Alexis! study. First, housing instability, substance use, engagement in sex work, and other individual-level, social, and structural disparities may interfere with study participation. The PHN alone and PHN+SMS text messaging arms were designed to address these issues and work with each participant to assess and minimize or remove barriers and link participants to an array of ancillary social services. Additionally, in the demonstration project, despite experiencing several health disparities including low educational attainment, low income, and housing instability, SMS text messaging alone demonstrated significant improvements in ART uptake, ART adherence, and achievement of an undetectable viral load, which were durable through 18-month follow-up. Second, episodes of short-term incarceration may interrupt study progress and follow-up assessment rates, due to factors such as actual or perceived participation in the street economy, or minor homeless infractions. Study staff monitor the public records database for participants who miss appointments. When an incarcerated participant is found, we begin a correspondence with the participant immediately upon release. Third, loss of ART or selling ART due to lifestyle needs ("diversion")—ART adherence will be stressed through the participant-centered treatment plan and via adherence-specific SMS text messages, including strategies for keeping medication safe, and a discussion on how ART adherence outweighs selling the drug. Finally, fear of drug-drug interaction—some participants may be concerned about ART and gender-affirming hormone therapy interactions and prioritize gender-affirming hormone therapy over ART uptake or adherence. These concerns will be acknowledged and corrected in PHN sessions and SMS text messages.

Conclusions

The public health significance of Text Me, Alexis! has the potential to be quite profound, as comparative- and cost-effectiveness research trials are critical steps in the development and adoption of scalable and effective HIV care intervention, especially among key populations that rely on service provision in resource-limited, community-based settings.

Acknowledgments

Funding for this study is provided by the National Institute on Drug Abuse (NIDA; #RO1DA056287; Multiple Principal Investigators: CJR and SMM). CJR and RJL acknowledge additional support from the National Institute of Mental Health (P30MH58107), SMM acknowledges additional support from NIDA (P30DA040500), and MJL acknowledges additional support from NIDA (K01DA051329).

Data Availability

The datasets generated during or analyzed during this study are available from the corresponding author upon reasonable request.

Conflicts of Interest

None declared.

Authors' Contributions

CJR and SMM conceived of the study design and wrote the original draft of the manuscript. TB wrote the statistical analysis sections for Aim 1 and the secondary aim; SMM and AJ wrote the statistical analysis sections for Aims 2 and 3. RJL provided oversight on all sections related to medication adherence and viral suppression. MJL, RPM, DR, and PJJ reviewed and edited the manuscript.

Multimedia Appendix 1
Summary Statement Peer Review Comments.
[PDF File (Adobe PDF File), 143 KB - resprot_v14i1e65313_app1.pdf]

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Abbreviations

ART: antiretroviral therapy
DSM-5: Diagnostic and Statistical Manual of Mental Disorders (Fifth Edition)
GLMM: generalized linear mixed model
HBM: health belief model
HIV-ASES: HIV Treatment Adherence Self-Efficacy Scale
ICER: incremental cost-effectiveness ratio
ISSB: Inventory of Socially Supportive Behaviors
LAC: Los Angeles County

PHN: peer health navigation
PROMIS: Patient-Related Outcome Measurement Information System
PROPr: PROMIS-preference score
QALY: quality-adjusted life-year
SCT: social cognitive theory
SST: social support theory
SUD: substance use disorder

Edited by T Leung; submitted 12.08.24; this is a non–peer-reviewed article;accepted 28.10.24; published 23.01.25.

Please cite as:
Reback CJ, Blue T, Jalali A, Landovitz R, Li MJ, Mata RP, Ryan D, Jeng PJ, Murphy SM
Comparative- and Cost-Effectiveness Research Determining the Optimal Intervention for Advancing Transgender Women With HIV to Full Viral Suppression (Text Me, Alexis!): Protocol for a Randomized Controlled Trial
JMIR Res Protoc 2025;14:e65313
URL: https://www.researchprotocols.org/2025/1/e65313
doi:10.2196/65313
PMID:39847410

Protocol

Self-Management Strategies for Low Back Pain Among Horticulture Workers: Protocol for a Type II Hybrid Effectiveness-Implementation Study

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Abstract

Background: Low back pain (LBP) is highly prevalent and disabling, especially in agriculture sectors. However, there is a gap in LBP prevention and intervention studies in these physically demanding occupations, and to date, no studies have focused on horticulture workers. Given the challenges of implementing interventions for those working in small businesses, self-management offers an attractive and feasible option to address work-related risk factors and manage LBP.

Objective: This study will (1) investigate the effectiveness of self-management strategies for nursery and landscape workers by comparing within-subject control and intervention periods and (2) determine if adoption and effectiveness differs between participants randomly assigned to review self-management videos only and those who also receive multimodal implementation support. We will also identify contextual factors impacting effectiveness and implementation.

Methods: A pragmatic, mixed methods, hybrid effectiveness and implementation design will be used to compare back pain with work tasks, disability, medication and substance use, and psychological factors between a baseline control and intervention periods. We aim to recruit 122 English- and Spanish-speaking horticulture workers with back pain, 30 supervisors, and 12 focus group participants. Participants will review short video modules designed to increase awareness of opioid risk and introduce self-management and ergonomic choices and use 1 self-management and 1 ergonomic strategy for 10 weeks. They will be randomly assigned to 2 implementation groups: video modules only or video + multimodal personalized support (checklist guidance, review of video feedback for ergonomic problem-solving, and text message reminders). Questionnaires will be administered at 3-month time points: baseline, pre- and postintervention, and at 3 and 6 months. Qualitative analysis of field notes, open-ended comments, and focus groups will expand understanding of results with comprehensive documentation of the context, barriers and facilitators, and reasons for adoption.

Results: The project was funded on September 29, 2023 (Centers for Disease Control and Prevention National Institute of Occupational Health and Safety, CDC NIOSH; U54OH011230-07S1), as a core research grant for the Southeast Coastal Center for Agricultural Health and Safety. The design, creation, and editing of English and Spanish videos was completed in June 2024 after comprehensive formative evaluation. Enrollment began in June 2024 with anticipated completion in 2027.

Conclusions: We hypothesize that both self-management interventions will result in reductions in work task pain and disability and that the video enhanced with multimodal personalized support will result in greater reductions than the video alone. If self-management is effective, mitigating pain positively impacts quality of life, productivity, and retention, while increasing the use of nonpharmacological alternatives to opioids addresses an important public health issue. Implementation aims will help inform reasons for results, barriers and facilitators, and potential for similar interventions in these and similar industries with physically challenging outdoor work.

Trial Registration: ClinicalTrials.gov NCT06153199; http://clinicaltrials.gov/study/NCT06153199

International Registered Report Identifier (IRRID): DERR1-10.2196/64817

(JMIR Res Protoc 2025;14:e64817) doi:10.2196/64817

KEYWORDS

low back pain; self-management; implementation; horticulture workers; video training; video feedback; text message reminders; agriculture; ergonomic; nonpharmacological

Introduction

Background

Low back pain (LBP) is the most common musculoskeletal disorder among agricultural and horticultural workers [1-5], negatively impacting worker's physical and mental health, increasing absenteeism, and shortening work longevity [6-11]. Further, LBP contributes to lower productivity, loss of experienced workers, and increased workman's compensation costs. The financial impact of high out-of-pocket costs and lack of paid leave often drive agricultural and horticulture workers to seek pain relief from prescription medications and illicit substances [12-14]. In one study of farmers with LBP, 71% relied on pain medication without consulting a physician compared to only 35% of white-collar workers [15].

Viable alternatives to pharmacological management of LBP have never been more important [16,17]. Despite guidelines recommending nonpharmacologic management, opioids are commonly prescribed for work-related injury and pain more frequently than for nonoccupational musculoskeletal disorders [18-22]. Although opioid prescribing has declined gradually since 2010, opioid fatalities from prescription and illicit synthetic opioids have continued to rise [20,23]. The precipitous increase in opioid overdose associated with fentanyl manufactured in clandestine laboratories [23,24] has elevated the importance of highlighting and promoting uptake of nonpharmacological alternatives for management of LBP [20]. In rural areas, opioid prescription rates are particularly high [25], and access to nonpharmacologic treatment options is limited [16]. A preliminary study supporting this protocol found that over half of agricultural workers (n=129) reported using opioids at some point [14]. Of those who had used opioids, most (77%) reported they received a prescription for a work-related injury. Participants explicitly linked work hazards and chronic pain with increased risk of opioid dependence, citing the need to continue working and "live with pain" as a cultural norm contributing to the problem [14]. While progression to opioid use disorder is complex, opioid misuse has devastating effects on health and work. A systematic review of the impact of prescription medications for occupational musculoskeletal injuries found that opioid use was associated with slower return to work, longer duration of disability, poorer self-reported work function, and poorer functional improvements [26]. Opioid prescriptions within the first 2 weeks of a work-related injury, opioid use for longer than 7 days, and higher dose supplies are associated with subsequent work disability or delayed recovery and greater work loss [26]. Owners of nursery and landscaping businesses in Florida reported problems with turnover, frequent absences, and low productivity among workers who used opioids, resulting in decreased labor availability [14]. Landscape and nursery work characteristics including low skill discretion, job strain (low control and high demand), high physical effort, and heavy lifting are risk factors for opioid use disorder [27]. Few opioid prevention efforts have been focused on underlying work-related factors such as musculoskeletal pain [18,28]. The substantial worker and employer burden of LBP in the horticulture industry and the devastating effects of opioid dependency highlight the need for efforts to manage and limit LBP and reduce unwarranted opioid use for musculoskeletal injury. Strategies to (1) increase workers' awareness of the risks and consequences of opioid use, (2) encourage workers to discuss options with health care providers after more acute injuries, and (3) provide alternatives for nonpharmacological strategies to manage pain or limit ergonomic stress [28] may increase knowledge and self-efficacy while reducing stigma [20,28].

Self-management is defined as the ability to manage pain, treatment, psychosocial, and lifestyle implications of a chronic condition [29,30], with the overall goal for individuals to safely manage symptoms and lifestyle without seeking unnecessary medical intervention [30-33]. Encouraging active involvement and empowering individuals to select options to manage work-related pain tailored to each worker's circumstances and preferences encompasses the principles of self-management for chronic conditions [6]. Effective self-management strategies should optimize pain coping strategies to manage and reduce symptom exacerbation through problem-solving [30]. Self-management is recommended for the management of chronic LBP in a number of guidelines and strategic initiatives [16,34,35], with moderate effectiveness for pain, and small to moderate effectiveness for pain-related disability reported in a systematic review and meta-analysis [36]. Increasing self-management of chronic pain that frequently limits work activities is one of the Health People 2030's targets [35]. However, most studies investigating effectiveness of self-management approaches have involved patients receiving

clinical care rather than groups who continue to work in physically demanding occupations. Self-management skills such as problem-solving, action planning, self-tailoring, and self-monitoring may provide a worker-centered approach for horticulture workers to promote self-efficacy and coping skills for adjusting work activities and managing pain [29,30,37].

There are limited training initiatives to address musculoskeletal pain for horticulture workers and most workers rely on supervisor's advice or learning by experience. Many studies have concluded that education can positively influence work-related musculoskeletal pain by promoting behavioral change, modifying health beliefs, and improving attitudes, although gaps in optimal implementation persist [38]. Although some studies reported additive effects of improving physical activity or ergonomic adjustments [38], none focused on agriculture, nursery, or landscape workers. Collectively, there is a crucial need to determine optimal implementation of effective self-management programs for workers, especially for those who do not have resources to receive treatment in typical health care settings [39,40]. Therefore, examining the effectiveness of training to assist workers with learning self-management and ergonomic strategies will provide valuable information, while studying implementation outcomes will help determine engagement, adoption, and feasibility.

Prior Work

This protocol builds from a preliminary study of streamlined individualized participatory ergonomic (PE) methods in clam aquaculture workers with similar physically challenging work [39,41]. Workers with chronic LBP were introduced to ergonomic concepts to reduce risk, selected 3 pertinent and acceptable strategies from a list, reviewed videos, and received text reminders. Significant improvements in disability, work-task pain, pain anxiety, and coping compared to baseline were observed ($P<.05$; n=19), with pain improvements greater than published minimal detectable change for 74% of the participants. The methods were both feasible and acceptable. These promising results led to recommendations to establish whether these approaches are effective in a larger cohort over longer timeframes, in different contexts, and with follow up [39].

We will investigate the effectiveness of self-management and ergonomic individual choices along with behavior change support for nursery and landscape workers. The first aim is to determine if self-management videos combined with multimodal personalized support is more effective than self-management videos alone for improving LBP management among horticulture workers. We hypothesize that compared to the video modules alone, the combined multimodal personalized support will result in (1) greater reductions in work task pain and disability, (2) lower prevalence of high-impact chronic pain, (3) greater reduction in substance use to manage pain, (4) greater reeducation in pain anxiety and depression, and (5) improved coping and self-efficacy. The second aim is to identify contextual factors that impact engagement, adoption, effectiveness, and implementation of nonopioid alternatives for LBP self-management. Understanding the external context and individual and team characteristics will help explain the results, provide important implementation perspectives, and inform translation.

Methods

Study Design

The exploration and preparation phases of the study were started in 2023, with the video training module creation, evaluation, modifications, and production completed in June 2024. A 2-arm pragmatic randomized controlled hybrid type II effectiveness and implementation study [42-44] will be conducted using mixed methods and a within-subject control period. The Standards for Reporting Implementation Studies (StaRI) standards checklist is included in Multimedia Appendix 1.

Ethical Considerations

The study was approved by the University of Florida Institutional Review Board (IRB202300756) and registered as a clinical trial through ClinicalTrials.gov (NCT06153199). Participants will be compensated for their time. Workers will receive US $25 for the baseline data collection and US $50 for subsequent steps for a possible total of US $225, while supervisors or owners will receive US $50 for the 2 data collection sessions for a possible total of US $100.

Employers will provide permission to discuss the study with workers and to conduct the study in the workplace. After determining eligibility, research staff will describe the purpose of the study, study-related procedures, risks, and benefits, and participants will sign an informed consent if they agree to participate. We will ensure that participants understand that participation is voluntary and that they can withdraw from the study at any time without consequences. A Certificate of Confidentiality (42 USC §241(d)) will protect participant privacy related to potentially sensitive information about the use of pain medication and other substances. If individual workers are not eligible or do not want to participate, they will be able to view the educational videos with their teams. If participants who are randomly assigned to the intervention enhanced with multimodal support are not comfortable being videotaped, we will provide deidentified video clips of other workers with blurred faces performing tasks similar to the tasks they have identified as difficult due to pain.

Recruitment

Recruitment Methods

We will recruit nursery and landscape workers in Florida through community partners and contacts from the Southeastern Coastal Center for Agricultural Health and Safety. We will use direct communication, email lists, websites, word-of-mouth referrals, and community meeting announcements to identify employers who are interested, followed by presenting the study to workers. We will recruit workers with a range of disability, pain impact, and persistence, anticipating that participants will be primarily male, with higher numbers of female participants in the nursery teams, and that approximately 50% will identify Spanish as their first language. Initial contact and permission will be through owners and supervisors to enroll nursery and landscape businesses and their employees.

Inclusion and Exclusion Criteria

Criteria for inclusion are (1) working full time (30 hours or more per week) in nursery or landscape businesses, (2) 18 years of age or older, (3) English or Spanish speaking, and (4) experiencing continuous or intermittent LBP over the past 3 months. We will exclude individuals who (1) report history of trauma, major spine surgery, or spinal nerve blocks in the past year; (2) are seeking disability or workmen's compensation, or (3) self-disclose pregnancy.

Sample Size Projections

A priori sample size was calculated using data from the pilot study comparing pain and disability measures pre and post–self-management PE interventions for 19 seafood workers [39]. For each participant and pain or disability outcome, averages of 4 baseline measurements and 2 postintervention measurements were used to calculate the difference in pre- to postintervention outcomes. Mean changes over a control period are assumed to have a mean 0 difference but share the same SD as the intervention period. Changes over the 2 periods for the same person are assumed to be independent. Data were simulated from a simple linear mixed model (LMM):

$$Y_{ijk} = \alpha_i + \beta_1 X_{ijk} Z_{ijk} + \beta_2 (1 - X_{ijk}) Z_{ijk} + \varepsilon_{ijk}$$

In this model equation, Y_{ijk} is the outcome of observation period k of individual j in cluster i, X_{ijk} indicates the intervention group (1: video + support, 0: video), Z_{ijk} indicates the intervention period (1: intervention period, 0: baseline period), α_i is the random intercept of cluster i, and ε_{ijk} is the error term. The variance of α_i was set as 5% of ε_{ijk}, such that the intraclass correlation is close to 0.05. For each set of simulated data, a generalized estimation equation model was used to test the null hypothesis β_1=0. We ran 1000 simulations to calculate the power for each of the different settings of the number of clusters and cluster sizes. Table 1 shows the power based on individual randomization. Fitting a LMM yielded comparable results. The planned enrollment of 102 participants (24 clusters) will provide adequate power for the primary outcomes, pain with most difficult work activities and total disability. An additional 20% enrollment for attrition results in a total anticipated sample of 30 clusters and 122 participants (teams of 3-5 participants) for the comparative effectiveness goals.

Table 1. Statistical power (%) based on individual randomization for differentiating between the 2 implementation groups using preliminary data.

Number of clusters	Cluster size	Projected Sample size	Power (%) calculated using results from Dunleavy et al. [39].			
			Pain with most difficult work activities (mean –16.1, SD 18.8)[a]	Average pain (mean –5.2, SD 17.3)[a]	Total disability (mean –2.5, SD 3.5)[a]	Difficulty level with most problematic work activity (mean 9.0, SD 28.5)[a]
20						
	3	60	96.9	28.4	88.7	33.8
	5	100	99.8	43.9	98.3	49.5
	10	200	100	73.5	100	73.5
25						
	3	75	98.9	32.3	93.3	40.7
	5	125	100	48.6	99.4	57.5
	10	250	100	80	100	84
30						
	3	90	99.5	38.2	97.1	44.3
	5	150	100	56.3	99.8	64.4
	10	300	100	87.3	100	88.8

[a]Mean difference, SD from Dunleavy et al [39].

Target Enrollment and Randomization

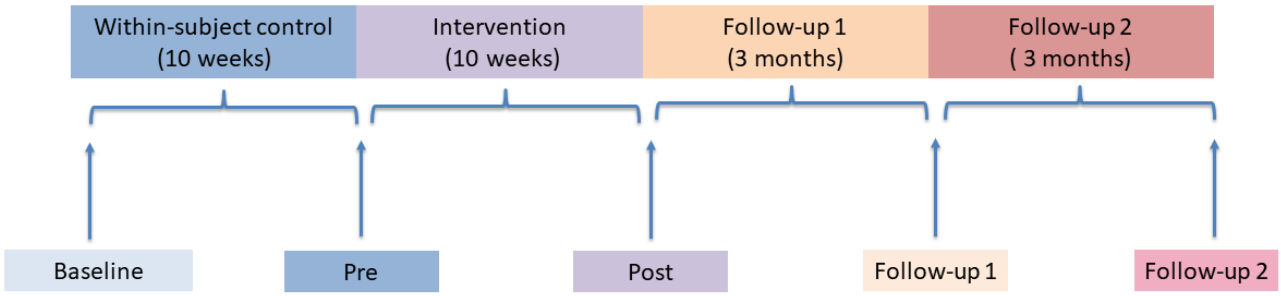
Our target enrollment of 122 workers will be recruited over 3 years starting in June 2024 with anticipated completion in 2027. For each team, we will enroll at least 1 supervisor or owner to provide support and comments on the overall feasibility and results, for 30 supervisors. In year 4, we will also invite 12 stakeholders to participate in focus groups (see aim 2) for a total expected enrollment of 164. Participants will be randomized to one the intervention groups after the baseline control period using stratified block randomization by type of work (nursery, landscape), and within each employer group to ensure a 1:1 distribution. The random assignment table was created prospectively by the statistician and participant numbers are generated in the REDCap (Research Electronic Data Capture) software (version 9.1.1; Vanderbilt University) [45] when baseline data are downloaded to reduce the risk of bias. Participants will receive incentives after completion of the surveys, training, and interviews.

Data Collection

Timelines

Five measurement periods will allow longitudinal comparison of change from the within-subject control period (10 weeks), across the pre- and postintervention period (10 weeks), and follow-up (3 and 6 months; Figure 1).

Figure 1. Timelines.



Questionnaires

Questionnaires in English or Spanish will be administered in the workplace on tablets using the REDCap platform [45]. The REDCap is a secure, web-based software platform with questionnaire support and data management functions [45]. Primary dependent variables will be collected at all timepoints—pain (severity, interference, and persistence); pain with specific work tasks; disability; work ability; and pain medication use [46-51]. Affective or cognitive characteristics impacting adoption and effectiveness (secondary dependent variables or potential confounders) such as coping, fear, anxiety, and depression will also be collected [52-55]. Branching logic will be used to pipe answers for the most difficult work activities and choices of strategies into subsequent questionnaires. In addition to demographics, medical and work characteristics will be collected. Disability will be assessed using Roland-Morris Disability Index [49], Patient Specific Functional Index (PSFS) for work tasks considered most difficult due to back pain [39,50,56-58], and Work Ability Index instruments [48]. Pain constructs from the National Pain Strategy recommendations (severity, interference, persistence, and impact) [46,47], along with pain with the specific work tasks identified in the PSFS, will be measured using Likert scales [39]. Substance use will be recorded using the National Institute on Drug Abuse quick screen [23] with additional questions on over-the-counter pain medication and other substances. Affective and cognitive measures include the Pain Anxiety Symptom Scale [53], Center for Epidemiological Studies Depression Scale short form [52], Coping Strategy Questionnaire [55,59,60], and Self-Efficacy for Chronic Condition management short form [54]. Instruments were translated by a certified translation agency if validated Spanish versions were not available.

Qualitative Methods

Understanding the context (circumstances and unique factors surrounding the study) will help explain results and provide implementation outcomes [43,61,62]. We will use relevant components of the Exploration, Preparation, Implementation, Sustainment conceptual framework, including inner (individual and team) and outer (industry, regulations, and environment) contextual factors (Figure 2) [63]. Qualitative data will be compiled from (1) researcher observations and field notes; (2) anchor-based and open-ended questions reflecting engagement (opinions of intervention delivery and support, recommendations to others), adoption (use of strategies in past 7 days), and feasibility (ease of use, barriers and facilitators); (3) perceived effectiveness (including global rating of change); (4) supervisor and worker comments; and (5) data collected during final stakeholder focus groups (Figure 3). Spanish-speaking research team members will contribute to observations and if needed, will translate comments. We will record comments, expansions, and clarifications and will ask workers specifically about the acceptability of introducing information about opioid risk and self-management at home and in the workplace. Supervisors and owners will be asked to provide their opinions from an organizational perspective. Recommendations will be confirmed, prioritized, and expanded ensuring robust and iterative analysis.

In addition, 2-3 focus groups will be conducted during the last quarter of the study. Industry representatives, employers, supervisors, and select participants will be invited to contribute their opinions. We will invite industry leaders committed to support wide-spread dissemination and translation of interventions, and workers able to comment on their real-world perspectives with 1 focus group conducted in Spanish. Focus group questions will help explain findings and patterns identified throughout the study and generate recommendations for future interventions. Question prompts will reflect any similarities or differences generated from earlier data analysis to confirm themes and conclusions, further ensuring triangulation and rigor. Interview and focus group recordings will be recorded using participant numbers only, transcribed, and translated if appropriate [64]. Comprehensive data analysis will be conducted progressively throughout the study, contributing to triangulation and trustworthiness of the qualitative analysis [64,65].

Figure 2. Contextual framework: selected components from the EPIS (Exploration, Preparation, Implementation, Sustainment) Model.

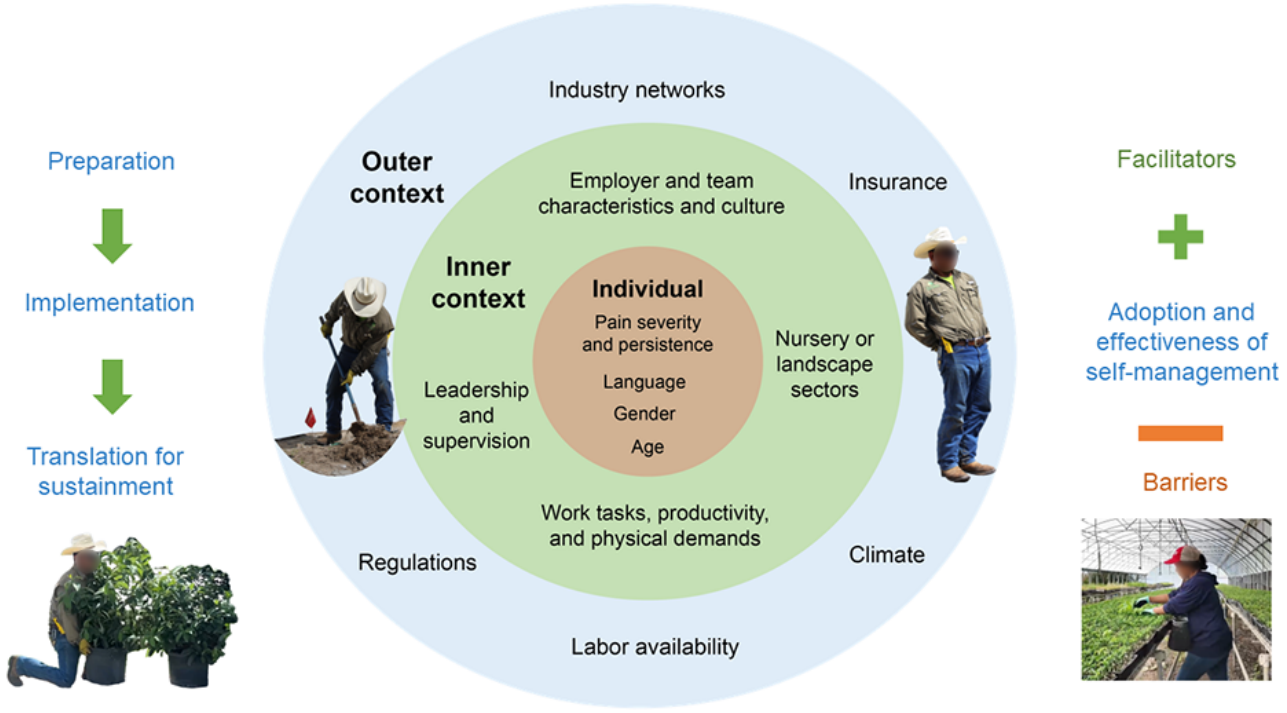
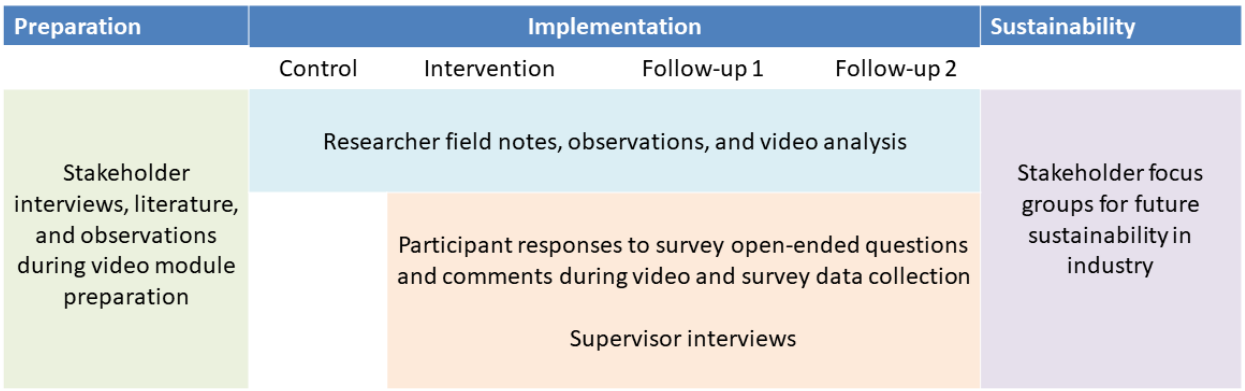


Figure 3. Qualitative methods.



Risk Exposure for Tasks

Participants will be videotaped while performing their self-identified most difficult work tasks at baseline and after the intervention. After categorizing video clips by tasks, subtasks, and variations using hierarchical task analysis, the risk for each task will be categorized using the Rapid Entire Body Assessment (REBA) checklist [59,60]. The REBA is a commonly used measure to reflect ergonomic risk in the workplace and reflects extreme postures in tree nursery workers better than other observational instruments [66]. We will use a software system (Tumeke) [67], which identifies and reports the REBA for the postures and movements in the cycle with the highest risk to help with consistency of analysis. The risk assessment measures will be documented for specific tasks rather than used to compare individual change due to the variability of tasks and potential difficulty capturing the exact same tasks for all participants. Tasks will be recorded as changed or unchanged.

To further understand the impact of work adjustments and variations, simulations of various ergonomic scenarios will be conducted in laboratory settings with 3D analysis. Tasks with multiple variations and those which are changed will be selected and replicated. These simulations will involve creating different work environments and task setups to replicate the typical conditions encountered by the participants. By analyzing these simulated scenarios, we aim to identify potential ergonomic improvements and assess relative risk for variations of the tasks rather than evaluating individual change.

Intervention

Video Training Module Design and Preparation

Three short video modules were created specifically for nursery and landscape workers, tasks, and environments. The instructional design was informed by stakeholder discussions, review of current evidence, targeted in-depth interviews with industry experts (insurance safety consultants, association leadership, owners, supervisors, and workers; n=15), and work

observation conducted during the preparation phase. Stakeholders also completed surveys which helped prioritize a preliminary list of work tasks considered most problematic for back pain.

Nursery and landscape worker characteristics informed design of multimedia visual representation of work activities and content with representation of genders and ethnicities in the videos and resource materials. Scripts were designed and evaluated for language consistent with lower than eighth grade literacy level to meet the lowest anticipated educational level, while structure and organization to reduce cognitive load, and design accounting for multiple language versions was built in from the first draft (Textbox 1).

The videos emphasize the importance of managing and limiting pain using active nonpharmacological self-management and conserving work longevity to facilitate ongoing support of family. The modules cover (1) the need to manage pain without relying on medication and substances, as well as the risk of opioid use; (2) self-management strategies for pain at home and at work (general exercise, specific back exercise, nutrition and hydration, deep breathing and positive thinking, rest, relaxation, and sleep); and (3) work-specific ergonomic strategies to address physical risk factors during nursery and landscape tasks. The videos encourage selection of relevant strategies for pain management of exacerbations, emphasize prevention through lifestyle and behaviors such as exercise, nutrition, and sleep, and proactively planning work tasks and adjusting movement to minimize risk (Figures 4 and 5). Sector-specific video clips of relevant work activities were filmed in nursery and landscape work settings and represent workers with a mix of genders and ethnicities, along with key stakeholder commentary to provide relevance.

Textbox 1. Design choices matched to characteristics.

Multimedia visual representation

- Videos and narration; minimal use of text with simple language, short sentences, images to represent key concepts, and advance organizers [68,69].
- Check list support materials (print) [68,69].
- Infographics and resource materials.
- Text messages include graphics and gifs for movement.

Health literacy and cognitive load considerations

- Literacy levels lower than eighth grade [68,70].
- Organization to maximize working memory and reduce cognitive load using advance organizers, smaller “chunks” and grouping of concepts [71].
- Graphics to represent choices as advance organizers.
- Short modules to minimize overload.
- Encouragement to choose relevant options for self-efficacy.
- Message design and visual representation, for example, focus on positive options for movement and work adjustments rather than what not to do or representation using symbols with negative connotations such as red crosses.
- Contrasting recommended movement in color with those that should be adjusted in black and white video.
- Music and screen transitions to divide concepts.

Multiple languages

- English version design and initial formative evaluation to identify and adjust vocabulary and grammar difficult to translate into Spanish.
- Length of clips adjusted to time needed for Spanish narration using transitions.

Feasibility for workplace

- Video delivered on iPads in 5-minute modules to maintain attention to use in the field for “toolbox” talks, team discussions, or as part of general safety meetings.
- Options based on the work and team location rather than requiring classroom settings to promote feasibility.

Figure 4. Self-management strategy options.

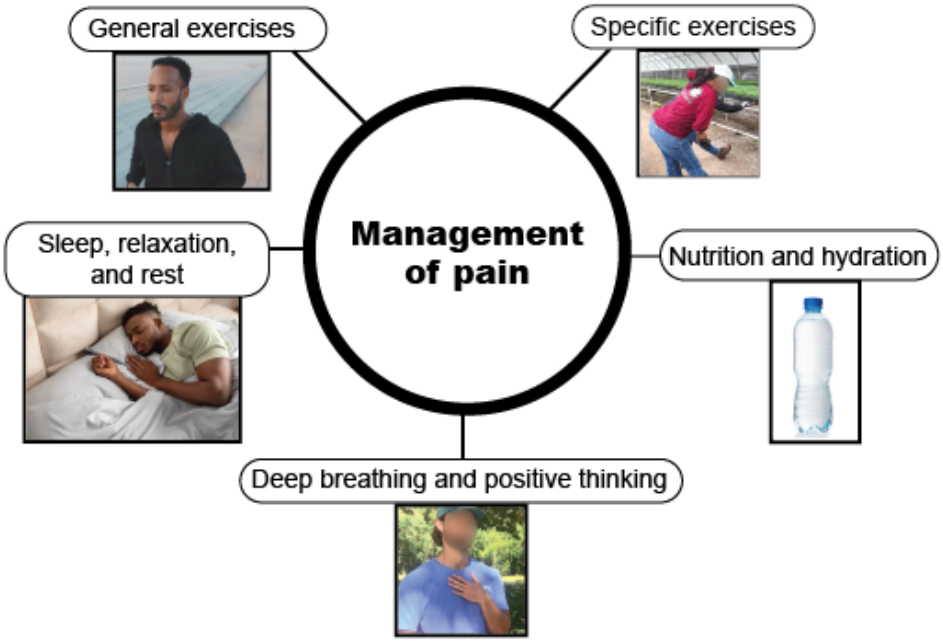
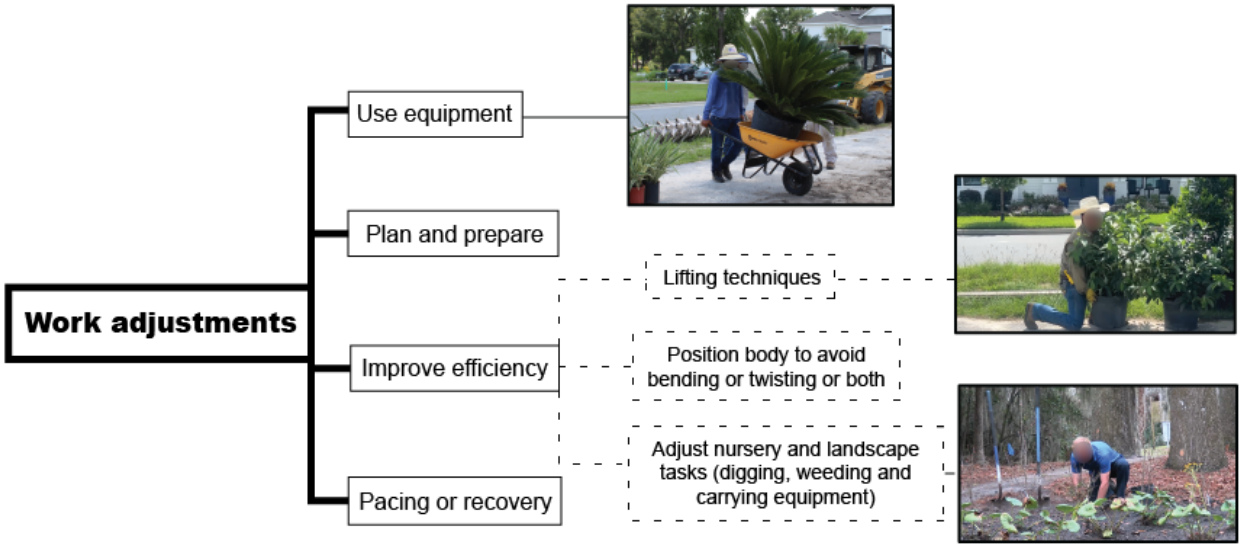


Figure 5. Ergonomic strategy options.



Video Formative Evaluation

The design incorporated iterative feedback from instructional design and health literacy experts and input from the research team who have expertise in pain management, rehabilitation, psychology, opioid misuse, and ergonomics. The scripts were evaluated for health literacy and inclusivity, followed by formative review by the experts in our multidisciplinary team. The adjusted English script was evaluated by owners, supervisors, workers, communication and industry experts, as well as bilingual stakeholders for words and concepts that are difficult to translate.

Supervisors, workers, and outside stakeholders (n=27) reviewed the video for content, format, representation, understanding, and provided comments. Additional video clips were added, and some content reorganized for flow and organization to reduce cognitive load. Final narration was completed after the second revision. The script was translated into Spanish by a certified agency and reviewed again for consistency, language, messaging, and cultural acceptability, prior to adding the Spanish narration and titles. Spanish speaking supervisors, workers, and stakeholders (n=12) also evaluated the Spanish videos with minor changes.

Self-Management and Ergonomic Options and Implementation Strategies

The self-management and ergonomic options (Figures 4 and 5) and implementation strategies (Table 2) were selected using evidence, stakeholder interviews, and established theoretical frameworks (health beliefs [72,73], self-determination [74-76], social cognitive [77,78], and Bronfenbrenner's Ecological Systems Theories [79]). The theoretical frameworks will help to interpret effectiveness outcomes for the group and for

different subgroup characteristics and determine if interventions are modifiable to fit with internal and external contexts [80].

After the within-subject control period, participants will be randomly assigned to 1 of the 2 implementation arms. Workers in both groups will view the tailored educational video modules in the workplace and select 1 self-management (Figure 4), and 1 ergonomic strategy (Figure 5), to use during the 10-week intervention period. Workers assigned to the arm enhanced with additional support (video + support) group will be provided checklists to use while reviewing the videos and asked to consider strategies they do not use or could use more frequently [81]. To assist workers with problem-solving, participants in this group will be shown video recordings of their own work and encouraged to problem-solve ergonomic alternatives [39,41,81]. Finally, the workers in the video + support group will receive weekly SMS text message reminders to support their specific choices. These automated messages will be delivered using the Mosio text platform [82] at the beginning (ergonomics) and at the end (self-management) of the week. The messages are preprogrammed and will include graphics and gifs to represent concepts from the videos. Supervisors will also be asked to support workers for ergonomic choices and provide their opinions of engagement, adoption, and feasibility.

Table 2. Implementation outcome measures.

Implementation strategy	Engagement	Adoption	Feasibility
Tailored short educational video modules delivered in the workplace using iPads	• Acceptability, relevance—questions during or after training • Opinions of the videos and delivery	• Number of ergonomic and self-management strategies used • Frequency of strategy use • Intent to use strategies in the future	• Ease of use of strategy • Facilitators or barriers • Time for delivery • Feasibility in the workplace environment
Worker choice of preferred strategies matched to self-identified most difficult work tasks	• Acceptability	• Number of ergonomic and self-management strategies used • Frequency of strategy use • Intent to use strategies in the future	• Ease of use • Barriers and facilitators
Supervisor involvement	• Supervisor engagement (observation)	• Uptake and involvement of workers from supervisor's perspectives	• Supervisor interviews—feasibility, reasons for adoption, fit with organization, and environment • Barriers and facilitators
Visual feedback for positions and movements	• Qualitative comments and questions during review of video	• Use of strategies	• Time • Recognition of positions and postures • Opinions of relevance and acceptability
Ergonomic problem-solving	• Involvement in problem-solving • Supervisor comment discussion among workers	• Use of strategies	• Opinions of ergonomic strategies and problem-solving • Supervisor observations of suggestions for work tasks, changes in work practices
Text message reminders including images and gifs	• Questions and return texts		• Feasibility for workers • Opinions of text messages

Data Analysis

Aim 1

LMMs or generalized linear mixed models (GLMM) will be used to compare within-subject changes in the primary and secondary outcomes (1) over time (baseline, pre, and post) between the intervention periods and the control period and (2) between video and video + support interventions, depending on the distributional feature of the outcome. A general regression structure will be used:

$$g(EY_{ijk}) = \alpha_i + \gamma_j + \beta' X_{ijk}$$

In this equation, Y_{ijk} is the change of the outcome over observation period k of individual j in cluster i; $g(EY_{ijk})$ is the link function for the mean of Y_{ijk}; α_i and γ_j are random intercepts specific to cluster i and individual j, respectively; and X_{ijk} and β are vectors of covariates and associated coefficients. X_{ijk} indicates intervention (1: intervention video+support, 0: control video only), and baseline characteristics (demographics, occupation, and baseline pain or disability levels). For continuous outcomes that are symmetrically distributed (after transformation), the following traditional LMM will be used:

$$Y_{ijk} = \alpha_i + \gamma_j + \beta' X_{ijk} + \varepsilon_{ijk}$$

where ε_{ijk} are normal random errors. For skewed continuous outcomes, a GLMM with a gamma distribution will be used. Intervention effects will be represented by mean differences in the continuous outcome between the comparison groups. For

categorical outcomes such as prevalence of chronic high impact pain, we will either dichotomize the outcome and fit a logistic mixed model or directly fit a Bayesian multinomial logit model that is available in the R package. Intervention effects will be represented by odds ratios. We will also reparameterize the model to obtain relative risks for measuring intervention effectiveness. These models will account for correlations within each team, as well as within each subject. Results will be verified by general estimating equation models in case within-team or within-subject correlation structures are mis-specified. Missing values for either outcome or covariates will be managed by multiple imputation or the Expectation-Maximization algorithm.

Aim 2

Qualitative analysis will help explain effectiveness and implementation outcomes concurrently [43,61]. Contextual factors that support or hinder engagement, adoption (use of interventions), feasibility, and effectiveness will be described. We will examine general barriers and facilitators and specific patterns for workers in the nursery and landscape sectors. The qualitative analysis will be used to develop a comprehensive matrix of team context, organization, and individual characteristics to explain effectiveness of interventions and implementation results. Using directed deductive content analysis, initial codes will be developed from analysis of preparatory interviews for (1) contextual factors; 2) barriers and facilitators contributing to the degree of impact of the interventions; and (3) opinions of ease of use, overall satisfaction, and reasons for engagement, adoption, and feasibility results. We will use NVivo qualitative analysis software (version 14; Lumivero) to code content and identify categories and subcategories to describe patterns and relationships that emerge. We anticipate comparing themes for (1) intervention groups, (2) participants with different degrees of pain severity and persistence, (3) individuals and teams who adopt and implement the strategies consistently compared to those who do not, (4) individuals who respond positively to the interventions compared to those who do not improve, and (5) subsectors of the industry. Once themes are identified, interconnections, interactions, and relationships will be described and explained. Recommendations for future implementation and sustainability will be confirmed and prioritized.

Results

Preparatory literature searches, stakeholder interviews, and observations were started in January 2023 and completed in August 2023. The stakeholder interviews confirmed the limited formal training for prevention of musculoskeletal repetitive strain injury and overall need for addressing LBP in the industry. The project was funded on September 29, 2023 (CDC NIOSH U54OH011230-07S1), as a core research project for the Southeast Coastal Center for Agricultural Health and Safety. The video recording and creation started in April 2023 and was completed in June 2024. Formative evaluation of drafts 1 and 2 of the videos, revisions, translation into Spanish, and narration were completed in April 2024, and final video edits were completed in June 2024. The first group was enrolled in June 2024. As of December 6, 2024, we have enrolled 14 participants and 4 supervisors from 3 employers. Data collection is anticipated to be completed in late 2027 or early 2028 with plans for final analysis and dissemination of findings shortly thereafter. Qualitative data for Aim 2 will be coded and analyzed progressively for team characteristics and trends.

Discussion

Importance of Study Findings

In this paper, we present the protocol for a randomized within-subject controlled hybrid intervention study with coprimary aims to examine the effectiveness of self-management videos combined with multimodal personalized support compared to self-management videos alone for improving LBP and disability in nursery and landscape workers, as well as to identify contextual factors that impact implementation including engagement, adoption, effectiveness, and feasibility. Improving self-management strategies to reduce transition from intermittent to high-impact chronic LBP will contribute to important Healthy People 2030 objectives [35] while addressing research and practice gaps to mitigate musculoskeletal pain.

In nursery and landscape businesses, prevention of musculoskeletal injuries has not typically received high priority. Despite the size and growth of the industry, horticulture has rarely been included with other agriculture sectors in studies addressing musculoskeletal injury prevalence [5] or risk factors [5,6]. There is a death of intervention studies to prevent or mitigate LBP in agriculture [2,10,66], with few intervention studies specifically targeting nursery and landscape populations [5]. Feasible, easily implemented interventions to manage pain and reduce risk factors are essential for small businesses in the horticulture industry who face major challenges with labor availability. Variability in work environments, seasonal fluctuation in workloads, weather constraints, and productivity requirements make the adaptability, efficiency, and ease of adoption paramount for any training intervention. Current “training on the-job” from more experienced workers and supervisors is challenging with turnover and difficulty retaining experience workers who can pass on best practices. Efficient delivery methods providing structured evidence-based information and strategies would provide consistency. Short videos tailored for both sectors are a pragmatic option to address the needs while remaining flexible for work priorities and productivity. This study will contribute to knowledge about the effectiveness of interventions specifically tailored to the characteristics, work tasks, and work settings for these workers.

Awareness of the risks and consequences will highlight the importance of nonopioid alternatives [14]. Opioid education is not effectively integrated into workplace safety training but embedding discussion of opioid risk within a more holistic approach to prevention and mitigation of LBP may promote help-seeking behavior and reduce stigma and communication barriers [20]. Introducing the risk of opioids along with options to manage pain using self-management and ergonomic alternatives is likely to be received more positively than opioid education alone.

Awkward postures, repetitive actions, and intermittent lifting, digging, or shoveling have been identified as inherent ergonomic risk factors for landscape workers [5]. Similar risks are present in nursery work with awkward stooped trunk postures, repetitive low load lifting, and intermittent heavy lifting [10,11]. Larger companies often have more access to mechanical equipment, while small work units seldom have sufficient resources for major engineering redesign recommended in the NIOSH hierarchy of controls [6]. Modifying the way people work or reinforcing the use of available equipment in small businesses is, therefore, more realistic than major equipment modifications. Typically, smaller companies do not have access to ergonomic and safety experts, and may not provide health care benefits. Feasible, easily implemented interventions to manage pain and reduce risk factors are, therefore, needed for businesses in the nursery and landscape industry.

PE approaches involve workers in identifying possible solutions to reduce work-related stress and have been used in a variety of ways in large manufacturing, construction, and health care settings [83-86]. The evidence for effectiveness of PE in large corporations is mixed for group changes for time off work, return to work, self-assessed productivity, and prevalence of LBP [85,87-94]. In contrast, PE has been found to improve overall perceived health, decrease back pain intensity, and reduce absences due to back pain [94]. Comprehensive PE interventions are often time-consuming and challenging to implement across large corporations. Solutions suggested by workers may be feasible, but changing organizational processes can be difficult. Thus, PE has been suggested to be especially beneficial for small teams, enterprises with restricted finances, and rural or less developed areas [86,95,96]. Although PE has not been studied extensively in agricultural settings [39,41,86,95,96], there is some evidence of lowered ergonomic risk and improved management of symptoms among farmers [86]. In another study, construction workers reported significantly less general fatigue after a typical workday, and increased influence on their work compared to controls [81]. A modified approach to encourage workers to choose relevant options for changing their work activities to minimize ergonomic stresses may be feasible to empower nursery and landscape workers to manage back pain [40].

In this study, changes in the primary (pain, disability, and medication use) and secondary (pain-related anxiety, coping, self-efficacy) measures from the preintervention to postintervention timepoints will be compared to a within-subject baseline within-subject period. We will also compare 2 forms of training implementation—video modules alone and video enhanced with multimodal personalized support. We hypothesize that the video + support will facilitate greater engagement, and increased adoption, thereby contributing to greater reductions in work task pain and disability compared to a baseline control period than the video alone. If either intervention is effective, mitigating pain and enhancing knowledge, skills, and attitudes to manage pain successfully is likely to impact quality of life, productivity, and retention. Improvements in pain and disability could result in decreased use of pain medication and other substances, important outcome public health priorities. Even if observed differences are not significant, identifying characteristics of those who respond will contribute evidence for preventing the transition from low to high-impact chronic pain. The mixed methods will help explain results and surrounding inner and outer contextual factors, facilitators and barriers contributing to implementation success for individuals, teams, and specific strategy choices [44]. Qualitative analysis will also inform recommendations and provide ideas for sustainability of effective interventions. Analysis from multiple perspectives will also help explain emerging or complex factors inherent with the dynamic workplace environment and business models, to guide decisions for others considering these approaches. If self-management is effective for horticulture workers (or specific subgroups), simultaneously studying implementation outcomes (engagement, adoption, and feasibility) will facilitate translation of the intervention from research to practice and scaling to the workforce. Potential limitations that may impact the success of this study are consistent with other hybrid effectiveness implementation studies. First, although we anticipate that our recruitment goals are achievable, external factors such as productivity requirements may impact owner and supervisor willingness to allow workers to participate. As attrition is expected, we plan to enroll additional participants to achieve adequate power. We will emphasize benefits for employers such as limiting absenteeism, improving retention, and reducing potential risks of medication or substance use to manage pain while working. Second, we also anticipate that owners and supervisors who agree to participate are already committed to supporting workers. This may result in a sample of workers associated with positive contextual factors that may not be generalizable to all employers. However, these factors will be documented to help interpret results from an implementation perspective. Third, weather and seasonal variations are likely to impact productivity and, therefore, willingness to participate, particularly for landscape companies. These factors will also impact scheduling for data collection, for example, hurricane or weather delays. We have built in a 2-week window for data collection to accommodate the scheduling but there may be a need for additional flexibility. Finally, cultural, language, and educational literacy variations are expected. All instruments and materials have been translated and checked thoroughly while research assistants who speak Spanish fluently are essential.

Conclusions

Interventions to reduce the burden of LBP that consider the unique characteristics and business models within the nursery and landscape sectors are lacking. Given the high incidence of LBP, the risk of opioid use, impact on labor availability and productivity, and the limited attention to musculoskeletal disorders in these sectors, this study will provide valuable information to address both employer and worker needs. The hybrid type II effectiveness and implementation study will investigate the effectiveness of self-management interventions for pain and disability, along with the engagement, adoption, and feasibility, for 2 forms of implementation while also documenting the context, facilitators, and barriers for nursery and landscape businesses [44]. Increased awareness of opioid risk and options for alternate nonpharmacological strategies to manage pain will also provide an important contribution to a

high priority public health challenge. We anticipate self-management will result in reduced pain and disability. Further, targeting self-management can empower workers and improve pain coping, reducing pain anxiety, depression, and associated use of pain medications. Short video training modules presenting realistic strategies to manage pain and limit work stress are likely to be feasible in the workplace while multimodal personalized support is likely to facilitate engagement and adoption of context-specific solutions. The qualitative methods used will help elucidate whether these options are feasible for small- to medium-sized horticulture businesses, document barriers and facilitators, and describe the inner and outer contextual factors influencing adoption and effectiveness. If the video and multimodal personalized support intervention is more effective than viewing training modules alone, this knowledge will inform best practices and may be easily adapted for other physically challenging agricultural sectors.

Acknowledgments

This study was funded by the Centers for Disease Control National Institute of Occupational Safety and Health (CDC NIOSH) of the US Department of Health and Human Services (U54OH011230-07-00) as core research project for the Southeastern Coastal Center for Agricultural Health and Safety, awarded to the University of Florida on September 30, 2023. The content is solely the responsibility of the authors and does not represent the official views of, nor an endorsement by, the CDC/NIOSH of the Department of Health and Human Services. The Southeastern Coastal Center for Agricultural Health and Safety provided support for the funding application, organization, contacts for recruitment, opportunities to discuss the study with community partners, and the stakeholder advisory board. The authors would like to thank the community partners including Ed Bravo, and the Florida Nursery Growers Landscape Association for assistance with exploration prior to grant submission, preparation, and support for stakeholder recruitment, as well as Big Trees Landscaping, Tropic Traditions, University of Florida Grounds and Maintenance, and Anthony Zaleski for assistance with video recording of work tasks in preparation and for the video modules. Shena Hays and Hillary Carter from the University of Florida College of Public Health and Health Professions Instructional Design and Media team provided video capture and editing for the training modules while Truly Hardemon and Lior Flum assisted with input and review of the instructional design and video content. The authors would also like to thank Cyrus Saleem for assistance with the survey design, Jane Morgan-Daniels and Margaret Ansell for review of the materials for health literacy recommendations, and Maria Vanegas for Graphic contributions. The University of Florida Redcap survey platform support is funded by a National Center for Advancing Translational Sciences grant (UL1TR001427).

Data Availability

Deidentified data will be made available to researchers upon written request. A data-sharing agreement will be developed and signed that provides commitments to (1) use the data only for research purposes and not to identify any individual; (2) securing the data using appropriate computer technology and security protocols; and (3) destroying or returning the data after analyses have been completed. This data sharing plan may be modified as recommended by the funding agency or university policies at the time of study completion.

Authors' Contributions

Study conceptualization, funding acquisition, and methodology was performed by KD, JMB, BH, KKG, and HLR. The data analysis plan was developed by KD, JMB, BH, KKG, HLR, and YY. with project administration contributions from KD and JMcB. The original draft was created by KD, with full writing, review and editing completed by KD, JMB, JMcB, KKG, HLR, and YY. All authors reviewed and approved the submission.

Conflicts of Interest

None declared.

Multimedia Appendix 1
STARI (Standards for Reporting Implementation Studies) checklist.
[PDF File (Adobe PDF File), 140 KB - resprot_v14i1e64817_app1.pdf]

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Abbreviations

CDC: Centers for Disease Control and Prevention
GLMM: generalized linear mixed model
LBP: low back pain
LMM: linear mixed model
NIOSH: National Institute of Occupational Health and Safety
PE: participatory ergonomic
PSFS: Patient Specific Functional Index
REBA: Rapid Entire Body Assessment
REDCap: Research Electronic Data Capture
StaRI: Standards for Reporting Implementation Studies

Edited by T Leung; submitted 30.07.24; this is a non–peer-reviewed article;accepted 22.11.24; published 28.01.25.

Please cite as:
Dunleavy K, Radunovich HL, Beneciuk JM, Hu B, Yang Y, Blythe JM, Gurka KK
Self-Management Strategies for Low Back Pain Among Horticulture Workers: Protocol for a Type II Hybrid Effectiveness-Implementation Study
JMIR Res Protoc 2025;14:e64817
URL: https://www.researchprotocols.org/2025/1/e64817
doi:10.2196/64817
PMID:

Protocol

Novel Smartphone App and Supportive Accountability for the Treatment of Childhood Disruptive Behavior Problems: Protocol for a Randomized Controlled Trial

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Abstract

Background: Although evidence-based treatments have been developed for childhood behavior problems, many families encounter barriers to treatment access and completion (eg, local availability of services, transportation, cost, and perceived stigma). Smartphone apps offer a cost-efficient method to deliver content to families.

Objective: The aim of this study is to evaluate the effectiveness of the UseIt! mobile health system as both stand-alone and coach-assisted interventions via a randomized controlled trial. The UseIt! System is designed to reduce disruptive behaviors in young children.

Methods: A nationwide sample of parents of children aged 5 years to 8 years with disruptive behaviors (N=324 dyads) are randomly assigned to the stand-alone app (UseIt!; n=108), the coach-assisted app (UseIt! plus supportive accountability; n=108), or the control app (mindfulness app; n=108). The UseIt! App provides parents with tools and troubleshooting to address disruptive behaviors, along with a behavior diary to track behaviors and strategies over time. The coach-assisted condition includes a bachelor's level paraprofessional who provides weekly phone calls to promote engagement with the app. The control condition is composed of a mindfulness app. The web-based, self-assessed outcome measures (post treatment and 6-month follow-up) include measures of app usage, parenting knowledge (eg, knowledge of parent management training and cognitive behavioral therapy skills), and strategies (use of evidence-based parenting strategies), symptom reduction (eg, behavior problems), and parent mental health (eg, anxiety, stress, and depression). We hypothesize that both intervention conditions will show greater parent knowledge and use of skills along with greater symptom reduction relative to the control condition. Further, we hypothesize that those assigned to the coach assisted condition will report greater knowledge, skill use, and symptom reduction than the stand-alone app. We will use intent-to-treat analyses to regress outcomes on study conditions to evaluate for differences across conditions.

Results: Recruitment of study participants began in December of 2022 and is ongoing. We have recruited over half of our intended sample of 324 parent-child dyads (n=214) as of December 2024. These dyads have been randomly allocated to each of the intervention conditions, with 71 assigned to the coach-assisted condition, 72 assigned to the stand-alone app, and 71 assigned to the control app condition. Data collection is projected to be completed by late 2026.

Conclusions: The current study aims to address a gap in the literature regarding the feasibility, effectiveness, and utility of a smartphone app that includes a coach-assisted arm. Digital therapeutics have the potential to enhance the reach and scalability of skills-based psychosocial interventions. Findings from this study will advance scientific knowledge and have implications for clinical practice.

Trial Registration: ClinicalTrials.gov NCT05647772; https://clinicaltrials.gov/study/NCT05647772

International Registered Report Identifier (IRRID): DERR1-10.2196/67051

(JMIR Res Protoc 2025;14:e67051) doi:10.2196/67051

KEYWORDS

mobile health; disruptive behaviors; parent management training; randomized controlled trial; externalizing behavior

Introduction

Background and Rationale

In the United States, approximately 1.5 million school-age children meet *DSM-5* (*Diagnostic and Statistical Manual of Mental Disorders* [Fifth Edition]) diagnostic criteria for a disruptive behavior disorder (DBD) [1]. DBDs, a category of disorders that broadly involves problems concerning the self-control of behaviors (eg, conduct disorder [CD] and oppositional defiant disorder [ODD]), account for more than half of all mental health referrals for children [2,3]. Longitudinal studies reveal that these problems in early childhood can be risk factors for persistent problems later in life, including substance use disorders and internalizing disorders, if left untreated [4]. DBDs are typically treated with psychosocial evidence-based therapies [5] that include parent management training (PMT) skills (eg, praise, rewards, consequences, and time-outs) and cognitive behavioral therapy (CBT) skills (eg, problem-solving and emotion labeling) [6]. Meta-analyses point to the substantial effectiveness of these interventions at reducing symptoms and maintaining treatment gains over time [7,8]. Despite the effectiveness of evidence-based treatments, many families do not have access to these services, and often stop attending or fail to practice new skills between sessions. Barriers to access include local availability of services, transportation, cost, and perceived stigma. Barriers to noncompletion include poor motivation and low engagement, along with competing demands for time, transportation problems, and copayment costs [9].

The Promise of Digital Therapeutics

Recent advances in technology, in particular mobile health (mHealth) systems, have the potential to overcome these barriers and promote better data collection for researchers [10]. mHealth technologies, including smartphones, create an opportunity to develop personalized interventions that are delivered to families in their day-to-day settings [11]. A smartphone-based mHealth system has numerous potential advantages for improving access to, and engagement in, evidence-based treatments for childhood behavior problems. Such applications can deliver content to improve understanding of skills, provide opportunities for learning through skills practice, and give feedback to families regarding areas for improvement [12,13]. In a recent meta-analysis, of 25 clinical trials, mobile technology use was associated with superior treatment outcome across all study designs and types of control conditions (effect size=.34) [14]. mHealth technologies can also be used to collect data on between-session treatment adherence and skills practice. Evaluating the extent to which patients and families are using the skills they are learning outside of treatment sessions is especially important for psychosocial treatments for disruptive behavior problems which are overwhelmingly skills-based. Remote digital assessments have many advantages over traditional retrospective self-reports including reduced recall bias, the ability to obtain a more representative sample of behavior across situations and contexts, and the ability to track changes in behavior [15-17].

Rigorous evaluations of mHealth interventions targeting child behavioral concerns are in their nascent stage. A 2024 systematic review of mHealth interventions targeting behavioral problems in youth indicated a wide range of effect sizes, from small to large, across the 11 studies reviewed. Most sample sizes were small (ie, less than 100), and the few larger studies did not focus on clinical outcomes (eg, satisfaction, acceptability, and app usage, without behavioral outcomes) [18]. Other recent studies reflect similar findings (ie, improvements in child and parental symptoms, with a wide range of effect sizes), but have similar limitations (ie, small sample sizes, outcome measures focused on satisfaction or acceptability of apps rather than empirically based measures of symptom improvement) [19-22].

The Role of the Coach in mHealth

There is growing evidence in the field of digital therapeutics that some degree of human interaction is important to sustain app usage and achieve meaningful outcomes [23-25]. Although various models have been proposed, the “Coaching” model affords many of the benefits of human interaction (eg, support and accountability) at a level of service that remains highly scalable [23]. Mohr’s Supportive Accountability (SA) Model, which is flexible and can be tailored to clinical conditions and service users, details that the intervention is supported by a coach who provides a social presence and accountability to boost motivation and engagement. Effectiveness studies have shown that various paraprofessionals can successfully be trained as coaches for a wide range of interventions and clinical populations [23].

Previous Pilot Trials of the UseIt! mHealth System

The UseIt! app combines aspects of PMT and CBT to provide parents with evidence-based skills to decrease disruptive behaviors in their children. To date, we have completed 2 pilot randomized controlled trials (RCTs) to test preliminary target engagement and effectiveness of the UseIt! mHealth system. The first trial tested the UseIt! mHealth system as a stand-alone intervention (N=34). Parent-child dyads enrolled in the study and were randomly assigned to either the UseIt! mHealth app condition (n=17) or to a waitlist condition (n=17). Overall, results supported the feasibility of the intervention, but attrition was high in the waitlist control group. This informed our decision to have an active control group rather than a waitlist control group in the current study. The second pilot trial tested the UseIt! mHealth system as an adjunct to therapy in community settings (N=39 parent-child dyads). Though treatment targets moved in the expected direction, high clinician turnover in community settings limited the sustainability and scalability of this approach. This informed our decision to include a bachelor’s level paraprofessional “coach” rather than a clinician in this study.

Study Aims and Hypotheses

Primary Aim

We aim to evaluate the effectiveness of the UseIt! mHealth system as both a stand-alone (n=108) and coach-assisted (n=108) intervention compared with a control app condition (n=108). We expect that (1) the 2 UseIt! intervention conditions will score higher on parenting knowledge (primary outcome) and show greater posttreatment reductions in disruptive behavior symptoms (secondary outcome) compared with the control condition, and (2) the coach-assisted UseIt! condition will score higher on parenting knowledge and show greater posttreatment reductions compared to the stand-alone UseIt! condition.

Secondary Aims

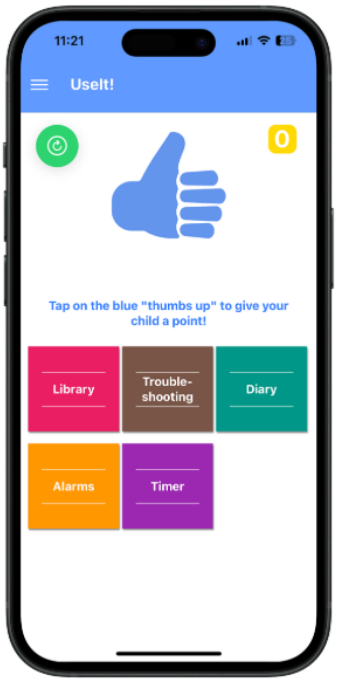
We will also test mechanisms of therapeutic change. In particular, we will test whether gains in knowledge of parenting skills are associated with reductions in disruptive behavior symptoms. Finally, we aim to evaluate the effectiveness of the components of UseIt! mHealth system. We will compare app usage across the stand-alone and coach-assisted conditions and test whether the app usage indices are associated with target engagement, knowledge of parenting skills, and symptom reduction at post-treatment. We expect that families who use the app more often will have higher skill acquisition and usage scores at post treatment ("dose" effects) though we do not have specific hypotheses regarding individual app features.

Methods

The UseIt! Smartphone App

The UseIt! system includes a free cross-platform mHealth app that runs on both iOS and Android devices. The app is securely connected to a portal where app feature usage is stored. The portal was designed for the research team to track and monitor the usage of the app by parents. The app contains six features: (1) a troubleshooting guide that provides detailed skill recommendations for problem situations, (2) a behavior diary for tracking behaviors and skills used each day, (3) a digital library that provides definitions and instructions for each skill, (4) a point counter for parents to award points to their children, (5) a skills-alarm for reminding parents to practice the various skills, and (6) a timer for use with parenting skills (eg, time-outs, managing screen time, routines). Users can examine diary entries, viewpoints awarded, and set the skills alarm through the app. See Figure 1 for a screenshot of the app's home page.

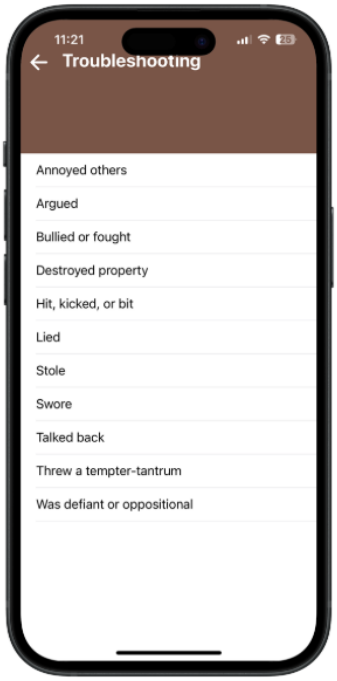
Figure 1. Home page of the UseIt! smartphone app.



Troubleshooting Guide

The UseIt! troubleshooting guide contains information to help parents effectively respond to problem behaviors. Parents are presented with a list of potential negative behaviors (eg, bullied or fought). After selecting a behavior, appropriate skill options (eg, time-out) are displayed with tips to effectively apply each skill. Once a skill has been used and the behavior has stopped, parents are reminded to praise their child for positive behaviors (Figure 2).

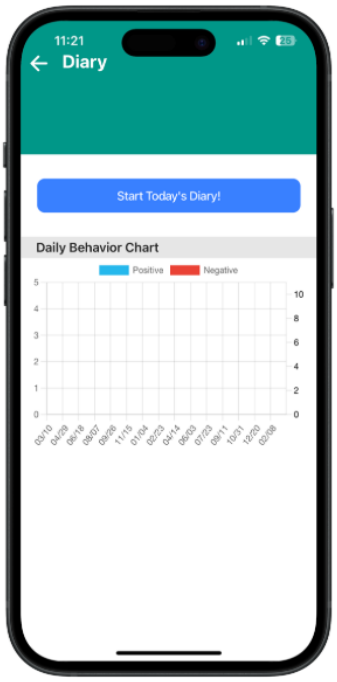
Figure 2. Troubleshooting guide.



Behavior Diary

The behavior diary cues participants (via a notification) to complete a series of questions about behaviors and PMT and CBT skills used each day. The results are displayed graphically and can be reviewed by the user to track progress over time. This allows the user to keep track of what skills the family has tried for different behaviors (both positive and negative child behaviors) and which ones have been helpful in various contexts (Figure 3).

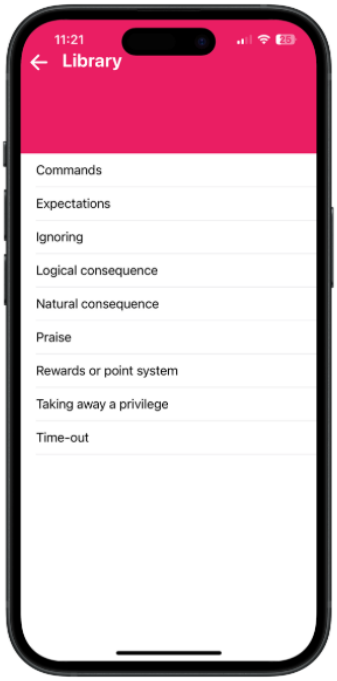
Figure 3. Daily behavior diary.



Digital Library

The UseIt! digital library provides detailed information about using strategies for positive and negative child behavior. Each skill is defined and presented with tips for how and when to effectively use each skill. The digital library contains more information than the troubleshooting guide and is designed as an information source for reviewing PMT and CBT topics (Figure 4).

Figure 4. Digital library.



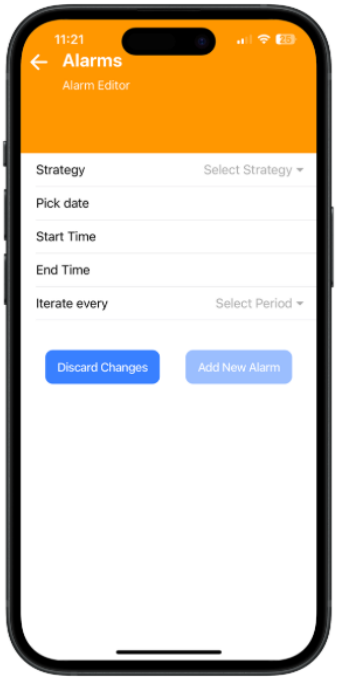
Point Counter

Treatment for disruptive behavior disorders typically includes prizes for treatment adherence, positive behaviors, and skill use. Parents can award points to children for target behaviors (eg, cleaning dishes) and skill usage. The UseIt! point counter features an on-screen button ("Give your child a point") which parents press to reward their child with a point. The feature functions as a digital rewards program that parents can use to keep track of points and reward their children. See Figure 1 for a view of the point counter window.

Skills Alarm

Skills alarms can be set at any time via the app. Users can set dates and times for notifications to activate. These notifications remind parents and children to practice specific skills throughout the week (eg, "remember to praise your child"). Parents are able to view a list of active and inactive alarms (Figure 5).

Figure 5. Skills alarm.



Timer

Timers can be set for use with a variety of skills (eg, time-outs, screen time management, and routines) to promote use of the skills.

Recruitment

We use a 2-pronged recruitment strategy to maximize enrollment. The two recruitment avenues are (1) the Clinical and Translational Science Institute patient registry (Pitt+Me) at the University of Pittsburgh and (2) BuildClinical. The Clinical and Translational Science Institute patient registry (Pitt+Me) is an institutional research participant registry that uses enhanced study descriptions and social media to engage the community in research. BuildClinical is a clinical trial recruiting system that helps investigators recruit participants for clinical trials more efficiently. Using study-specific digital advertisements displayed on search engines, health websites, and social media platforms, BuildClinical generates participant referrals. BuildClinical also provides tools to streamline the recruitment and prescreening process. The platform stores information in a HIPAA (Health Insurance Portability and Accountability Act)-compliant manner and allows for remote enrollment.

Participant Eligibility

Inclusion criteria for this study are that (1) parents or guardians must have a child between the ages of 5 and 8 years, (2) the child must be above the 90th percentile for either or both ODD and CD on the Vanderbilt Assessment Scale, (3) the child must be in residence with the parent or guardian for at least 80% of the time, (4) the parent or guardian must consent to study participation, and (5) the parent or guardian must have a smartphone device with daily internet access. Exclusion criteria are the child (1) having a known preexisting behavioral or mental health diagnosis requiring alternative treatment (eg, bipolar disorder, major depression, and pervasive developmental disorder) or (2) currently receiving treatment for childhood disruptive behavior.

Sample Size Determination

Power analyses were conducted in PASS (version 13.0.8; NCSS) to ensure that the sample size is adequate to test the primary hypotheses with adequate statistical power. All analyses assumed 0.80 power and 2-sided tests. Estimated sample sizes are determined based on an assumed 5% attrition and missing data post treatment (102 per group) and 10% total attrition at 6-months (97 per group). Using an analysis of covariance approach to test for differences across 3 groups post treatment (n=108 each) and assuming R^2=0.20 from 5 covariates, we expect 0.80 power (α=.05) to detect an effect size difference of Cohen *f*=0.16 among the 3 groups, *f*=0.14 (*d*=0.28) between both UseIt! treatment groups versus the control group, and *f*=0.18 (*d*=0.36) between any 2 groups.

Design

The study is a RCT with 3 conditions. Parents of children aged 5 to 8 years (n=324) are randomly assigned to one of 3 conditions: a stand-alone UseIt! app condition, a UseIt! app and Coach condition, and a control app condition (Smiling Mind app). Data are collected via web-based surveys at baseline, post treatment (4 months after baseline), and at 6-month follow-up. Randomization takes place after the baseline is completed.

Study Conditions

Stand-Alone UseIt! App Condition

Participants are assigned to the UseIt! App as a stand-alone intervention for 4 months.

UseIt! App + Coaching Condition

Participants are assigned to the UseIt! App and are provided with an mHealth “Coach” for 4 months. The primary objective of the coaching condition is to promote engagement with the UseIt! mHealth platform. The mHealth coach is a bachelor’s-level paraprofessional with a degree in psychology or an allied discipline (eg, social work) who provides support to parents in the coach-assisted condition. We selected a bachelor’s-level coach over a master’s-level coach to enhance the scalability of this intervention condition. The coach uses the SA coaching model using the training guidelines outlined by Dopke and colleagues [26]. During the intervention phase of the study, parents are contacted by the coach once per week by phone and also allowed to contact the coach during regular business hours. The coach provides motivation and accountability but does not provide therapeutic or clinical support. The primary goal of the coach is to increase participant engagement with the UseIt! mHealth system. Specific coaching content and tasks include (1) social support, (2) promoting engagement with the app, (3) goal setting (4) monitoring progress, and (5) encouragement and motivation. Parents are provided with appropriate referrals for any crises. The coach is instructed to respond to questions that lie outside the domains of motivation and accountability (ie, content-specific therapeutic support) by redirecting the parent to the content-specific app features (ie, Troubleshooting and Library). Only the parents interact with the coach. To maintain the scalability of the condition, the target time spent with each family is 15-30 minutes per week. The coach maintains a “coach-log” to track the frequency, duration, and content of contact with each participant.

Control Condition (Smiling Mind App)

Parents in the control app condition are assigned to use a mindfulness app called Smiling Mind [27] for 4 months. We selected a mindfulness app because it is an active control condition, but one that we do not expect to engage the same treatment targets as the UseIt! mHealth system. Meta-analytic findings indicate that mindfulness-based interventions for school-age children are associated with medium to large effect sizes for disruptive behaviors [28]. For parents, dispositional mindfulness has been found to be associated with lower rates of children’s externalizing and internalizing problems [29], and a mindfulness-based program was associated with decreased parent reports of child attention-deficit/hyperactivity disorder symptoms and decreased parental stress [30]. Other studies with youth found that a combined approach (parent and youth mindfulness training) improved externalizing problems and attention [31]. As an active control condition, we expect that a mindfulness app will likely have some influence on parenting

and child behavior. This provides us with a rigorous control condition while also allowing us to test the specificity of target engagement. We expect the Smiling Mind app will only enhance mindfulness, but not PMT and CBT skills (other than mindfulness). We selected the Smiling Mind app [27] in particular because (1) it can be downloaded at no cost, (2) it is available for both Android and Apple (iPhone) devices, and (3) app-use can be tracked.

Study Procedures and Randomization

Participants provide their contact information to the Pitt + Me or BuildClinical systems after accessing the study advertisement. Trained research assistants then contact families and conduct the initial screening to determine study eligibility. If determined eligible, a future call is scheduled to obtain consent from the parent, and assent from the child to participate. After consent, parents are provided a Qualtrics link to complete the initial baseline assessment. After completion of the assessment, families are randomly assigned to group 1 (standalone UseIt! app; n=108), group 2 (UseIt! app + coach; n=108), or group 3 (control app condition; n=108). We use stratified randomization to ensure that the groups are equivalent on key clinical features (screening severity and referral source (ie, Pitt + Me or BuildClinical). Parents assigned to the Coach condition are walked through the initial setup and login process, along with a brief training on how to use the applications over the phone. Families can be set up and trained in approximately 30 minutes. If parents cannot be reached after 3 weeks, instructions are sent via email. Parents assigned to the stand-alone UseIt! app condition are sent a tutorial video with the same information. Parents use the app condition assigned for 4 months before the administration of the posttreatment assessment, via Qualtrics. Six months following the posttreatment assessment, parents again are prompted to complete the 6-month follow-up assessment via Qualtrics.

Measures

Table 1 for a summary of study constructs, measures, and assessment time points.

Table 1. Measures.

Construct	Measure or instrument	Time point
PMT[a] and CBT[b] skill knowledge	Knowledge of Effective Parenting Test	Baseline, post treatment, 6-month follow-up
Symptom severity	Vanderbilt Assessment Scale	Baseline, post treatment, 6-month follow-up
Parenting practices	Alabama Parenting Questionnaire	Baseline, post treatment, 6-month follow-up
Parent depression	7-item Generalized Anxiety Disorder Scale	Baseline, post treatment, 6-month follow-up
Parent anxiety	9-item Patient Health Questionnaire	Baseline, post treatment, 6-month follow-up
Parenting stress	Parental Stress Scale	Baseline, post treatment, 6-month follow-up
Social support	Social Provisions Scale	Baseline, post treatment, 6-month follow-up
PMT and CBT skill use	Parenting Skill Use Diary	Baseline, post treatment, 6-month follow-up
App use	Automatically recorded	Active app phase
Mindfulness	Mindful Attention Awareness Scale	Baseline, post treatment, 6-month follow-up
Service use	Service Assessment for Children and Adolescents	6-month follow-up
Supportive accountability	Supportive Accountability Inventory	Post treatment (coach condition only)
Usability	Post-Study Usability Questionnaire	Post treatment
Technological literacy	Technology Self-Assessment Tool	Baseline

[a]PMT: parent management training.

[b]CBT: cognitive behavioral therapy.

Primary Outcome: PMT and CBT Skill Knowledge

The knowledge of effective parenting test [32] is a 21-item measure of parental knowledge of effective parenting skills. The measure was developed as a potential treatment target for evidence-based psychosocial treatments of disruptive behaviors in children. The knowledge of effective parenting test assesses parental knowledge of domains including praise, rewards and point systems, attending and ignoring, commands and expectations, consequences, and time-outs. Parents are presented with a series of video and text-based parenting scenarios and questions with 4 multiple-choice response options. Scores range from 0 to 21. The measure has good reliability (Cronbach α=0.84). The measure has also demonstrated convergent validity with other measures of parenting knowledge and parenting-related constructs (eg, child behavior and parental psychopathology).

Secondary Outcomes

Symptom Severity

The Vanderbilt Assessment Scale-Parent Report (VASPR [33]) is a 55-item parent-report screen for attention-deficit hyperactivity disorder (ADHD), ODD, and CD. It also includes 7 items on internalizing symptoms and 8 items on school performance and social functioning. Symptom items are rated using a 4-point scale and the performance items are rated on a

5-point scale. The measure has Cronbach alphas ranging from 0.79 to 0.95 and strong evidence of construct validity.

Parenting Practices

The Alabama Parenting Questionnaire (APQ [34]) is a 42-item measure that assesses five dimensions of parenting: (1) positive involvement, (2) monitoring, (3) positive discipline, (4) consistency, and (5) corporal punishment, using a 5-point scale ranging from 1 to 5. The internal consistency of the scale is acceptable with α values for the 5 domains ranging up to .80. The measure has well-established construct validity.

Parent Depression

The Patient Health Questionnaire-8 (PHQ-8 [35]) measures symptoms of depression using a 4-point scale from "not at all" to "nearly every day." Total scores range from 0 to 24. The measure has a reported Cronbach α of .82 and strong construct validity.

Parent Anxiety

The General Anxiety Disorder-7 Scale (GAD-7 [36]) is a 7-item measure of anxiety. Items are rated on a 4-point scale from "not at all" to "nearly every day." The measure includes an item to assess the duration of anxiety symptoms. The measure has excellent internal consistency (Cronbach α=0.92), good test-retest reliability (intraclass correlation [ICC]=0.83), and strong convergent validity with other measures of anxiety.

Parenting Stress

The Parental Stress Scale (PSS [37]) is an 18-item measure of stress related to parental experiences. Items are rated on a 5-point scale from "strongly disagree" to "strongly agree." Scores range from 18 to 90. The internal consistency of the scale is acceptable with a Cronbach α of 0.83, a test-retest reliability of 0.81 (ICC), and strong convergent validity of both other parental stress measures (ie, Parental Stress Index), and other measures related to parenting stress (eg, loneliness, marital satisfaction, and social support).

Social Support

The Social Provisions Scale [38] is a 24-item measure that assesses 6 dimensions of support, including attachment, social integration, opportunity for nurturance, reassurance of worth, reliable alliance, and guidance. The measure uses a 5-point scale ranging from 1 to 4, strongly disagree to strongly agree. The measure has been validated across samples, with Cronbach α ranging from 0.65 to 0.76 for the 4 subscales, and a total reliability estimate of 0.91. The measure also demonstrated convergent validity with related measures of social support.

PMT and CBT Skill Use

The Parenting Skill Use Diary [39] assesses daily use of parenting skills in everyday parenting contexts (eg, child sharing and helping, hitting, and fighting). Respondents are presented with a checklist of behaviors to report on for the past week. For each behavior they select, they are next asked to identify which skills (eg, praise, reward, time-out, and loss-of-privilege) they used in responding to the behaviors. The instrument has demonstrated the ability to capture significant between-person variability in appropriate PMT skills. A weekly summary score discriminated between parents or guardians whose children screened positive versus negative for CD (area under the receiver operating characteristic curve [AUC]=0.72) and ODD (AUC=0.70).

App Use

Parents assigned to both UseIt! conditions (ie, stand-alone app and coach conditions) have their data stored on the secure portal, accessible to the research team. We collect the behavior diary tracked by parents, which displays data on child behavior (both positive and negative) along with CBT and PMT skills. We are also collecting data on time spent on the app along with modules accessed. App usage (eg, modules used and time spent) is also tracked for the Smiling Mind app (control condition).

Mindfulness

The Mindful Attention Awareness Scale [40] is a 15-item scale designed to assess core characteristics of mindfulness. Parents are asked how often they are engaging in a variety of mindfulness-related behaviors, such as finding it difficult to stay focused on what is happening in the present moment, finding themselves preoccupied with the future or past, and not noticing feelings of physical tension or discomfort until the really grab their attention. The measure's response scale ranges from 1 (almost always) to 6 (almost never). The measure is scored as an average of all 15 items. The measure has adequate validity (Cronbach α=0.87 and convergent validity with other measures of mindfulness (eg, mood disturbances and stress).

Service Use

An abbreviated version of the Service Assessment for Children and Adolescents (SACA [41]; 25 items) was used to measure mental health service usage. The SACA asks about various inpatient and outpatient treatment services for mental or behavioral health problems that have been used by the child in the past 6 months [41]. Most items are yes or no questions. The measure is a widely used research tool with strong evidence of reliability and validity.

Supportive Accountability

The Supportive Accountability Index (SAI [42]) is an 8-item measure of how well a given platform functioned to help keep parents accountable to accomplish a given goal. The measure was included to assess the effectiveness of the Coach in the coach condition of the app in helping to keep parents accountable with skill learning and use. Items are rated on a 1-7 scale, from 1=strongly disagree to 7=strongly agree. Total scores are summed, ranging from 8-56. The measure has acceptable validity (Cronbach α=0.68) and good convergent and divergent validity.

Usability

The 19-item Post-Study System Usability Questionnaire (PSSUQ [43]) is used to assess overall user satisfaction with the UseIt! apps. Internal consistency of the PSSUQ is excellent (α=.91 to .96).

Technological Literacy

The Technological Self-Assessment Scale (TSAT [44]) is a 13-item parent report screen for technological ability. The

measure was created for this study by the research team to provide an indicator of parent knowledge and experience with their computers and phones. For example, items ask parents if they know how to search for information on the internet if they have ever downloaded an app, and if they have social media accounts. Items are scored Yes or No, and scores range from 0 to 13.

Data Analyses

Primary Analyses

Our primary analytic strategy will use intent-to-treat analyses. We will examine reasons for any missing data and perform multiple imputation (eg, Multiple Imputation for Chained Equations [45]) for data missing at random. To evaluate the effectiveness of the UseIt! mHealth system as both a stand-alone (n=108) and coach-assisted (n=108) intervention compared to a control app condition (n=108), we will regress the primary and secondary outcomes on the study condition. We will also perform a priori tests to compare both UseIt! groups to the control and to compare the coach-assisted and stand-alone UseIt! groups. Cohen *d* effect sizes will be estimated for between-group differences as well as pre-post changes within each group.

Secondary Analyses

We will also test whether gains in knowledge of parenting skills are associated with symptom reduction. We will regress the posttreatment knowledge of parenting skills on study condition, pretreatment knowledge, and their interaction. We will also compare app usage across stand-alone and coach-assisted conditions and test whether the app usage indices are associated with target engagement and symptom reduction at post-treatment. App usage outcomes will include the number of each of the app features that are used, along with frequency and duration (in minutes). We will use generalized linear models with the appropriate link (eg, log link for count data and identity link for continuous outcomes) to regress each usage outcome on study condition (stand-alone versus coach).

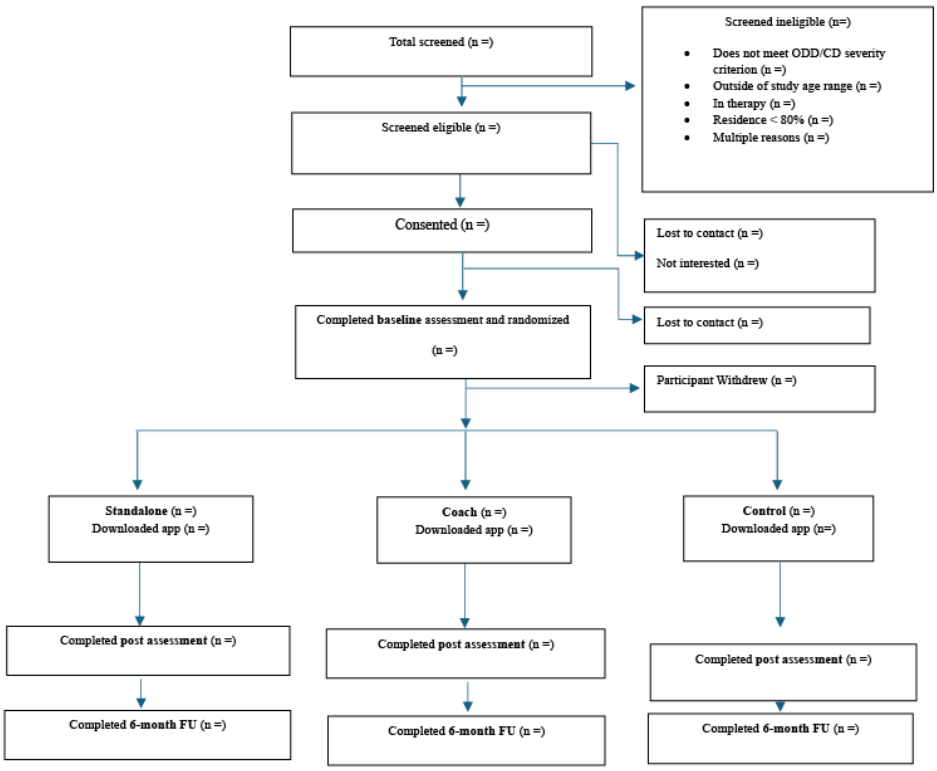
Ethical Considerations

Ethical approval has been obtained from the institutional review board at the University of Pittsburgh (protocol # STUDY22030138). Informed consent from parents is obtained by trained research staff. So as not to artificially inflate the rates of app usage, participants are not compensated for using the app but only for assessments completed. Participants in each condition are compensated US $20 for baseline assessment completion, US $40 for the postassessment, and US $60 for the 6-month follow-up assessment. All study data are deidentified and stored securely.

Results

The study was funded in September 2022. Study recruitment began in December 2022. As of December 2024, we have recruited over half (n=214) of our target sample of 324 parent-child dyads. Of these, 72 parents have been assigned to the stand-alone condition, 71 to the coach condition, and 71 to the control condition. Recruitment is ongoing and completion is expected in another 12 to 14 months. Follow-up data collection is expected to be completed by the end of 2026. Figure 6 displays the trial flowchart for this study.

Figure 6. Trial flowchart. FU: follow-up.



Discussion

mHealth parenting programs have the potential to improve outcomes for parents and children [14]. Further, supportive accountability, defined as a degree of human interaction throughout the program, has the potential to enhance outcomes for mHealth interventions by increasing motivation and engagement [23]. The current study aims to add to the literature base on effective mHealth interventions to treat disruptive behaviors in children. The study will allow us to test the degree to which the UseIt! app can modify parenting (ie, skill acquisition and usage) and whether such target engagement is associated with symptom reduction. The UseIt! mHealth system also allows researchers unique access to data on child behaviors and parent skills tracked on a daily basis. This data will not only allow parents to track behaviors and skills for themselves (allowing parents to visualize progress) but will also allow researchers a system to track change over time. The coaching model used in the study is highly scalable, providing a flexible model of coaching that can be tailored to a variety of clinical conditions and service settings. We expect that those assigned to the coach condition will have the largest increases in parent knowledge and skill use, along with the largest decreases in child behavior problems. We also expect that those assigned to the UseIt! stand-alone app condition will report greater improvements in parent knowledge, skill use, and child behavioral concerns, compared with the control app condition.

Strengths and Limitations

This study has several strengths and adds to the existing literature. To our knowledge, it is the largest RCT of an mHealth smartphone-based app targeting child behavioral concerns to date. The trial adds to the literature base of the SA model [23] and aims to provide preliminary evidence to the effectiveness of the model in the context of a smartphone-based app targeting parents. We selected clinically relevant outcome measures for the trial, including validated measures of parenting knowledge, parent skill use, parent mental health, and child behavior problems. We also collect app usage data, both for use as a moderator of intervention effects, and to inform future work to promote increased usage in other studies. A few limitations are also worth noting. First, we expect up to 10% attrition over the course of the study. We have taken several steps to minimize attrition, including increasing participant compensation at each time point. We also factored 10% attrition into our power analysis to determine sample size, ensuring that the trial will still be fully powered. Another limitation is that outcome measures are based primarily on parent report. This limitation is mitigated by substantial evidence that parents are accurate reporters of child behavior problems.

Conclusions and Future Directions

In summary, the current study aims to address a gap in the literature regarding the feasibility, effectiveness, and utility of a smartphone app that includes a coach-assisted arm for treating disruptive behaviors in young children. Digital therapeutics have the potential to enhance the reach and scalability of skills-based psychosocial interventions, as even small effects can be meaningful on a population level if the intervention can be delivered efficiently on a large scale at a low cost. The UseIt! mHealth system is able to deliver therapeutic content to parents across a variety of settings and has the potential for meaningful impact. Findings from the current trial will advance scientific knowledge and have the potential to enhance clinical practice.

Acknowledgments

This study was supported by grants to the first author from the National Institutes of Health (R01HD106930; R34MH106619; R21HD090145; K01MH093508) and the Klingenstein Third Generation Foundation (Fellowship in Access to Care). The authors would like to thank Abby R Angus and Emma K Toevs for assistance with the study.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer-review report from CPDD - Child Psychopathology and Developmental Disabilities Study Section (National Institutes of Health, USA).
[PDF File (Adobe PDF File), 127 KB - resprot_v14i1e67051_app1.pdf]

Multimedia Appendix 2
CONSORT-eHEALTH checklist (V 1.6.1).
[PDF File (Adobe PDF File), 620 KB - resprot_v14i1e67051_app2.pdf]

Multimedia Appendix 3
Spirit Checklist.
[DOC File , 121 KB - resprot_v14i1e67051_app3.doc]

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Abbreviations

ADHD: attention-deficit/hyperactivity disorder
APQ: Alabama Parenting Questionnaire
AUC: area under the receiver operating characteristic curve

CBT: cognitive behavioral therapy
CD: conduct disorder
DBD: disruptive behavior disorder
DSM-5: Diagnostic and Statistical Manual of Mental Disorders (Fifth Edition)
GAD-7: General Anxiety Disorder-7 Scale
HIPAA: Health Insurance Portability and Accountability Act
mHealth: mobile health
ODD: oppositional defiant disorder
PHQ-8: Patient Health Questionnaire-8
PMT: parent management training
PSS: Parental Stress Scale
PSSUQ: Post-Study System Usability Questionnaire
RCT: randomized controlled trial
SA: Supportive Accountability
SACA: Service Assessment for Children and Adolescents
SAI: Supportive Accountability Index
TSAT: Technological Self-Assessment Scale
VASPR: Vanderbilt Assessment Scale-Parent Report

Edited by A Schwartz; submitted 11.10.24; this is a non–peer-reviewed article;accepted 14.02.25; published 11.03.25.

Please cite as:
Lindhiem O, Tomlinson CS, Kolko DJ, Silk JS, Hafeman D, Wallace M, Setiawan IMA, Parmanto B
Novel Smartphone App and Supportive Accountability for the Treatment of Childhood Disruptive Behavior Problems: Protocol for a Randomized Controlled Trial
JMIR Res Protoc 2025;14:e67051
URL: https://www.researchprotocols.org/2025/1/e67051
doi:10.2196/67051
PMID:

Protocol

Healthy Mom Zone Adaptive Intervention With a Novel Control System and Digital Platform to Manage Gestational Weight Gain in Pregnant Women With Overweight or Obesity: Study Design and Protocol for a Randomized Controlled Trial

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Abstract

Background: Regulating gestational weight gain (GWG) in pregnant women with overweight or obesity is difficult, particularly because of the narrow range of recommended GWG for optimal health outcomes. Given that many pregnant women show excessive GWG and considering the lack of a “gold standard” intervention to manage GWG, there is a timely need for effective and efficient approaches to regulate GWG. We have enhanced the Healthy Mom Zone (HMZ) 2.0 intervention with a novel digital platform, automated dosage changes, and personalized strategies to regulate GWG, and our pilot study demonstrated successful recruitment, compliance, and utility of our new control system and digital platform.

Objective: The goal of this paper is to describe the study protocol for a randomized controlled optimization trial to examine the efficacy of the enhanced HMZ 2.0 intervention with the new automated control system and digital platform to regulate GWG and influence secondary maternal and infant outcomes while collecting implementation data to inform future scalability.

Methods: This is an efficacy study using a randomized controlled trial design. HMZ 2.0 is a multidosage, theoretically based, and individually tailored adaptive intervention that is delivered through a novel digital platform with an automated link of participant data to a new model-based predictive control algorithm to predict GWG. Our new control system computes individual dosage changes and produces personalized physical activity (PA) and energy intake (EI) strategies to deliver just-in-time dosage change recommendations to regulate GWG. Participants are 144 pregnant women with overweight or obesity randomized to an intervention (n=72) or attention control (n=72) group, stratified by prepregnancy BMI (<29.9 vs ≥30 kg/m^2), and they will participate from approximately 8 to 36 weeks of gestation. The sample size is based on GWG (primary outcome) and informed

by our feasibility trial showing a 21% reduction in GWG in the intervention group compared to the control group, with 3% dropout. Secondary outcomes include PA, EI, sedentary and sleep behaviors, social cognitive determinants, adverse pregnancy and delivery outcomes, infant birth weight, and implementation outcomes. Analyses will include descriptive statistics, time series and fixed effects meta-analytic approaches, and mixed effects models.

Results: Recruitment started in April 2024, and enrollment will continue through May 2027. The primary (GWG) and secondary (eg, maternal and infant health) outcome results will be analyzed, posted on ClinicalTrials.gov, and published after January 2028.

Conclusions: Examining the efficacy of the novel HMZ 2.0 intervention in terms of GWG and secondary outcomes expands the boundaries of current GWG interventions and has high clinical and public health impact. There is excellent potential to further refine HMZ 2.0 to scale-up use of the novel digital platform by clinicians as an adjunct treatment in prenatal care to regulate GWG in all pregnant women.

International Registered Report Identifier (IRRID): DERR1-10.2196/66637

(JMIR Res Protoc 2025;14:e66637) doi:10.2196/66637

KEYWORDS

pregnancy; gestational weight gain; physical activity; healthy eating; overweight; obesity; intervention

Introduction

Background

High maternal prepregnancy BMI and high gestational weight gain (GWG) elevate the risks for poor pregnancy outcomes (eg, gestational diabetes and hypertension) and fetal outcomes (eg, large for gestational age birth weight) [1-6]. High BMI and GWG may also "program" the child's metabolism for life [7,8] and increase the future risks for obesity and type 2 diabetes in both mothers and their offspring [1-6]. As such, managing GWG has high clinical and public health significance, and it can improve maternal health and impact the etiology of obesity or diabetes in offspring at a crucial time in the life cycle [1-6,8].

Guidelines from the Institutes of Medicine (IOM) [1] and National Academy of Medicine [2] recommend that the optimal total GWG should be based on a woman's prepregnancy BMI category (ie, overweight: 6.8-11.3 kg; obese: 5.0-9.1 kg). However, evidence from a meta-analytic review including over 1 million pregnant women found that nearly 50% of women exceeded their recommended goals [9], and this was prevalent among those with normal weight as well as those with overweight or obesity. Furthermore, data from a meta-analysis of almost 200,000 women from 25 international cohort studies in the LifeCycle Project [6] showed the highest risk for adverse outcomes among women with both high BMI and high GWG. Given these concerns as well as the rapidly changing landscape of health care delivery since the COVID-19 pandemic, there is a critical and timely need for scalable approaches to effectively regulate GWG. One such strategy that may reach more pregnant women and reduce the burden on prenatal clinicians who monitor GWG is an automated approach that relies on a digital platform with remote delivery and passive remote data collection to monitor and effectively and efficiently regulate GWG.

Prior Work

Our team's prior work successfully constructed energy balance models to predict maternal GWG [10] and infant birth weight [11]. Expanding the work of Thomas et al [12], we built a novel dynamic mathematical model of energy balance and behavior to predict GWG [13,14]. It describes how physical activity (PA) and energy intake (EI) behaviors are influenced by social cognitive determinants (attitude, subjective norm, perceived control, intention, and self-regulation) [15-17] and depicts how components (ie, education, behavior coaching, goal setting, nutrition counseling, and engaging in PA and healthy eating activities) impact PA and EI social cognitive determinants and behaviors to regulate GWG. We also explored how the energy balance model could be extended to explain infant birth weight [11,18].

Prior research has shown that behavioral interventions can impact GWG [19-27] and more specifically that participants who received behavioral intervention components (eg, counseling, guided PA, and prescribed diet) had a lower mean GWG, decreased likelihood of exceeding GWG guidelines, and lower risk for adverse maternal and infant outcomes [20]. There was also evidence for a dose-response relationship whereby intensive interventions with more subject contact were associated with a stronger impact on GWG [20]. Moreover, the findings from qualitative and prospective cohort studies support an intensive approach to managing GWG in pregnant women with overweight or obesity because they may be more likely than women with underweight or normal weight to overestimate the amount of weight they should gain, underreport EI, and have low motivation to engage in PA on their own [28-41]. Taken together, there is ample evidence from the literature for an approach that considers the unique needs of pregnant women with overweight or obesity and personalizes intervention dosages to regulate GWG.

Many GWG interventions use a "one size fits all" approach and are not designed to consider individual variability in how women gain weight over the course of gestation. Our approach adapts personalized dosages for each woman in a way that gives more intensive treatment only to the women who need more assistance to regulate GWG. We piloted a proof-of-concept study [42] and feasibility-initial impact randomized trial [8,10,19,43-45] to examine the impact of the Healthy Mom Zone (HMZ) intervention on GWG. The social cognitive theory–based components [15-17] noted above were designed with the Multiphase Optimization Strategy [46] translational science framework [47-50], and control systems methodology [51-55],

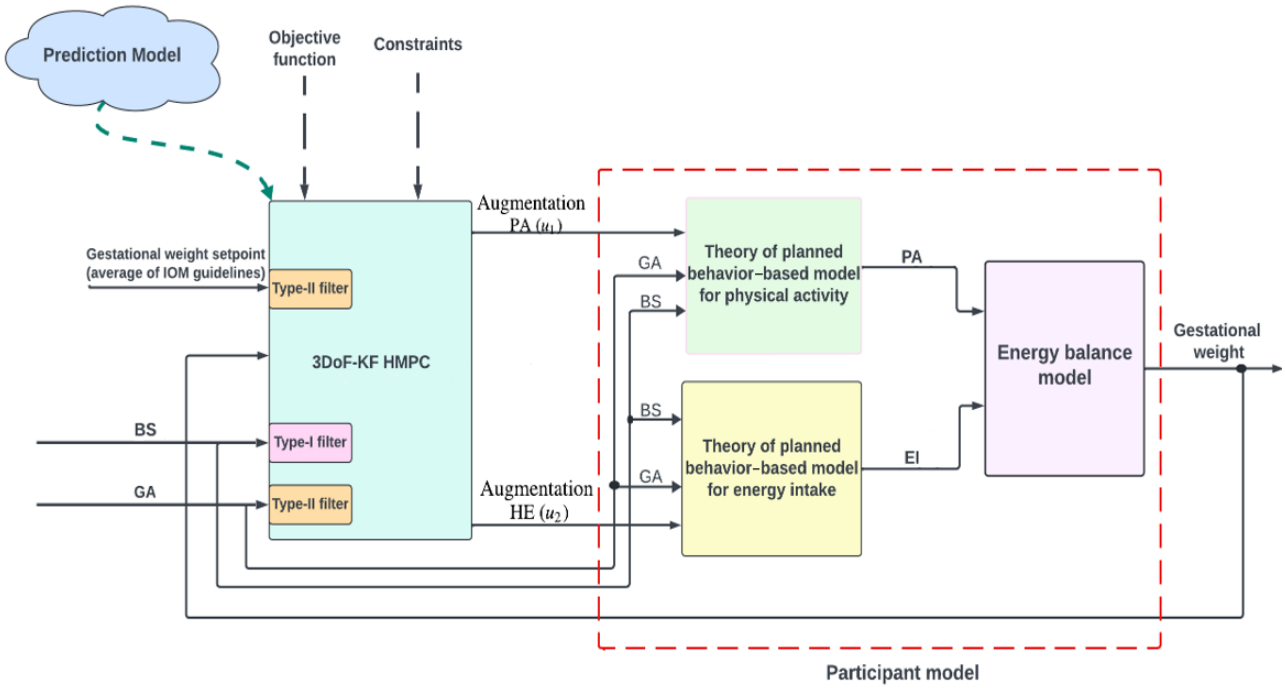
with the long-term goal to scale-up use by clinicians as an adjunct treatment to prenatal care in order to regulate GWG. This multiphase approach [46] builds an intervention in a principled manner whereby key constraints expected to impact scalability (eg, implementation feasibility and subject or staff burden) are considered from the start so that the end goal is an optimized (effective and efficient) and scalable intervention that delivers the best possible outcome [46]. Our translational science framework [47-50] guided by the Quality Implementation Framework [49] and Quality Implementation Tool [50] aligns with the paradigm shift in the literature to prospectively examine implementation markers (eg, subject acceptability, dosage exposure, and staff burden) from the start of an intervention to identify and resolve challenges during delivery that impact efficacy and scalability [49,50].

Our feasibility trial that randomized 31 pregnant women with overweight or obesity to the adaptive GWG intervention (delivered in person or remotely) or a control group over the course of pregnancy and used mobile health tools and online surveys to measure study outcomes showed high measurement compliance (85%), low burden (eg, average 1 min per day to complete measures), and low attrition (3%) [19]. The control system driven by decision rules and a woman's observed GWG informed when to adapt dosages (GWG within goals [1,2], maintain dosage; GWG greater than goals, adapt dosage) [19]. Participants in the intervention group had a 21% lower mean GWG and were more likely to have GWG within goals than controls. Exploratory analyses showed promise for the HMZ intervention to impact secondary outcomes, including PA minutes, active kcal, EI kcal, and PA and EI social cognitive determinants. Furthermore, maternal nighttime awakenings were related to higher GWG [45], and maternal eating behaviors (uncontrolled eating or restraint) were related to GWG and infant birth weight [44].

Because our long-term goal is to deliver the best possible impact on GWG and maternal or infant outcomes and develop an approach that is scalable for future use in the real world, we used these feasibility findings to make refinements to the intervention content (eg, promoting healthy sleep or eating behaviors), delivery (all content available for remote delivery to ensure scalability), and decision process for evaluating and predicting GWG. More specifically, our initial control system was manually operated (ie, plotted each woman's weight in individual participant files) and not particularly scalable. We thus improved this system by designing a new model-based control system with a hybrid model predictive control algorithm and our dynamic model of energy balance and behavior (Figure 1) [10,13,56]. This enables projections of within-person GWG over time (even when data are missing at the current time point) and has been found in past studies to yield robust personalized suggestions and accurate inferential results even with missingness [56-68]. We also built an architecture for a novel digital platform that makes it possible to deliver just-in-time recommendations directly to a subject in ways that target a broader array of outcomes and can reach more women. The platform provides a web-based interface equipped with secure user access control that automates the linkage of subject data collected with mHealth tools to the new model-based predictive control system that implements a Control Optimization Trial approach [10,51] consisting of semiphysical system identification and Hybrid Model Predictive Control. The platform displays graphical or numeric summaries of a woman's past weight, behaviors (eg, PA, EI, and sleep), social cognitive determinants, and other factors; computes optimized dosage changes across multiple maternal variables; and produces a host of personalized PA or EI strategies to regulate GWG. This refined version of the intervention is denoted HMZ 2.0.

In order to activate recruitment, examine participant compliance with the measurement protocol, pilot test the HMZ 2.0 data transfer pipeline, examine intervention session delivery and user acceptability of the digital platform, and conduct simulations for controller-recommended dosage changes, we conducted a 28-day pilot study.

Figure 1. Dynamic model of energy balance and behavior to predict gestational weight gain (GWG). The intervention components are education, counseling, goal-setting, self-monitoring, and physical activity (PA)/healthy eating (HE) active behavior strategies (eg, guided activity sessions and cooking demonstrations). The figure depicts the block diagram of the closed-loop control system framework for managing GWG in pregnant women with overweight or obesity and describes the influence of intervention components, baseline intervention dosage, and gestational age (GA) on GWG. The participant model consists of 2 behavioral models targeting PA and energy intake (EI) behaviors, respectively, and an energy balance model. Outputs from the behavioral models serve as inputs to the energy balance model, which calculates changes in GWG by assessing the difference between EI and energy expenditure. The hybrid model predictive controller (HMPC) uses filtered signals of set point and measured disturbances (baseline intervention dosage and GA). A Type-I filter is used to filter the baseline, represented by a binary signal that indicates the preintervention phase (0) or the intervention phase (1). In contrast, a Type-II filter is used to filter the set point and GA. The HMPC-based optimizer determines a sequence of control actions, referred to as PA and HE dosage augmentations. BS: baseline; IOM: Institutes of Medicine.



HMZ 2.0 Pilot Study Results

We recruited and enrolled 10 pregnant women (mean age: 32.1 years; mean gestational age at enrollment: 14 weeks). Participants completed the HMZ 2.0 preintervention measurement protocol lasting 7 to 9 days (depending on the day of enrollment), completed daily and weekly study measures over a 3-week period while also participating in three 60-minute weekly intervention sessions (content from the first 3 weeks of the HMZ 2.0 baseline intervention) delivered by a trained staff member through the HMZ 2.0 digital platform, and completed the postintervention measurement protocol (7-9 days) and a poststudy brief interview to understand user acceptability. The results of this pilot study are presented below.

We had 59 participant contacts, of which 31 (53%) were assessed for eligibility and 10 (32% of eligible participants) were enrolled in the pilot study. Successful recruitment of participants involved social media (30%), community-based flyers and handouts (eg, campus locations and local events such as farmer's markets; 30%), word of mouth (20%), and clinic referrals (20%).

Participant compliance with the HMZ 2.0 measurement protocol was excellent, with compliance rates of 88% for the daily or weekly online surveys and MyFitnessPal app, 92% for using the Fitbit Aria Wi-Fi scale each day to assess weight, and 98% for wearing the Fitbit Charge 6 monitor each day to assess PA, sedentary behavior, and sleep behaviors. Moreover, the flow of data through the HMZ 2.0 pipeline was exceptional. Data transfer from devices and Research Electronic Data Capture (REDCap) to the digital platform was smooth, with <2% evidence of technical problems or glitches, and 100% of problems were resolved without issue.

A total of 30 intervention sessions (3 per participant) were delivered, of which 80% (24/30) were delivered with a hybrid approach (in person with the platform) and 20% (6/30) were delivered with a fully remote approach using Zoom and the platform. Attendance and compliance with the sessions were 100%. All the women (10/10, 100%) liked the utility of the HMZ 2.0 digital platform, and 90% (9/10) liked to see their real-time data and set weekly goals with trained study staff. In the poststudy brief interview, 1 woman commented that it was "nice to use [the platform] prior to sessions so I was able to come prepared and ask questions." Another woman said, "The platform was easy to move from page to page." A third woman noted, "We covered different topics during the sessions, so I liked being able to go back to the platform and look at the content again." The participants also provided constructive feedback on the platform and suggested the following refinements: soften the color scheme on the website pages, include a page with session schedule and location information, and include a link to directly email the study staff to reduce the burden of looking through study materials for contact information. The platform was refined to address these concerns.

Simulations to illustrate the estimated model are presented in Figure 2, which shows the Control Optimization Trial framework for the recommended dosages within the system identification phase, adhering to the 2-week and 3-week delay. The first panel displays the participant's weight in pounds (black solid line) and the setpoint (solid magenta line), which indicates the mean of the IOM guidelines (dashed red line) [1]. Different colors are used to represent the various intervention phases. The preintervention phase lasts for 7 to 9 days (9 days in this case), followed by a 2-week baseline period. During both the preintervention and baseline phases, no augmentations or dosages are administered. The first dosage is recommended after 2 weeks in the dosage 1 phase, starting on gestational day 126. The second dosage follows 2 weeks after dosage 1 in the dosage 2 phase. The second panel contains 2 subpanels: one for the manipulated variable augmentation PA and another for PA kcal. The last panel similarly includes subpanels for augmentation healthy eating and EI kcal. The simulation results show that the hybrid model predictive controller effectively manages the participant's weight within the IOM bounds once the controller is activated. As illustrated, both in the system identification and controller phases, recommendations for PA or healthy eating dosages lead to reduced EI (healthy eating dosage recommended) or increased PA (PA dosage recommended), ultimately facilitating weight reduction through decreased EI and increased PA.

After the dosage 2 phase, the controller phase begins, during which the controller recommends further dosages based on predicted participant weight and the logic outlined in Figure 3, which illustrates the conceptual framework for the controller's augmentation or dosage recommendations, operating similarly to a finite state machine. Each state is represented by 2 digits: the first digit denotes augmentation PA (PA dosage) and the second digit indicates augmentation EI (healthy eating dosage), and either the PA dosage or EI dosage is updated at any given time. The controller recommends dosages with a minimum user-specified delay of 2 weeks between all dosages, except between dosage 2 and dosage 3, where a 3-week delay is specified. Transitions between dosages are governed by an auxiliary signal a_k. If a_k equals 1, the controller can transition from the current dosage state to the next; otherwise, it remains in the current dosage state.

Figure 2. Simulation illustrating the various stages of the control optimization trial implemented in the Healthy Mom Zone (HMZ) 2.0 intervention using an estimated model of an HMZ 1.0 representative participant. EI: energy intake; HE: healthy eating; HMPC: hybrid model predictive controller; IOM: Institutes of Medicine; PA: physical activity; RMSE: root mean square error.

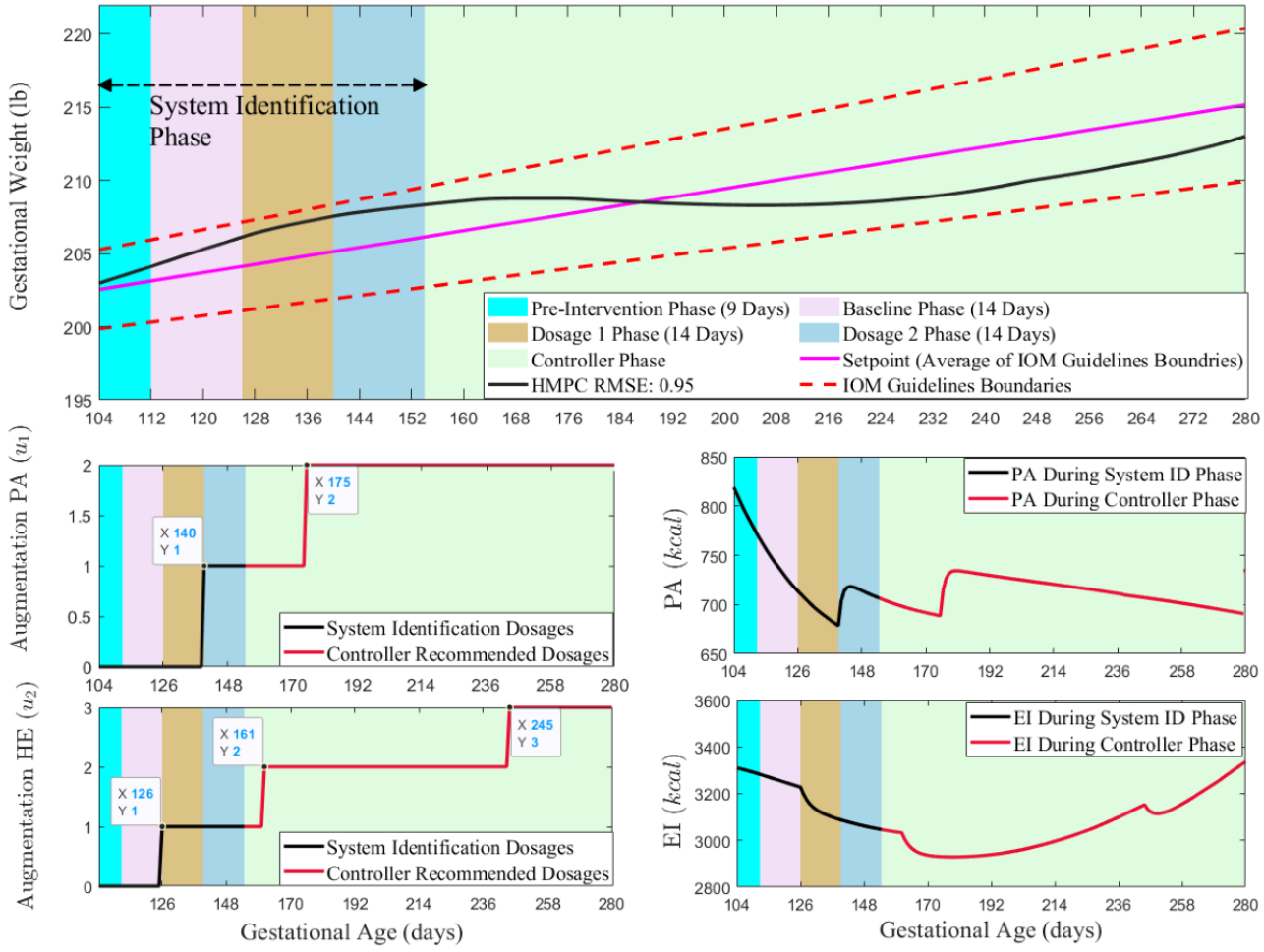
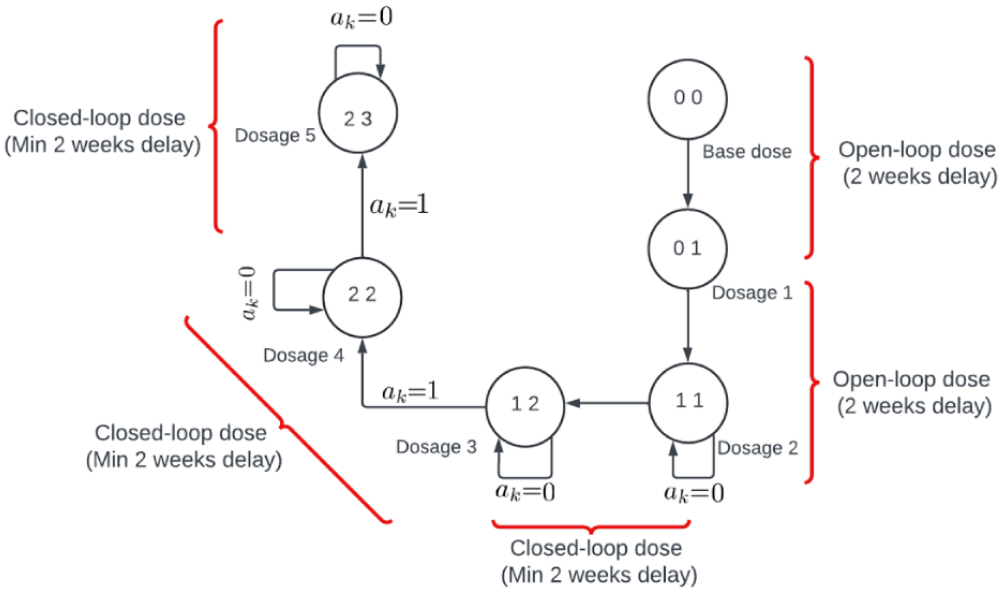


Figure 3. Dosage sequence pattern for the hybrid model predictive controller within the Healthy Mom Zone (HMZ) 2.0 intervention.



Goal of This Study

The goal of this study is to describe the protocol for a randomized controlled optimization trial to examine the efficacy of the enhanced HMZ 2.0 intervention with the new automated control system and digital platform to regulate GWG and influence secondary maternal and infant outcomes while collecting implementation data to inform future scalability. Aim 1 is to examine the efficacy of the intervention in terms of GWG (primary outcome) and maternal PA and EI behaviors and social cognitive determinants on comparing intervention and control groups. It is hypothesized that the intervention group will (1) have lower pre- to postintervention GWG and be more likely than controls to achieve GWG within the guidelines [1,2], and (2) have higher PA kcal (and total kcal) and PA or EI determinants and lower EI kcal than controls. Aim 2a is to measure pre- to postintervention differences in secondary maternal sleep and eating behaviors. It is hypothesized that the intervention group will have fewer nighttime awakenings and less uncontrolled eating than controls. Aim 2b is to examine the impact of the intervention on birth weight and adverse pregnancy, labor, and delivery outcomes. It is hypothesized that the intervention group will show lower birth weight adjusted for gestational age and will have lower occurrences of adverse pregnancy, labor, and delivery outcomes than controls. Aim 3 is to examine the impact of implementation markers on intervention efficacy in terms of GWG and secondary outcomes. It is hypothesized that subject engagement, acceptability, dosage exposure, and staff burden or acceptability will moderate the effect of the intervention on study outcomes. This information will inform how to scale-up the HMZ 2.0 intervention for future use by prenatal clinicians.

Methods

HMZ 2.0 Intervention Description

HMZ 2.0 is a multidosage, individually-tailored, adaptive intervention with social cognitive theory and behavior components [15-17]. The “baseline dosage” is delivered to all intervention participants, and it consists of up to 24 weekly modules (depending on gestational age at study enrollment) including the following:

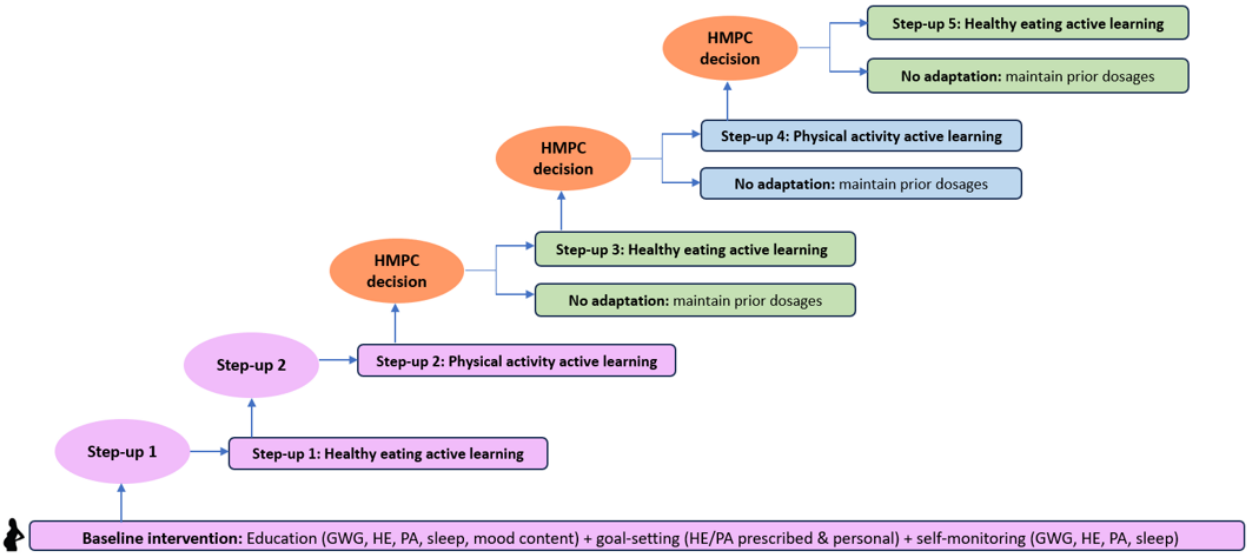
- Education: Knowledge-based content on meeting guidelines (GWG, PA, EI, sleep behaviors, and good sleep hygiene) [1,2,69-75]; mood (eg, depressive symptoms, stress, and anxiety); safely engaging in prenatal exercise; and awareness of stressful situations that prompt uncontrolled and emotional eating, hunger cues, cravings, and mindful eating choices [76,77]. We also provide knowledge about recently published evidence-based studies on how a mother’s health impacts her baby (eg, sleep, brain development, and food preferences) and developmental milestones (eg, when eyebrows develop), which is shared over the course of the intervention. Our pilot work [42] demonstrated that women specifically asked for education materials that provided this information.
- Personalized behavior coaching or counseling: Individually tailored behavior coaching from a prenatal fitness instructor and registered dietitian on GWG, PA, and EI that uses information and feedback from a woman’s prior week to inform the future week’s motivational cues and strategies to increase PA, improve diet quality, and overcome barriers (this can be delivered in person or through a remote synchronous or asynchronous approach for future scalability).
- Goal setting and action planning: Guided and self-selected PA and EI goals [69-71,78] using implementation intentions to target when, where, and how each woman will work toward goals and how these PA or EI goals relate to GWG. Example goals include targets for daily steps (eg, 10,000 steps) and activity time (eg, 30 minutes), as well as fruit or vegetable intake for lower energy density [79] and increasing water intake to maintain good hydration [80,81]. HMZ trimester-specific prenatal PA and recipe booklets (developed by our team) provide detailed examples for PA (eg, 150 min/week of moderate-intensity activities; 10,000 steps/day) and EI kcal goals [78].

- Self-monitoring: Women use mHealth tools (eg, Wi-Fi weight scale, activity monitor, and dietary intake app) to self-monitor GWG, PA, or EI [82]. The HMZ digital platform visually displays their daily or weekly data. Feedback is given to each woman on how to use the devices and self-monitor their behaviors in relation to their GWG and PA or EI goals [19,43,78,83].

Adaptive Intervention Dosage Changes

The model-based predictive control algorithm in the HMZ 2.0 digital platform continually and automatically evaluates GWG. It relies on a dynamic model and solving a receding horizon online optimization problem that identifies when a woman's forecasted GWG is anticipated to exceed the GWG guidelines [1,2,84-86], and based on a structured sequence of decisions that form part of the model, a dosage change is recommended (Figure 4). Only women who have a forecasted need for added support to regulate GWG will receive adaptive dosages in addition to the baseline intervention. Dosages are additive such that a woman receives more intensive support for eating healthy and engaging in PA with each adaptation up to a maximum of 5 adaptive dosages. The web-based user interface provides an easy and intuitive way to integrate expert-supervised dosage change recommendations to regulate GWG. The HMZ 2.0 prenatal fitness instructor and registered dietitian review the participant's data and recommend individually tailored behavioral strategies that are delivered through the HMZ 2.0 digital platform. Each woman's unique preferences and past successes with PA or EI strategies are considered when customizing the dosage adaptation to promote engagement, enjoyment, and compliance, which can in turn influence GWG. These active learning strategies include, for example, multiple PA-guided workouts with a variety of prenatal cardiovascular and resistance training exercises (preapproved for safety and with physician consent for participation) [69,70], as well as healthy eating cooking demonstrations, portion size control strategies to substitute high energy density foods with low energy density options such as water-rich fruits or vegetables [43,71], using food scales and portion size containers, customized grocery planning, and meal replacements. There are a host of easy-to-adopt and practical recommendations for integrating PA or EI strategies into daily life (eg, walking in 5- to 10-minute increments throughout the day to increase PA kcal by 200 kcal/day, reduce sitting by 5 min/hour from 9 AM to 5 PM, and replace 8 ounces of whole milk with skim milk to reduce EI kcal by 100 kcal/day) to facilitate behavior change while adhering to safety standards [69,70]. All dosages can be delivered in person or through a remote approach (synchronous and asynchronous for selected sessions), depending on the participant's preference.

Figure 4. Healthy Mom Zone (HMZ) 2.0 adaptive intervention design. Participant weight is measured daily and continuously evaluated against the Institutes of Medicine (IOM) gestational weight gain (GWG) ranges. All intervention women will receive the baseline intervention plus step-up 1 plus step-up 2 during the system identification open-loop experiment. Dosages 3 to 5 are delivered to selected intervention participants based on hybrid model predictive controller (HMPC) decisions in the closed-loop experiment. HE: healthy eating; PA: physical activity.

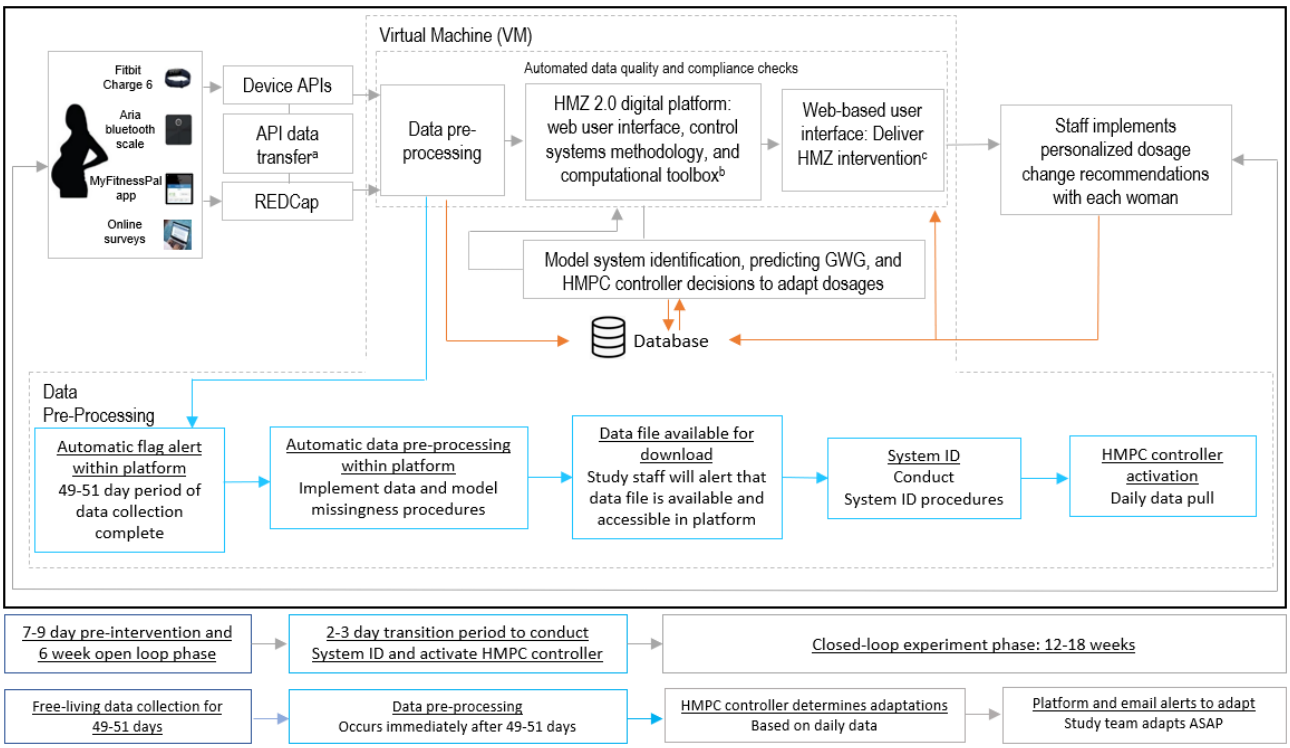


HMZ 2.0 Automated Data Pipeline and Digital Platform

The data pipeline for HMZ 2.0, illustrated in Figure 5, is orchestrated by Apache Airflow [87], a workflow management platform, where daily jobs are scheduled, including (1) retrieving deidentified data from various sources, such as the application programming interface (API) of the REDCap [88] database; (2) preprocessing survey data, including aggregating subscales and back-calculating EI [89,90]; (3) imputing missing data via multiple imputation [91,92] and machine learning–facilitated [93-95] techniques programmed into the platform; (4) feeding the imputed data into the advanced hybrid model predictive control system to generate the adaptive decision-making process; and (5) continuously monitoring errors and warnings in the Airflow monitoring dashboard during steps 1-4, scanning data quality, and initiating automated alerts that notify different pillars of the study team based on the issue type. As the participants in the study cohort change with time, tasks for each new participant are dynamically created. The scripts are version controlled, and data generated throughout the pipeline are saved in a PostgreSQL relational database to ensure data reproducibility. The HMZ 2.0 web-based platform has been

built with Django, an advanced Python web framework to scale-up future production and access (see Figure 6 for the digital platform architecture and website examples). Heterogeneous user interfaces have been built for study staff (and future clinicians), participants in the intervention group, and participants in the control group. The web-based platform provides an access-controlled admin dashboard where authorized users can manually update settings, curate data, or export deidentified datasets for further analyses. For example, during intervention sessions, study staff can access participants' general information, data, educational content, goals, and intervention dosages, and participants will have access to selected resources that are tailored to their specific needs.

Figure 5. Healthy Mom Zone (HMZ) 2.0 data transfer pipeline. API: application programming interface; GWG: gestational weight gain; HMPC: hybrid model predictive controller. *Real-time deidentified 24-hour data stream into REDCap, **Access control (user ID) by authorized study staff, ***Access control (user ID) by intervention study staff (and in the future, dissemination to clinicians).



Recruitment

Recruitment began in April 2024 and will continue through May 2027. Pregnant women with overweight or obesity (N=144) are being recruited for this study. Our team has extensive expertise with recruiting pregnant women. Our past studies have yielded over 3100 subject contacts, with recruitment rates of 84%-92% across our studies [19,96-102]. Well-established methods from our past studies are used for recruitment procedures as follows:

- Clinic: Nurses identify eligible women at the 1st prenatal visit (eg, appointment schedule and electronic health record) and refer them to the study team for screening. A study flyer with study contact information and a QR code is included in the clinic's prenatal packet and posted in exam rooms.
- Community: Study flyers are posted in local areas (eg, daycares and churches) and hospitals, and shared at community events (eg, farmer's markets and celebratory events).
- Social media: Study information is shared on Facebook, Instagram, X, YouTube, and study websites.

Using well-established procedures from our past studies [19,96-102], interested participants, regardless of recruitment method, are screened for eligibility. If interested, participants scan a QR code that directs them to a REDCap survey to complete a screening questionnaire or they send a message by email, text, or voicemail, and a trained study staff member will reply to complete the screening questionnaire over the phone.

The staff member reviews the participant's responses to determine eligibility. The inclusion criteria are as follows: age range 18-45 years; singleton pregnancy with ≥8 and <18 weeks gestation; any parity; any race or ethnicity; BMI of 24-45 kg/m^2 (>40 with provider consent); have not gained >25% of total GWG (based on BMI and IOM guidelines) from prepregnancy to the date of enrollment [103]; able to read or understand English; access to a computer or phone; able to attend sessions either on-site or remotely; randomization to conditions; no absolute contraindications to PA (and presence of relative contraindications only with health care provider consent to participate); and not a current heavy smoker (>20 cigarettes per day) [19,69-71] . The exclusion criteria are as follows: outside the age, BMI, gestation, or GWG range; not able to participate (cannot read or understand English, no access to a phone or computer to attend sessions remotely, and cannot use a device or service assistance); absolute contraindications to PA [69-71] or relative contraindications to PA noted by the participant's health care provider as precluding study participation; current

heavy smoker (>20 cigarettes per day) at study entry; and multiple pregnancy. Eligible women are scheduled for the preintervention assessment. Women not meeting the eligibility criteria are thanked for their time and given information on other studies that may be of interest.

Safety Considerations

Prior to enrollment, a study team member informs the participant's health care provider about their potential participation and obtains consent from each provider. The provider completes the consent form (hard copy or REDCap link) confirming eligibility for participation, and the participant is officially enrolled. This process is repeated at mid-study (eg, between the 2nd and 3rd trimesters) to ensure the participant does not have any new medical conditions that may impact study participation.

Because this study includes pregnant women, a vulnerable population as defined by the National Institutes of Health, there is a Data Safety and Monitoring Board with experts in obstetrics and gynecology, prenatal weight gain, PA and nutrition interventions, and fetal growth that will: (1) review the study methodology and procedures, data on recruitment, enrollment and adherence to the inclusion/exclusion criteria, and participant's progress through the study; (2) assure the safety of the study participants; and (3) make recommendations to the research team. Adverse events that the Data Safety and Monitoring Board will be notified of and oversee include: (1) insufficient GWG: indicators of insufficient GWG are weight loss of less than 3% in a week or 0% weight gain in a 4-week cycle [104]; (2) depressive symptomology: all women regardless of initial preintervention assessment scores will be given resources on managing depressive symptoms and a comprehensive list of available resources and supportive services, and depressive symptoms will be monitored monthly [105]; and (3) absolute or relative contraindications to exercise [69-71].

Participants in the intervention group complete verbal assessments of pregnancy symptoms (eg, mild muscle cramping, headaches, and symptoms of labor) and contraindications to exercise (eg, bleeding, severe abdominal cramping, nausea, etc) during activity sessions. The study safety protocol includes steps to understand symptoms, ratings of perceived exertion, and responses if appropriate, including stopping the activity, seeking medical attention, and calling a participant's emergency contact and provider. If a woman experiences a contraindication to PA in pregnancy that precludes her continued participation, she will remain in the study and complete measures as appropriate (intent to treat) but will not engage in PA until provider consent to return to activity is obtained. We also monitor changes in health status and health symptoms. For example, women who develop gestational diabetes during the study will remain in the study and receive the standard of prenatal care by their obstetrician or health care provider, in which an established standard of care plan is provided for the treatment and management of gestational diabetes.

Ethical Considerations

This study has been approved by the Pennsylvania State University Institutional Review Board (IRB; STUDY00019075), and Arizona State University is an IRB-approved participating site (SITE00001437). All members of the study team have appropriate CITI training certifications. Any and all changes made to the protocol will be communicated to participants and other relevant individuals or parties immediately. All study participants provide their informed consent prior to enrollment into the study with the option to decline enrollment or stop participation at any time. Data collected are deidentified, and access is only granted through lock and key as well as secure accounts with passwords. Participants are compensated up to US $250 in gift cards for either Target or Walmart. Compensation is provided based on the completion of study milestones, such as completing the pre- and postintervention assessments, allowing electronic health record data to be extracted, and attending and completing more than 85% of study sessions and the measurement protocol. Both the intervention and control group participants can receive the same amount of compensation. This study is registered at ClinicalTrials.gov (NCT05807594).

Randomization Procedures

A trained staff member randomizes each participant after the preintervention measures via a randomization module in REDCap [88]. The study's biostatistician has developed the randomization scheme using variable-size random permuted blocks to ensure the number of subjects in each group is balanced after each set of *B* randomized subjects, where *B* is block size. The biostatistician programs the REDCap module, and the remaining study staff do not have access to the randomization scheme. Randomization to control (n=72) and intervention (n=72) groups uses 1:1 allocation; subjects are entered consecutively. Randomization is stratified by prepregnancy BMI status (<29.9 vs ≥30 kg/m^2). A staff member calls each woman to inform her of study assignment. She is then provided with study information and education materials for her group assignment. The investigator is blinded to intervention assignments.

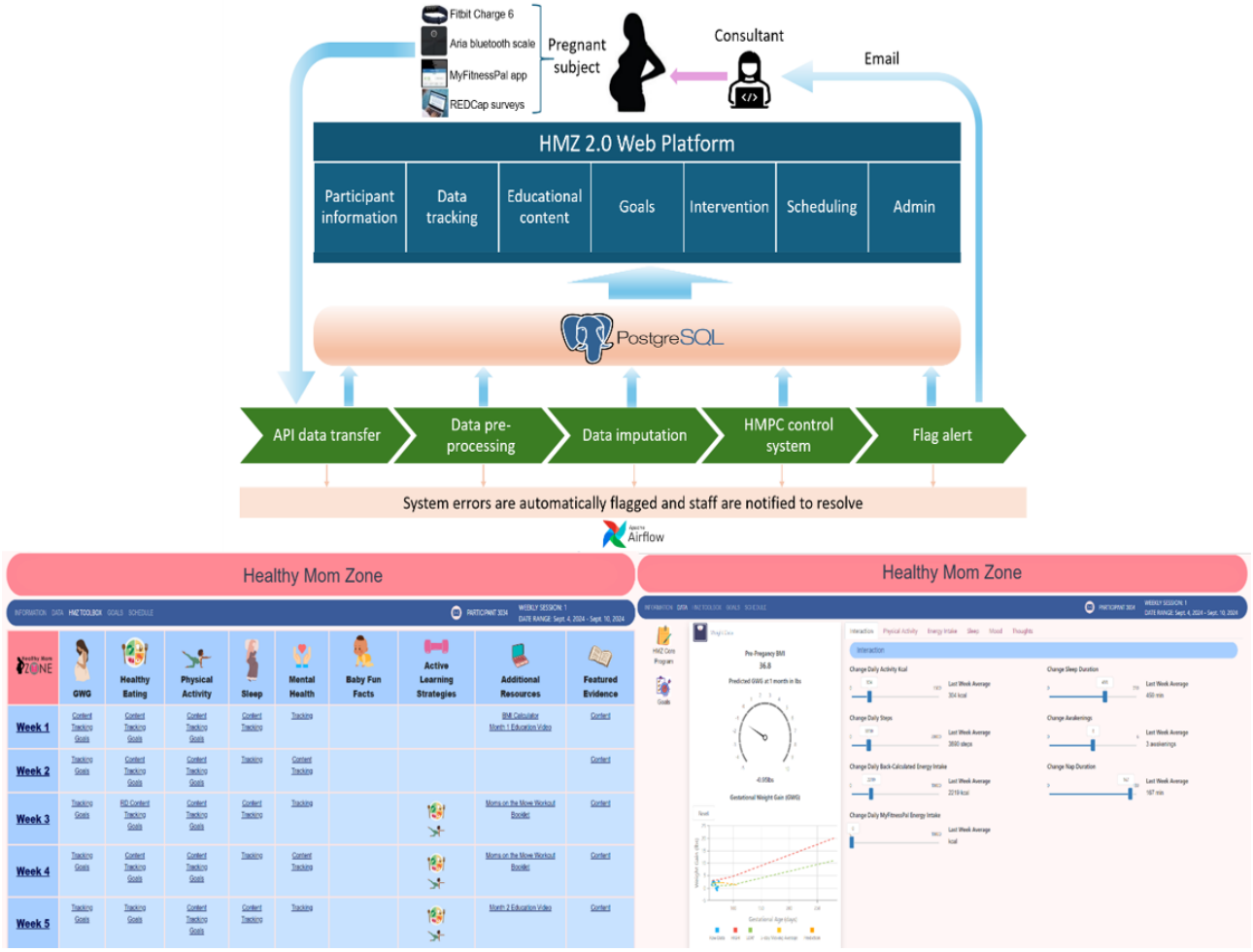
Treatment Conditions

Intervention Condition

Women randomized to the intervention group receive the HMZ 2.0 intervention, described in detail above in the section "HMZ 2.0 Intervention Description," which includes the baseline intervention (education, personalized behavior coaching or counseling, goal setting or action planning, and self-monitoring) and adaptive intervention dosage changes (for the participants who need them). This baseline intervention continues through the duration of the study. Each week over the course of the study, GWG is monitored and evaluated against the recommended upper and lower bounds of the IOM GWG guidelines [1]. Depending on each participant's response to the baseline intervention (eg, GWG within or above guidelines) and her forecasted GWG, the automated control system may recommend a dosage change to adapt the intervention. This adaptive dosage begins after the first 4 weeks of the baseline

intervention (to allow the participants to get used to the intervention and reduce burden) and includes EI and PA active learning interactive components that "step-up" the intensity of the dosage. Dosage change recommendations are automatically delivered through the HMZ 2.0 digital platform (architecture of the platform is described above); staff implement the recommended dosage change with the participant. As illustrated in Figure 6, there are up to five dosage "step-up" adaptations that can be recommended by the automated control system to regulate GWG.

Figure 6. Healthy Mom Zone (HMZ) 2.0 digital platform architecture and website examples. API: application programming interface; HMPC: hybrid model predictive controller.



Attention Control Condition

Consistent with guidelines for comparator groups [106], all women in the study receive prenatal care offered by recruitment sites with routine provider visits, counseling about prenatal behaviors (eg, no smoking), and clinical oversight of health. To match attention to the intervention group, women in the control group receive (for the first 4 weeks of the study) one-on-one weekly education sessions delivered by trained study staff, and thereafter, they receive monthly education content delivered as asynchronous videos and get check-in support from study staff (eg, phone, text, and email) for the remainder of the study. Content includes topics, such as preparing for labor or delivery; benefits of behavioral pain management strategies (eg, mindfulness-based relaxation, imagery, music, massage, and deep breathing) to regulate pain after childbirth with nonpharmacological approaches [107]; and baby or child safety, health and development, behaviors, and nutrition. Content is drawn from evidence-based guidelines and materials designed by members of the study team for a patient-provider toolbox to reduce opioid pain management use after childbirth [107], as well as The American Academy of Pediatrics, The March of Dimes, The Centers for Disease Control, and The American College of Obstetrics and Gynecology [108-111]. The matched control group education content is also provided to the intervention group as supplemental material.

Both the intervention and control groups receive the same measurement protocol and frequency of measurement to understand and compare the impact of the intervention on primary and secondary study outcomes. Data are collected from each participant daily (GWG: Aria Wi-Fi scale [112]; PA, sedentary behavior, or sleep: Fitbit Charge 6 monitor [112], logs for device wear time, and PROMIS Sleep Disturbance [113,114] assessment; and self-reported hydration behaviors); weekly (self-reported online in REDCap; social cognitive determinants and EI diet quality: MyFitnessPal app on 2 weekdays and 2 weekend days) [19,115]; and monthly (self-reported online in REDCap; eating behaviors [19,116,117], psychosocial measures, cognition, pain, and temperament measures).

Control Optimization Trial Procedures

Control systems methodology [51-54] in a novel Control Optimization Randomized Controlled Trial (RCT) [51] is used to test the efficacy of the enhanced HMZ 2.0 intervention with a novel digital platform and a new automated control system to regulate GWG and influence secondary outcomes. This idiographic approach uses individual dynamic models (integrating behavioral and energy balance models) informing how each woman responds to HMZ 2.0 to make personalized decisions about intensifying dosages to regulate GWG. We are not aware of any other studies using this unique strategy to regulate GWG. Women start the intervention with an "open-loop" experimentation phase and receive the HMZ 2.0 baseline intervention (dosages are not yet adapted during this time). Semiphysical models estimated using concepts from system identification [85,118-120] allow individual energy balance and behavior models to be built for each subject [51]. Model and dosage personalization is further enhanced by leveraging our team's expertise in time-varying dynamic systems (systems that show changes in statistical properties over time) and multilevel models that integrate individual- and group-based dynamics and missing data issues [56-68]. Model components are measured with real-time data procedures to predict corresponding deviations from each woman's target GWG range: overweight, 6.8-11.3 kg total and 0.23-0.32 kg/wk; obese, 5.0-9.1 kg total and 0.18-0.27 kg/wk [1,2]. Model estimation is used to confirm individual models and identify if certain constructs provide maximum impact for the control system. The goal of this open-loop phase is to arrive at a set of personalized dynamic models that capture the effects of dosage augmentations, gestational age, and the baseline intervention. Once the models are identified and the controller commissioned, models will not be updated, but the tuning parameters can be adjusted, if necessary. While there is no set threshold of data compliance for building individual models (models can be built with as little as 50% missing data handled with maximum likelihood estimation) [56-68], we will rely on strategies to achieve high compliance (90%; 10% missing data) similar to that in our feasibility study [19].

These personalized individual energy balance and behavior models are used in the "closed-loop" experimentation phase for the rest of the study period during which a woman's responsivity to HMZ 2.0 is considered and dosages are adapted to regulate GWG. Continuous mHealth data are automatically linked to the control system, which considers GWG over a prediction horizon to minimize discrepancies between a woman's observed GWG and her goal [1,2]. It considers the anticipated rate of GWG change as predicted with the individual model. Currently trained with data from the feasibility trial [19] and pilot data collected on HMZ 2.0 participants, the control system uses the values of each woman's modifiable factors (eg, PA or EI kcals) in the current week to simulate ways in which these behaviors can be "controlled" or altered to drive GWG closer to the goal in the following week. We are cognizant of potential system identification issues that may arise with limited data available from each subject. If needed, selected parameters from the energy balance models can be constrained to be invariant across subjects to borrow strengths from other subjects and aid model estimation [121,122]. We will identify the optimal balance between control system performance (how well it can produce desired effects as efficiently as possible) and robustness (how well it can produce desired performance under disturbances and uncertainty; eg, poor compliance, change in responsiveness to dosages, and measurement variability) [10,51]. The controller has tuning parameters that allow adjustment of how fast or slow the control system makes recommendations to enable a judicious balance between effectiveness and responsiveness. Computations are performed with toolkits in MATLAB (MathWorks) and IBM ILOG CPLEX Optimizer. Study staff work with subjects to address concerns or technical issues. We will also explore how the individual subject data may inform modifications to the maternal energy balance and behavior model [10,19] and infant birth weight model [11,18].

Primary and Secondary Outcomes

Table 1 summarizes the HMZ 2.0 measurement protocol and timepoints. More details of the primary and secondary outcomes are provided below.

Table 1. Healthy Mom Zone 2.0 measurement protocol and timepoints.

Variable measure	Timepoint
Energy balance model outcomes	
GWG[a] /weight (primary outcome)	
High precision adult scale (10 s)	Pre- and postintervention
Aria Wi-Fi Smart Scale (15 s)	Pre- and postintervention and daily
Prenatal records: total GWG	Pre- and postintervention
PA[b] and sedentary behavior	
Fitbit Charge 6: activity kcal (passive)	Pre- and postintervention and daily
ActiGraph GT3X: activity min (passive)	Pre- and postintervention and daily
PA log: monitor wear time (1 min)	Pre- and postintervention and daily
Resting metabolic rate	
Predicted equation	Pre- and postintervention and daily
EI[c]	
EI kcal: back-calculation method	Pre- and postintervention and daily
EI diet quality: MyFitnessPal app (5 min)	Pre- and postintervention and monthly
PA or EI social cognitive determinants	
Attitude, subjective norm, perceived behavioral control, and intention (3 min)	Pre- and postintervention, daily, and weekly
Behavioral, normative, or control beliefs (2 min)	Pre- and postintervention and monthly
Retrospective self-regulation (1 min)	Pre- and postintervention, daily, and weekly
Secondary outcome measures	
Sleep behaviors	
Pittsburgh sleep quality index (2 min)	Pre- and postintervention and monthly
FitBit Charge 6: sleep behaviors (passive)	Pre- and postintervention and daily
Sleep log: sleep behaviors (30 s)	Pre- and postintervention and daily
PROMIS Sleep Disturbance (30 s)	Pre- and postintervention and daily
Eating behaviors	
3-factor eating inventory: cognitive restraint, disinhibition, and hunger (3 min)	Pre- and postintervention, weekly, and monthly
Maternal-infant labor or delivery and adverse pregnancy outcomes	
Diagnoses of gestational diabetes, insulin use, preeclampsia, and depression	Postintervention only (at delivery)
Labor or delivery issues and other complications	Postintervention only (at delivery)
Infant APGAR score and mode of delivery (vaginal or cesarean)	Postintervention only (at delivery)
Infant birth outcomes	
Birth weight (adjusted for gestational age at delivery), length, sex, gestational age at delivery, and date of birth in the electronic health record	Postintervention only (at delivery)
Clinical and safety protocol measures	
Height	
Stadiometer (5 s)	Preintervention only
Blood pressure	
Screen for preeclampsia (2 min)	Preintervention only
Demographics, medical history, and obstetric history	
Age, race or ethnicity, income, education, medical or pregnancy history, etc (7 min)	Pre- and postintervention
Depressive symptoms and monitoring health	

Variable measure	Timepoint
Center for Epidemiological Studies Depression Scale (3 min)	Pre- and postintervention and monthly

[a]GWG: gestational weight gain.

[b]PA: physical activity.

[c]EI: energy intake.

Primary Outcome

Participant GWG

Weight and GWG are assessed daily at preintervention, during the intervention, and at postintervention at home using the Fitbit Aria Wi-Fi Smart Scale [112] (weights are wirelessly uploaded to an online program). GWG is standardized, and the target weight gain is determined for each woman based on the BMI status (overweight, 14.1-22.7 kg; obese, 11.3-19.1 kg) [1,2]. For the criterion measure to determine when to adapt the intervention, weight gain is calculated to determine if a woman is gaining less than her goal, at the exact amount of her goal, or more than her goal. GWG over the course of the study is calculated as the last measured weight during the study subtracted by the first measured weight during the study. Weight at enrollment is measured, and prepregnancy weight and GWG from the first prenatal visit to the last predelivery weight are abstracted from clinical records.

Energy Balance and Behavior Model Primary Constructs

PA and Sedentary Behavior

PA and sedentary behavior are assessed daily at preintervention, during the intervention, and at postintervention. Participants wear the wrist-worn Fitbit Charge 6 [112] 24 hours per day from the preintervention assessment until the end of the postintervention assessment. The Fitbit Charge 6 allows for continuous passive (low subject burden) PA assessment in the energy balance model [12] to predict GWG. The device measures total kcal, activity kcal, steps, and minutes in sedentary, light, or moderate PA. The waist-mounted ActiGraph GT3X [123] is worn at pre- and postintervention and for the first 2 weeks of the open-loop phase during waking hours to assess PA and sedentary behavior (activity kcal, steps, and minutes in sedentary, light, or moderate PA). Participants track their PA and monitor wear time by completing a self-report PA log and the Leisure Time Exercise Questionnaire [124] daily for cross-validation of the Fitbit data [125].

EI Behavior: Back-Calculation Estimation

EI is estimated daily at preintervention, during the intervention, and at postintervention from measured weight (Aria Wi-Fi scale) [112], PA (Fitbit Charge 6 activity monitor) [112], and resting metabolic rate (RMR), with k=1, 2,… N relating to day 1 to day N. T is the sampling time (T=1 day) [8,12,68-71], and RMR is estimated daily as follows:

$$eRMR = 0.1976W^2 - 13.424W + 1457.6 \quad \textbf{(1)}$$

The noise in weight is small relative to the total weight, but the extent of this noise can affect the calculated rate of GWG per day, so a 5-day moving average filter is used to preprocess (smooth) measured weight before “true” daily EI is estimated [117-119]:

Our team effectively used this back-calculation method for estimating EI in the HMZ proof-of-concept study [42] and feasibility-initial impact randomized trial [8,10,19,43-45].

Secondary Outcomes

Secondary Energy Balance and Behavior Model Constructs

The following aspects are considered:

- Theory of Planned Behavior [15,126]: Involves healthy eating or limiting unhealthy eating, PA attitude, subjective norm, perceived behavioral control, intention, and beliefs. The Theory of Planned Behavior constructs in the dynamic model of energy balance and behavior [13-17] inform individualized model-based interventions for each intervention participant. Participants complete online surveys daily at pre- and postintervention and during the open-loop phase, and daily and weekly during the intervention to assess their attitude, perceived behavioral control, subjective norm, intention to eat healthy and limit unhealthy eating, and participation in PA. Participants complete a one-time online survey at pre- and postintervention and monthly to assess their beliefs about eating healthy, limiting unhealthy eating, and participating in PA.
- Retrospective self-regulation for EI or healthy eating and PA [17]: Retrospective self-regulation in the dynamic model of energy balance and behavior [13-17] informs individualized model-based interventions for each intervention participant. Participants complete two 6-item online surveys daily at pre- and postintervention and during the open-loop phase, and weekly during the intervention to determine how good they are at regulating their EI or healthy eating and PA and how these behaviors impact GWG over the course of pregnancy.

Maternal Health

Participants complete the following measures at preintervention, during the intervention, and at postintervention:

- Diet composition or quality and eating behaviors: Participants use the MyFitnessPal online app on 2 weekdays and 2 weekend days at pre- and postintervention, weekly during the first 2 weeks of the open-loop phase, and once a month during the intervention to assess their diet composition and quality. This information aids in personalized counseling of diet quality for the intervention group [19]. The Three Factor Eating Questionnaire

[116,117] is completed at pre- and postintervention, weekly during the open-loop phase, and monthly during the closed-loop phase and is used to assess 3 dimensions of eating behaviors: dietary restraint (cognitive control of eating behavior), dietary disinhibition, and susceptibility to hunger.

- Sleep behaviors: The Pittsburgh Sleep Quality Index [127] assesses the quality and patterns of sleep and measures subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication, and daytime dysfunction. The PROMIS Sleep Disturbance short-form survey [113] assesses difficulties and concerns with getting to sleep and staying asleep; evaluates the perceptions of the adequacy of and satisfaction with sleep; and measures sleep quality, sleep depth, and restoration associated with sleep. Participants also complete a daily self-report sleep log [128] to measure time to sleep and wake, minutes of sleep, nighttime awakenings, time spent awake after sleep onset, daytime naps, and daytime nap duration, and wear the Fitbit Charge 6 Activity Monitor [112] each night to assess time to sleep and wake, minutes of sleep, nighttime awakenings, and light and deep rapid eye movement sleep.

Maternal and Infant Outcomes

Prenatal, labor, and delivery data will be abstracted from the participant's electronic medical record. Maternal and infant outcomes include: mode of delivery (vaginal or cesarean), adverse pregnancy outcomes (eg, diagnosis of gestational diabetes, insulin use, preeclampsia, depression, labor or delivery issues, and other complications), birth weight, length, sex, gestational age, date of birth, APGAR score, and any complications related to the infant during labor and delivery. In the event that labor or delivery data are missing or unavailable from the medical record, the investigators will obtain information from the participant's self-report.

Implementation Marker Procedures

Our team has ample experience with evaluating program implementation [96-98,129-133], including in the HMZ proof-of-concept study [42] and feasibility trial [19]. The Quality Implementation Framework [49] and Quality Implementation Tool [50] will guide examination of the following markers:

- Subject engagement and participation: Fidelity monitoring evaluations are conducted for each subject and staff after each session. A trained staff observer reviews video recordings of 50% of intervention and attention control sessions and follows a review checklist to measure engagement (degree of subject responsiveness with content, discussion, and activities) [134,135].
- Subject acceptability: Subjects and staff complete weekly checklists to assess attendance (0%-100% attendance at pre- and postintervention assessments; 0%-100% attendance at intervention and attention control sessions), compliance (0%-100% compliance with mHealth tools and surveys during free-living pre- and postintervention sessions and over the course of the study for all subjects; 0%-100% compliance with attention control or HMZ 2.0 activities), and quality and completeness of data (0%-100% of usable data for each subject).
- Dosage exposure is assessed by (1) weekly checklists completed by subjects or staff regarding the amount of program content delivered or received (goal 85%+ coverage) [19]; (2) fidelity monitoring by a trained staff observer who reviews video recordings from the same sample of 50% of video recordings noted above; and (3) tracking of the number of dosage changes determined by the model-based control system, number of days between dosage change recommendation and implementation by staff, and number and type of PA or EI strategies suggested or used.
- Staff engagement: Fidelity monitoring is conducted by a trained staff observer who reviews video recordings from the same sample of 50% of video recordings noted above and follows a checklist to measure engagement (enthusiasm, preparedness, session delivery effectiveness, and responsiveness to the subject).
- Staff burden: Weekly checklists are completed by staff for the amount of time spent preparing for sessions, responding to or following up with subjects, and using the HMZ 2.0 digital platform, and for issues with delivering dosage recommendations to the subjects.
- Study delivery costs: A trained staff member tracks and calculates the time and financial costs of the study. Postintervention semistructured interviews with HMZ 2.0 subjects elicit key facilitators and barriers to study participation. The interview guide has been developed with standard procedures [136,137] from our past studies [10,19,42-45,107,138-140]. Expert feedback will be obtained from key clinician stakeholders (ie, registered dietitians, nurses, obstetrics or gynecology providers, etc) on the strengths and limitations of using the HMZ 2.0 digital platform, potential barriers to scaling-up use in prenatal care (eg, clinician beliefs about technology and connectivity issues), and suggestions for improvements. This valuable feedback will be used to make additional refinements to HMZ 2.0 to scale-up future use by prenatal care clinicians.

Statistical Analysis

For study aims 1 and 2, time series methodology will be used on a subject basis (ie, cubic polynomial spline 3-lag auto-regressive models with maximum likelihood as the estimation method) followed by a fixed effects meta-analytic approach to combine information in order to compare the intervention group to the control group [141-143]. Mixed effects models will be used when the meta-analytic approach does not fit the data [56,62-65]. Potential confounding variables (eg, maternal age, parity, and income; infant sex; and adverse maternal-infant outcomes) [6,144] will be included in the models as covariates when appropriate. We will explore the extent to which prenatal sleep and eating behaviors impact postintervention GWG, PA, or EI and infant birth weight to inform modifications to the maternal energy balance and infant birth weight models. The intent-to-treat principle will be followed. Our statistical approach is robust if data are missing at random (multiple imputation will be considered if missing data are problematic) [145]. Hypothesis tests will invoke a

2-sided significance level of .05. Analyses for the synthesis of mHealth data and the predictive control system are informed by MATLAB toolkits and past experience [51,146,147]. Model personalization will use control-theory models, and requisite computations will be performed for optimal dosage changes [112,113,128,148-150]. For study aim 3, descriptive statistics will be used to examine the percentage and frequency for implementation markers. Formative methods will be used to organize, code, and rank order interview data [136,137]. Study findings will be used to further optimize HMZ 2.0 for effectiveness and scalability. Data will be collected and stored in REDCap [88]. Deidentified data will be exported from REDCap [88] to statistical packages. Subject confidentiality will be maintained with subject IDs. Data security is ensured with Penn State standard procedures.

Power Calculations

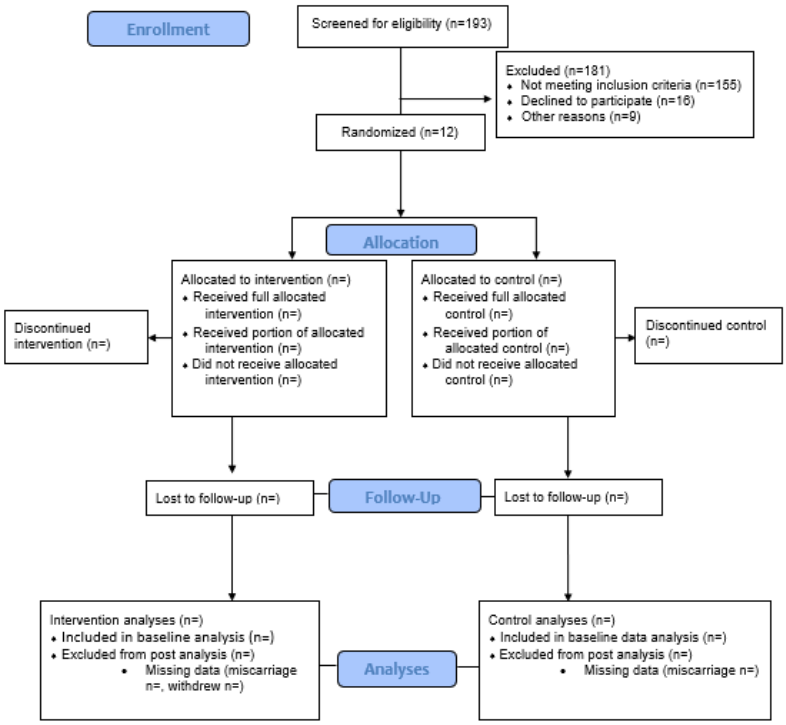
The primary outcome is GWG: absolute difference between the intervention and control groups for the mean change in GWG from the start to the end of the trial. From our feasibility study [19], we found that the difference between the intervention and control groups with respect to the absolute mean change in GWG from the start to the end of the trial was 1.9 kg (SD 4.9 kg), with an approximately 21% relative reduction for the intervention group compared to the control group. We compared the mean change in our feasibility trial [19] to that in several other GWG studies comparing intervention and control groups [29,151-154] and found that the intervention group gained on average 1.8 kg less than controls (range: 1.1-3.1 kg). The sample size of 144 randomized to the intervention (n=72) and control (n=72) groups in the proposed research is informed by our feasibility trial showing a mean difference of 1.9 kg (SD 4.9 kg), a 21% relative reduction in GWG in the intervention group compared to the control group, and a 3% dropout. Given our experience with the feasibility trial [19], the series of refinements that we performed following the feasibility trial (eg, adding content on sleep and eating behaviors given their effects on GWG; modifying all content for remote delivery given 100% compliance found for remote sessions in the feasibility trial; replacing the initial control system to make dosage change decisions with the new, automated, dynamic model-based predictive control system that outperformed the initial system for regulating GWG; and adding the novel HMZ 2.0 digital platform to adapt dosages), and the findings from our HMZ 2.0 pilot study (average weekly GWG over the 4-week study period: 0.3 kg, SD 0.4 kg; overall GWG from pre- to postintervention: 1.2 kg, SD 0.8 kg), we expect the HMZ 2.0 intervention to be more effective. We anticipate that our mean difference will be closer to what a recent study [155] found for the mean difference in GWG between the intervention and control groups (mean 3.6 kg, SD 5.7 kg). Conservatively, considering this larger SD of 5.7 kg and anticipating a larger dropout rate of 10%, the sample size of 144 yields 80% statistical power with a 2-sided significance level of .05 to detect an absolute difference of at least 2.9 kg in GWG between groups. Sample sizes for semistructured interviews are adequate to observe data saturation [136,137,141].

Results

HMZ 2.0 Control Optimization Efficacy RCT

Recruitment began in April 2024 and will continue through May 2027. All data are expected to be collected by December 2027. Currently, we have 193 participant contacts, of which 119 (91%) have been assessed for eligibility and 12 (50% of eligible participants) are enrolled in the RCT (Figure 7). Full results will be uploaded on the ClinicalTrials.gov website at the end of the trial, which is anticipated in January 2028.

Figure 7. Healthy Mom Zone (HMZ) 2.0 CONSORT (Consolidated Standards of Reporting Trials) diagram.



Discussion

Overview

To our knowledge, there are no other adaptive behavioral interventions aiming to regulate GWG with a theory-driven, energy balance model–based predictive control system, highlighting the novelty of our approach. We have made every effort to obtain robust and unbiased results in this trial. We have established the proof-of-concept and tested the feasibility of the intervention dosages, safety protocols, and strategies to retain subjects for this trial. The hypotheses to be tested are based on a sound foundation of preliminary data [10,11,13,14,19,42-45,140]. We have also pilot tested several aspects of HMZ 2.0. Findings from the HMZ 2.0 pilot study showed successful recruitment from multiple methods, excellent participant compliance with the measurement protocol and transfer of data from devices and online surveys to the digital platform, user acceptability of intervention sessions delivered through the platform, and utility of the predictive controller for informing dosage change decisions. We will use a randomized study design for the control optimization trial to test the efficacy of the HMZ 2.0 intervention and automated data pipeline and digital web-based platform compared to an attention control group. Data will be collected from all subjects to measure primary and secondary outcomes with valid and reliable measures. We will show the reproducibility of mHealth measures by having all subjects complete the same measures over time. Intervention content, measurement and implementation evaluation protocols, and intervention materials are available for reproducibility. The HMZ 2.0 digital platform and new model-based predictive control system have been built in MATLAB Compiler for reproduction with limited license restrictions. The HMZ 2.0 digital platform is a central hub for the automated data pipeline and web interface for intervention delivery. The data pipeline uses Apache Airflow for robust and dynamic scheduling and implements a multilayer real-time monitoring system. The web interface leverages the Django framework to deliver a rich user experience with role-based access control. The digital platform greatly improves the efficiency of this collaboration study by facilitating information sharing and reducing the turnaround time among researchers, consultants, and patients. Since both Airflow and Django are readily scalable (eg, through parallelism and caching), this digital platform can easily accommodate scale-up in the future.

Limitations

There are many strengths of this study, including clinical and public health significance, novel methods, introduction of the HMZ 2.0 digital platform and model-based predictive control system with personalized dynamic energy balance models for each subject to automate dosage changes and predict GWG, use of a back-calculation method to estimate EI, pilot data [10,11,13,14,19,42-45,140] to support the rigor and reproducibility of the proposed methods, and strong potential for future scalability. Despite these strengths, participant compliance in RCTs is an ongoing challenge, and thus, we have incorporated strategies (eg, staff support, easy passive data collection, and remote delivery of the intervention) to facilitate compliance. We have also worked through technical aspects of the data pipeline and digital platform to reduce technical challenges. Lastly, there is a risk that the HMZ 2.0 study may be underpowered based on the assumptions used in the sample size estimation, but this is true for any power analysis.

Conclusions

The approach involving the HMZ 2.0 intervention and use of a control optimization trial [46] to examine the efficacy of the intervention in terms of GWG and related maternal-infant outcomes expands the boundaries of GWG interventions, uses novel methods and automated decision making, and has clinical and public health impacts in a high-risk population of pregnant women with overweight or obesity and their offspring. There is excellent potential to further refine HMZ 2.0 in the future to regulate GWG in women of all BMI categories and scale-up HMZ 2.0 for use by clinicians as an adjunct treatment in prenatal care. There may also be a way to optimize the digital platform in the future so that it can be safely and directly used by pregnant women. HMZ 2.0 may also serve as a model for how the control systems methodology and a digital platform can be used to automate dosage change decisions for other behavior interventions such as those involving regulation of diabetes, weight loss, and related health outcomes.

Acknowledgments

The project has been supported by the National Institute for Diabetes and Digestive and Kidney Diseases (NIDDK) through grant 1 R01 DK134863, and support has also been provided through the Office of Behavioral and Social Sciences Research (OBSSR) of the National Institutes of Health (NIH), the National Institute on Drug Abuse (NIDA) through grants R21 DA024266 (roadmap) and K25 DA021173, the United States Department of Agriculture (USDA) National Institute of Food and Agriculture (NIFA) (#2011-67001-30117, A2121 Childhood Obesity Prevention Training Program), and Penn State University (PSU) State Social Science Research Institute and Institutional and Computational Data Sciences. Prior support for this project has been provided by the National Heart, Lung, and Blood Institute (NHLBI) of the NIH through grant 1 R01 HL119245-01 and administrative supplement, and NHLBI R56HL126799, and the National Center for Advancing Translational Sciences, NIH through grant UL1 TR000127 and TR002014. The content is solely the responsibility of the authors and does not necessarily represent the official views or work of the NIH.

Data Availability

Data cannot be shared publicly because the data collected from human subjects have not been approved for public sharing. Moreover, since the data are of human subjects, a data transfer agreement is needed. Data are available from the principal investigator DSD (dsd11@psu.edu or 814-863-0456) and the Pennsylvania State University Office for Research Protections (orp@psu.edu or 814-865-1775) for researchers who meet the criteria for access to confidential data.

Authors' Contributions

DSD was responsible for intellectual design, framework, and writing of the manuscript, and organized and led a team for co-writing and providing insights on sections. AMP was responsible for co-writing the methods and results, figures, tables, and references, and provided edits to the manuscript. DER was responsible for assistance with the framework of the manuscript, provided insights on control systems engineering aspects of the paper, and provided edits to the overall manuscript. JSS and AMM were responsible for providing insights on the healthy eating aspects of the Healthy Mom Zone (HMZ) intervention and provided edits to the overall manuscript. SC was responsible for providing insights on intervention personalization, data collection, and analysis descriptions, and provided edits to the overall manuscript. CL and DS were responsible for providing insights on HMZ digital platform description and provided edits to the overall manuscript. JMP was responsible for providing insights on HMZ recruitment and retention descriptions, and provided edits to the overall manuscript. AK was responsible for co-writing of the analysis, power, and sample size descriptions, and provided edits to the overall manuscript. OK was responsible for providing insights on control systems engineering aspects of the paper and developing the figures and figure descriptions, and provided edits to the overall manuscript.

Conflicts of Interest

AK owns stock in Merck, a pharmaceutical company. However, Merck was not involved with this particular manuscript.

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Abbreviations

EI: energy intake
GWG: gestational weight gain
HMZ: Healthy Mom Zone
IOM: Institutes of Medicine
IRB: Institutional Review Board
PA: physical activity
RCT: randomized controlled trial
REDCap: Research Electronic Data Capture
RMR: resting metabolic rate

Edited by A Schwartz; submitted 18.09.24; this is a non–peer-reviewed article;accepted 12.02.25; published 13.03.25.

Please cite as:
Downs DS, Pauley AM, Rivera DE, Savage JS, Moore AM, Shao D, Chow SM, Lagoa C, Pauli JM, Khan O, Kunselman A
Healthy Mom Zone Adaptive Intervention With a Novel Control System and Digital Platform to Manage Gestational Weight Gain in Pregnant Women With Overweight or Obesity: Study Design and Protocol for a Randomized Controlled Trial
JMIR Res Protoc 2025;14:e66637
URL: https://www.researchprotocols.org/2025/1/e66637
doi:10.2196/66637
PMID:

Protocol

Acceptability and Preliminary Efficacy of a Novel Web-Based Physical Activity for the Heart (PATH) Intervention Designed to Promote Physical Activity in Adults With Obesity: Protocol for a Pilot Randomized Controlled Trial

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Abstract

Background: Even in the absence of weight loss, any level of physical activity (PA) can reduce the risk of cardiovascular disease among individuals with obesity. However, these individuals face multifaceted barriers that reduce their motivation and engagement in PA. They prefer programs that are convenient, fun to engage in, and feature people who they can relate to. Yet, there is a paucity of PA interventions that are designed to incorporate these preferences. We designed the web-based PA for The Heart (PATH) intervention to address this gap.

Objective: This study aimed to describe the protocol of a study that aims to examine the acceptability and preliminary efficacy of PATH intervention among insufficiently active adults with obesity aged at least 18 years.

Methods: This is a 6-month pilot randomized controlled trial (RCT), using a parallel design with 1:1 allocation to intervention or control group. The PATH intervention group is given access to the PATH platform, but the resources each participant can access are tailored according to their baseline fitness level. Control group receives a self-help PA handout. Both groups self-monitor their PA using Fitbit (Google) and have Zoom (Zoom Video Communications) meetings twice a month with either the health coach (intervention) or study coordinator (control). The outcomes at 6-months include acceptability, changes in PA, and cardiometabolic risk from baseline to 6-months.

Results: We screened 763 individuals for eligibility and 89 participants were enrolled and randomized to the intervention (45/504, 50.6%) and control arms (44/504, 49.4%). The average age was 48.7 (SD 12.17) years, and most participants were female (81/504, 90.1%), Black (45/504, 50.6%), and non-Hispanic (83/504, 93.3%). No systematic differences in baseline characteristics were observed between the study arms. The 6-month intervention is currently underway, and the completion of follow-up data collection is expected in February 2025, with results to be published soon after.

Conclusions: The PATH intervention offers a promising, evidence-based approach to overcoming the barriers that have hindered previous PA programs for adults with obesity. It can support new and existing programs to foster long-term maintenance of health-enhancing PA.

Trial Registration: ClinicalTrials.gov NCT05803304; https://clinicaltrials.gov/study/NCT05803304

International Registered Report Identifier (IRRID): DERR1-10.2196/67972

(JMIR Res Protoc 2025;14:e67972) doi:10.2196/67972

KEYWORDS

obesity; physical activity; cardiometabolic risk, body positivity, cardiovascular fitness, self-efficacy

Introduction

Only about 14% of adults with obesity attain the minimum levels of physical activity (PA) recommended by public health guidelines to achieve health benefits [1-3].Low levels of PA contribute to the high population burden of cardiovascular disease (CVD) as they increase the relative risk of stroke, coronary heart disease, and diabetes by 60%, 45%, and 30%, respectively [4-6]. Even in the absence of weight loss, regular PA can significantly reduce the risk of CVD among individuals with obesity [3,7,8]. However, individuals face complex and multifaceted barriers that reduce their motivation and engagement in regular PA for meeting current recommendations [9,10].

Barriers to PA associated with obesity include stigma, shame, poor fitness, and low self-efficacy. These evoke fears of embarrassment and pain, contributing to aversion and avoidance of PA [10-12]. To mitigate these barriers, web-based PA programs targeting adults with obesity have been developed. Preliminary data suggest improved retention for online programs, but the effects on PA are heterogeneous [13]. Limitations of these interventions include the absence of human contact, “one-size-fits-all” strategies, unmet weight-loss expectations, and generic content that fails to address barriers associated with obesity [10,14]. We [15] and others [9,10] have reported that individuals with obesity prefer programs that are convenient, fun to engage in, and feature people who they can relate to with respect to body size, fitness level, and age. Yet, there is a paucity of web-based PA programs that are intentionally designed to flexibly incorporate these preferences [10,16,17].

To address the limitations of previous interventions, our research team designed the web-based PA for The Heart (PATH) intervention. PATH leverages openly accessible platforms, such as YouTube (Alphabet Inc), to provide workout videos that match the specific preferences expressed in our formative studies and the extant literature. In developing PATH, we used an iterative bottom-up approach where our target population was engaged in the selection and rating of the workout videos. Then, highly rated workouts (≥3.5/5 stars) were vetted by the study team for content relevance and safety and then curated on our PATH website in 3 intensity levels (beginner, intermediate, and proficient) to foster gradual progression from low- to high-intensity PA. We added backend features that enable a remote health coach to help users set their PA goals and select a PA regimen that is safe for their fitness level. Each PATH user has a personalized dashboard displaying their recommended workouts and progress toward their PA goals.

We have successfully beta-tested the PATH platform (N=25) and completed a 12-week feasibility study where we met our recruitment goal (N=82) and attained excellent retention (96%). Intervention engagement was high, and the PATH group significantly increased objective moderate to vigorous PA (MVPA) indicating preliminary efficacy [18]. The feedback we obtained from this study included the need to provide resources that can help participants improve their diet, provide feedback on cardiometabolic health indicators, and the need to improve our machine learning algorithm designed to keep the PATH platform up to date.

We used this feedback to further refine the PATH platform by curating nutritional resources focusing on improving diet quality and added a user-facing dashboard with feedback on 5 measures of cardiovascular health including physical activity, blood pressure (BP), weight, heart rate, and sleep efficiency. Also, we optimized the platform’s machine learning algorithm (PATH Fresher) that continually identifies new workout videos that match those preferred by the PATH users to be used in future updates of the platform.

This study describes the latest protocol (version #7, 12/16/2024) of a 6-month pilot randomized controlled trial (RCT), using a parallel design with 1:1 allocation to intervention or control, and designed to assess the preliminary efficacy of the optimized PATH intervention for promoting adherence to PA guidelines among 88 insufficiently active adults with obesity. We hypothesized that participants who are randomized to the optimized PATH intervention will show greater increases in PA at 6 months compared with those assigned to the attention control group. We also hypothesized that the optimized PATH intervention group will have a more favorable cardiometabolic risk profile at 6 months compared with the attention control group.

Methods

Study Design

This is a 6-month, ongoing parallel group RCT including 89 participants with insufficient activity and obesity who are randomized 1:1 to either the PATH intervention or an attention control group. The PATH intervention group are given access to the PATH platform, but the resources each participant can access are tailored according to their baseline fitness level (details described below under optimized PATH intervention).

In addition, the intervention group receive text and or email reminders to log into PATH and do their workouts based on their preferred schedule and will have twice per month online meetings with fitness coaches to monitor progress and review PA goals. The control group receives the Be Active Your Way booklet which is an evidence-based self-help resource for promoting PA [19] and twice per monthly online meetings with the study coordinator to check-in on their progress in the study and maintain contact. The staff members conducting the study assessments are blinded to randomized group allocation.

Setting and Participants

The study is conducted at Emory University, with participants recruited primarily from the Atlanta metro region. Eligibility criteria include reliable access to the internet, age ≥18 years, BMI ≥30 kg/m^2, successful self-monitoring of PA (≥4 days with ≥10 hours wear time) via a waist-worn ActiGraph accelerometer during a run-in period, and classification as insufficiently active according to the PA Guidelines (<150 min of MVPA per week) based on self-reported PA from the Behavioral Risk Factor Surveillance System PA questionnaire [20]. Exclusion criteria include current participation in a lifestyle modification or weight loss study, pregnancy or intention to become pregnant within 6 months, mobility restrictions, use of implantable electronic medical devices, or any condition that requires supervised PA (eg, stroke). Those with any condition that the PA Readiness Questionnaire (PAR-Q+) [21] identifies as requiring primary care provider review before engaging in unsupervised PA will be required to obtain medical clearance before they are enrolled in the study.

Recruitment

Overview

To obtain our target sample (N=89), we leverage resources available to Emory investigators, including Georgia Clinical and Translational Science Institute, Research Match (registry of research volunteers), electronic mailings, announcements on social media sites, and fliers posted in the community. We are also recruiting from primary care practices affiliated with Emory Health care, with an aim to recruit a diverse sample that includes ≥25% men and ≥30% racial and ethnic minorities.

Screening and Online Questionnaires

Individuals who respond to recruitment solicitations are directed to a web link that provides a brief overview of the study and eligibility criteria. Those who are eligible are guided to follow a link to complete 9 brief questionnaires which are outlined with their validation references in Table 1. For participant convenience, the questionnaires are administered via the REDCap (Research Electronic Data Capture; Vanderbilt University) platform so that they can be completed online in one or multiple sittings within 30 minutes. Data from the questionnaires are used for eligibility screening and will eventually allow us to examine the impact of sleep disturbance, health status, stress, and risk of depression on study outcomes. The eligibility criteria are embedded within the online surveys so that the data collection is terminated when a potential participant enters information that makes them ineligible (eg, history of stroke). Those who complete the REDCap questionnaires and remain eligible for the study are scheduled for a 20-minute phone interview, during which the Mediterranean Eating Pattern for Americans [22] screener and the PA questionnaire [20] are administered by an interviewer. Those who do not meet current PA guidelines (<150 min of MVPA per week) are scheduled for a 15-minute phone call to set up the technology that they will be using in the study.

Table 1. The questionnaires and assessment schedule.

Questionnaires and scheduled assessments	Baseline	6 months
Screening, health history, and lifestyle questionnaires		
Sociodemographic and medical history questionnaires	✓	✓
PA[a] readiness questionnaire (PAR-Q+) [21]	✓	✓
Poffenbarger exercise habits questionnaire [23]	✓	✓
Barriers Self Efficacy Scale [24]	✓	✓
PROMIS SF[b] sleep disturbance questionnaire [25]	✓	✓
PROMIS SF sleep-related impairment questionnaire [25]	✓	✓
Center for Epidemiologic Studies Depression Scale (CES-D) [26]	✓	✓
NIH[c] toolbox perceived stress [27]	✓	✓
EQ-5D health status instrument (EQ-5D-5L) [28]	✓	✓
Questionnaires measuring PA and potential PA mediators		
Mediterranean eating pattern for Americans questionnaire [22]	✓	✓
BRFSS[d] physical activity questionnaire [20]	✓	✓
All of us research program lifestyle survey (smoking and alcohol)	✓	✓
Exercise Self-efficacy Scale [29]	✓	✓
Self-regulation Questionnaire [30]	✓	✓
Physical Activity Enjoyment Scale [31]	✓	✓
Social Support for Exercise Scale (SSES) [32]	✓	✓
Multidimensional Outcome Expectations for Exercise Scale [33]	✓	✓
Medication history and cardiometabolic assessments		
Medication history	✓	✓
Zoom supervised self-administered blood pressure	✓	✓
Zoom supervised self-administered weight	✓	✓
Zoom guided self-administered waist circumference	✓	✓
Self-reported data for PA index (frequency, intensity, and duration) [34]	✓	✓
Zoom supervised dry blood spot sample collection for HbA1C[e], adiponectin, and lipids (total, LDL[f], and HDL[g] cholesterol)	✓	✓
CVD[h] risk score computed using ASCVD[i] risk calculator [35]	✓	✓
Heart health score computed using life's essential data	✓	✓
American diabetes association risk score [36]	✓	✓
Fitbit charge 5 data on PA (continuous)	✓	✓
ActiGraph GT3X accelerometer data on MVPA[j] (7 days)	✓	✓
Users' feedback		
System Usability Scale [37] and post-intervention survey		✓

[a]PA: physical activity.

[b]PROMIS SF: Patient-Reported Outcomes Measurements Information System.

[c]NIH: National Institutes of Health.

[d]BRFSS: Behavioral Risk Factors Surveillance System.

[e]HbA_{1c}: hemoglobin A_{1c}.

[f]LDL: low-density lipoprotein.

[g]HDL: high-density lipoprotein.

[h]CVD: cardiovascular disease.

[i]ASCVD: atherosclerotic cardiovascular disease.

[j]MVPA: moderate to vigorous PA.

Technology Set-Up, Informed Consent, and Mediation

Before the technology set-up phone call, we provide potential participants with email instructions on how to install Zoom (Zoom Video Communications; for assessments and coaching), Withings (weight, BP), and Fitbit (PA) apps. During the phone call, the study staff members verified the software installation and provided login credentials for the apps. Next, study staff members review the study procedures and those still interested in the study receive a copy of the informed consent to review and sign via REDCap. Those who consent are asked to complete the All of Us Research Program Lifestyle Survey as well as questionnaires assessing exercise self-efficacy [29], self-regulation [30], PA enjoyment [31], social support [32], and outcome expectancy [33] (Table 1). These validated questionnaires are frequently used to identify facilitators and barriers [29-33] that are known to influence PA and cardiovascular outcomes [38-41]. These questionnaires can be completed in REDCap within approximately 30 minutes and will be repeated at the 6-month follow-up visit. An optional Adverse Childhood Experiences questionnaire will be used to explore difficult childhood experiences that may impact variables of interest in the study. The participants will be asked by the study staff members to give their verbal consent to receive this questionnaire at the end of the study assessment.

Baseline Assessment Via Zoom

Participants who meet all eligibility criteria during screening are scheduled for a baseline assessment via Zoom. Before the assessment, each participant will receive a package with all supplies including a Dry Blood Spot Kit, Fitbit Charge 5, ActiGraph GT3X, Withings Arm BP Monitor, Withings Scale, Perfect Waist Tape Measure, and Stretch Band. During the Zoom visit, the study staff members review the data in the PA readiness questionnaire (PAR-Q+) [21], to ensure that individuals who need primary care practitioner clearance obtain it before they are randomized to the intervention or attention control condition. We use the HIPAA (Health Insurance Portability and Accountability Act)-compliant online Fax (SRFax, Ziff Davis Inc) to send and receive faxes on behalf of participants.

The assessments commence with the study staff members reviewing the waist circumference self-measurement video and guidelines developed by the International Chair on Cardiometabolic Risk [42]. The staff members instruct the participants to go to a private location where they can measure their waist on bare skin using the Perfect Tape Measure. The participant shows the locked tape measure to staff members via the camera. There is evidence for strong correlation coefficients (0.8 to 0.9) between self and technician-measured waist circumference using this method [43-47]. Next, the staff members instruct the participant to wear light clothing and stand on the smart scale footpads with their bare feet to measure weight, percentage body fat, percentage body water, muscle, and BMI. The study team obtains these device-recorded measures via the Withings application programming interface (API) with the PATH platform.

We use the clinically validated Withings Arm BP Monitor for self-measurement of BP [48]. The smart monitor has a one-touch easy-to-read digital screen and a cuff that fits an arm circumference of 22-42 cm (larger cuffs available on request). Staff members will instruct the participant to apply the cuff on the bare left arm, then sit in a chair with both feet resting flat on the floor, with the back straight and supported. After 5 minutes of rest with the left arm resting on a flat surface at heart level, participants will be asked to turn on the BP machine and take 3 measurements at 1-minute intervals. The study team will immediately access the device-recorded BP via Withings API with the PATH platform. Participants with elevated BP (>130/80 mm Hg) will be referred to their primary care practitioner, with a request to update the study team if treatment is initiated. Those with severe hypertension (BP ≥180/110 mm Hg) will be asked to seek urgent medical attention before re-evaluation of their eligibility.

Blood samples for measurement of adipokines (tumor necrosis factor alpha [TNF-α], monocyte chemoattractant protein 1 [MCP-1], interleukin [IL]-1 beta [IL-1β], and IL-6, leptin, and adiponectin) and lipids (low-density lipoprotein [LDL], high-density lipoprotein [HDL], and total cholesterol) are collected via volumetric absorptive microsampling approach using Mitra dry blood spot kits [49]. Study staff members supervise participants collecting the fingerstick sample following the steps outlined in the sample collection tutorial [50]. The samples are mailed by each participant to the laboratory using the included return address. Once at the laboratory, the samples are stored at –80^{o} C and will be processed at the end of the study using established protocols for analysis [51].

Run-In Period

At the end of the baseline assessment, the staff members will instruct participants to wear the ActiGraph GT3X on their waist and Fitbit on their wrist to monitor PA for a 7-day run-in period. The run-in period will help potential participants appreciate study expectations and will provide objective data on baseline MVPA. Individuals will need to wear the Fitbit and ActiGraph GT3X for ≥10 hours on ≥4 days to be eligible in the study [52].

Randomization and Orientation

After the successful completion of the run-in period, nonblinded staff members randomize eligible participants with equal allocation (1:1) to either the PATH intervention or the attention control arm using the REDCap randomization software. Group assignments are generated via a REDCap stratified randomization scheme to achieve a balance between the treatment and control groups regarding age (18-45, 46-64, and ≥65 years), sex (male or female), and race (White or racial and ethnic minorities). The Randomization scheme was developed by the study statistician. After randomization, a study staff member meets with each participant on Zoom to orient them to their randomized group resources. If blinded staff members inadvertently become unblinded, the incident will be noted in the study's log, and they will not conduct end-of-study assessments on the participant. Participants in both groups are

instructed to wear Fitbit on their nondominant hand during the study using a 24-hour wear protocol.

The PATH Intervention

A health coach will provide each participant with a password-protected profile to access the PATH website and a detailed orientation on how to use all the resources included in PATH. In addition, the health coach will meet remotely with each participant twice per month. The PATH intervention provides counsel and guidance to participants in the development of multiple behavior change strategies to promote long-term adherence to the minimum threshold of PA Guidelines (150 MVPA min/week). The Fitbit and Withing APIs are integrated with our PATH platform to enable near-real-time monitoring of the participant's progress. The interface also enables us to capture longitudinal trends in PA and to display the progress toward their PA goal on each participant's dashboard. The coach will work with each participant in the treatment group to develop their PA prescription guided by the FITT-VP (frequency, intensity, type, time, volume, and progression) principle [53], which recommends the frequency, intensity, duration, type, volume, and progression of PA. Although there are no established standards on how to increase PA, available evidence suggests that it is safe to increase MVPA by 10 minutes per week [54]. Although the weekly MVPA goal translates to about 1000 steps of moderate activity per week [55], the participants are asked to target 500 additional steps per week to make sure that the goals are safe for everyone, including those with morbid obesity.

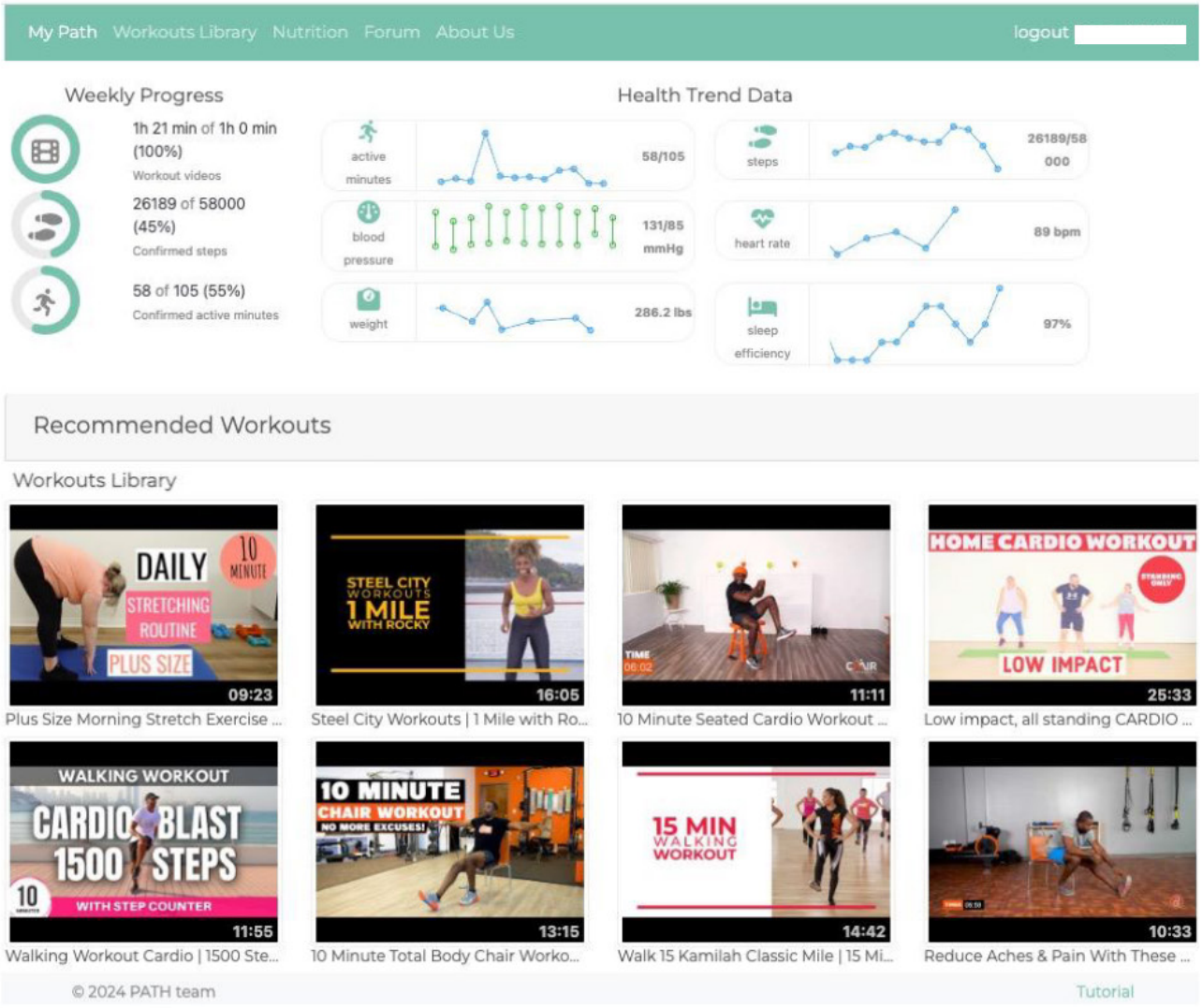
The coach works with each participant to develop a tailored plan geared toward increasing MVPA by ~10 minutes per week with each coaching encounter. Given the scheduled 12 coaching encounters during the 6-month study period, participants at all levels of fitness will have a chance to develop a PA regimen that is adherent to the PA Guidelines. Participants with relatively high baseline PA are advised to target the higher threshold of the PA Guidelines (300 MVPA minutes per week). Our PA prescription process begins by identifying a suitable PATH level for each participant based on their estimated cardiorespiratory fitness level, which is estimated using a predicted maximum rate of oxygen consumption during incremental exercise (VO_2 maximum) [53]. The VO_2 maximum is predicted using a validated, nonexercise prediction model for peak VO_2 whose covariates include sex, age, waist circumference, resting heart rate, and PA index [34].

Individuals with a predicted VO_2 maximum in the ≤35th percentile for their age and gender are considered for assignment to the Beginner PATH level (includes light-intensity PA metabolic equivalents [METs] of <30 METs). Those with VO_2 maximum above the 35th percentile rank are assigned to the intermediate PATH level, which includes moderate-intensity workouts (3.0-5.9 METs) in addition to the Beginner PATH content. Based on our pilot experience, it is unlikely that a participant will be assigned to begin at the Proficient PATH level which includes vigorous-intensity workout videos (≥6 METs). Rather, participants will be given access to the level based on their rating of perceived exertion (RPE) scores at the intermediate level and coach evaluation. The coach can change the PATH level based on their assessment of the participant's capabilities during the meetings.

After assigning the PATH fitness level, the health coach guides each participant in selecting their weekly PA goal and helps them start slowly with a plan to establish regular exercise frequencies of 3-5 days per week. The coach also guides participants to select activities with intensity to help them progress along the PA continuum (ie, from inactive to light PA and then MVPA). To foster safety, participants are instructed to use the RPE Scale [56] as a guide for adjusting the intensity of their PA regimen. The scale ranges from 6 (no exertion at all) to 20 (maximal exertion) and is embedded within each workout video on PATH. The coaches will also help participants set up Fitbit safe heart rate zones based on their fitness levels, with a goal of progressing to the Cardio Zone (70% and 84% of maximum heart rate) by the end of the study.

Participants are asked to use workouts that elicit perceived exertion ratings between 12 and 14 (ie, moderate intensity) on the RPE Scale. The coach reviews progress made every 2 weeks. More intensity is allowed, including the transition to the next PATH level, when most workouts within the assigned PATH level are perceived to be "fairly light" (≤11 on the RPE Scale). If a participant forgets to rate their workouts, their heart rate during the workout sessions is reviewed during the coaching session, and a goal that aligns with each person's capabilities is discussed between the health coach and participant. This method ensures the prescribed regimen is based on ability and fitness status. Although the health coach provides examples of workout videos that could help participants attain their personalized goals, each participant has access to all resources within their PATH level and is encouraged to select a regimen that includes their preferred workout videos and other types of PA appropriate for their fitness level. The workouts that are recommended by the health coach and those selected by each participant as favorites are featured on their PATH dashboard alongside the self-monitoring data (Figure 1).

Figure 1. Participants' physical activity for the heart platform dashboard.



The PA prescription is revised during the online meetings with the coach to reflect the progress made toward the study goal. Those who attain adherence to the PA Guidelines within the first 3 months will achieve the study goal and their plan for the remaining 3 months will be to maintain the improved PA regimen. However, each participant can opt to continue with a gradual increase in PA duration and intensity. To simplify access and support maintenance of PA, the workout videos are organized into categories (eg, walking, dance, and steps aerobics) and can be sorted by duration and METs. To reduce the risk of injury, the amount and intensity of PA are increased gradually, with emphasis on duration followed by intensity per the American College of Sports Medicine [53]. The coach, in consultation with the principal investigator (PI), may discontinue or modify any participant's PA prescription in response to the potential for harm, participant request, or improving or worsening disease. To complete the PA prescription, participants are asked to suggest their preferred schedule for receiving motivational PA reminders (eg, "Remember to work out on PATH today! Exercise doesn't have to leave you exhausted for it to make a difference in your health — M. Richardson"). The short motivational messages are randomly selected from a bank with >270 vetted messages. Also, participants are asked to provide a schedule for the Zoom meetings with a health coach to monitor progress and revise PA goals. During the study, the participants are encouraged to share their experiences on the PATH community forum to foster community and social support. An end-of-study survey will capture feedback on participant experiences and the most helpful aspects of the PATH intervention resources.

The Control Condition

After randomization, study staff members schedule a Zoom meeting with each control group participant where they are guided to use their tracker and Be Active Your Way Guide [19]. They also schedule a check-in meeting with them every 2 weeks, with the intention to keep the contact between the groups as similar as possible.

Protocols for Both Treatment and Control Arms

During the twice per month meetings with intervention and control groups, the participants receive early morning reminders to empty their bladder and step on the scale before meeting with the study staff members who supervise BP measurements on Zoom. These data are used to monitor trends in BP, weight, and body composition during the study period. Both the intervention

and control arms receive an email with a brief PDF addressing 1 diet component every 4 weeks. The diet information is also available to them as modules on the PATH platform (control group access on PATH is limited to the nutritional resources). At the end of the 6-month study assessments, both control and intervention group participants are given the option to continue using the PATH platform at their convenience without any interaction with the coaches.

Study Outcomes

Indicators of PATH Fresher Algorithm's Effectiveness in Identifying Workouts That Match User Preferences

Effectiveness of the PATH Fresher algorithm will be indicated by its ability to analyze PATH users' data, spin up new browser sessions in the background to activate the YouTube recommender system, and select new workouts like those highly rated (≥3.5/5 stars) by study users. At the end of the study, the coaches will vet the new workouts recommended by the PATH fresher algorithm. The acceptance of ≥50% of the top twenty recommended workouts for inclusion in PATH will indicate the effectiveness of the PATH fresher algorithm. The systems usability survey [37] will be completed by participants to survey satisfaction with the PATH platform.

Acceptability of the Disseminated Educational Resources Focusing on Improving Diet Quality

The resources will be curated from an extensive library of standard behavioral treatment content previously developed and validated by the SMARTER study team [57,58]. Their acceptability will be indicated by 70% of the participants rating the materials as helpful via a researcher-developed end-of-study survey (Multimedia Appendix 1).

Measures of PA and Adherence to PA Guidelines

The efficacy of PATH in enhancing adherence to PA guidelines will be evaluated at 6 months using MVPA data collected using the Actigraph GT3X device [59] worn on the waist for 7 days at 6 months. Adherence to PA guidelines will be defined as achieving ≥150 minutes of MVPA per week. Percent change in adherence will be calculated as follows: ([postintervention MVPA–baseline MVPA]/recommended MVPA×100). Between-group differences in % change in adherence and the proportion of individuals who attain the recommended MVPA will be evaluated. Established and novel methods will be used to process ActiGraph data which will be considered valid if ≥4 days with ≥10 hours of wear time are measured [59]. ActiGraph GT3X nonwear time was defined using the Choi wear time validation algorithm [60]. Fitbit valid data were indicated by ≥4 days with ≥500 steps per day as recommended by Thorndike et al [61] and Bizhanova et al [62]. Sustained PA engagement will be evaluated via Active Zone Minutes data collected via Fitbit Charge 5 and will be analyzed via the adherence strategy described above. Validation studies suggest that Fitbit is ideally suited for long-term self-monitoring of PA due to its user-friendliness and extensive use in RCTs [63].

Measures of Cardiovascular Outcomes

Cardiovascular outcomes will be indicated by change from baseline to end of 6-month study post intervention in CVD risk score calculated using the 2013 Atherosclerotic Cardiovascular Disease Risk Calculator [35]. The algorithm provides sex- and race-specific estimates for the first CVD events. The scores range from 0% to 100% with higher scores representing poor cardiovascular health status. The composite risk factors included in the algorithm are age, total and HDL cholesterol, systolic blood pressure (including treated or untreated status), diabetes, and current smoking status. These will be measured using the protocols outlined under baseline assessment. The main outcome will be between-group differences in risk score change from baseline. We will use the same strategy to evaluate changes in independent risk factors for CVD (secondary outcomes): waist circumference, weight, BP, Life's Essential 8, hemoglobin A_{1c} (HbA_{1c}), adiponectin, and lipids (total, low-density lipoprotein, and HDL cholesterol).

Sample Size Justification

Given our repeated measures study design, we anticipate some participant attrition. To ensure sufficient sample size with complete assessment through 6-months follow-up, we plan to enroll 88 participants (44 per treatment group) retaining at least 76 participants (38 per treatment group) assuming a 14% attrition through the 6-month follow-up based on attrition rates observed in the literature [64]. When estimating within-group changes to describe the effect of PATH on study outcomes using either proportions or means, with at least 38 participants per treatment group (76 total), we would have at least 80% power to detect small-to-medium effect sizes for the efficacy of the PATH intervention. For PA, this corresponds to a mean difference of 20 minutes of MVPA or 13.3% absolute change in terms of adherence to PA guidelines. For CVD risk factors, linear contrasts from either linear or generalized linear mixed modeling will be specified and estimated to compare the treatment groups on the 6-month change in CVD risk scores and risk factors at test wise (Bonferroni-adjusted) significance level of .05.

Statistical Analysis

Data will be analyzed using SAS (version 9.4; SAS Institute) to conduct exploratory data analyses for data screening, including missing data assessment, as well as repeated measures modeling, and modeling of attrition. Mplus (version 8.8; Muthén and Muthén) will be used for mediational analyses to explore possible mechanisms of action of the PATH intervention. Data will first be carefully screened with the results of these preliminary analyses informing the final analysis strategies to be applied to address study aims and exploratory analyses. Although hypotheses are stated as directional, hypothesis testing will be nondirectional with the significance level set to .05 and CI estimation at 95%. The randomness of missing data will be investigated using information on participant characteristics to help discern patterns in the missing data, identify possible missing data mechanisms, and inform strategies to handle missing data. If data are not missing at random, we will apply multiple imputations and 2 extreme case scenarios (worst or best case) to address missing data. If nonrandom missingness is suspected, we will use selection or pattern mixture modeling to explore the sensitivity of results to the assumed missing data patterns.

An intent-to-treat (ITT) approach will be used to test the efficacy of the PATH intervention on the distal outcome of adherence to the PA guidelines over time. Since key study end points are assessed at multiple time points, repeated measures modeling (eg, linear or generalized linear mixed modeling methods and or marginal modeling using generalized estimating equations as appropriate, both assuming a normal error structure) will be used to test the efficacy of the PATH intervention on the measures of adherence to the PA guidelines over time (baseline [0 months], and 6 months [long-term] follow-up). To test the hypothesis that the PATH intervention group will have greater adherence to PA guidelines compared with the attention control group, linear contrasts will be specified and estimated to compare adherence to PA guidelines between the treatment groups at 6 months relative to baseline values, respectively. The test wise significance level will be set to .05 (Bonferroni-adjusted). Point and interval (95% CIs) estimates based on linear contrasts will also be computed as both unstandardized and standardized effect sizes of the efficacy of the PATH intervention.

Analysis Strategy to Compare the Effects of the PATH Intervention on CVD Risk Factors

A similar repeated measures modeling approach as outlined above will be used to evaluate the efficacy of the PATH intervention compared with the attention control condition on CVD risk factors including CVD risk score, weight, BP, waist circumference, HbA_{1c}, and lipids at 6-month follow-up. These measures of CVD risk are either interval or ratio scaled, and a normal error structure (or following a suitable data transformation) will be assumed when modeling. As necessary, generalized linear mixed modeling assuming a binomial error will be applied to model CVD risk factors dichotomized based on clinically meaningful cut points. To test the hypothesis that the PATH intervention group will have a greater reduction in CVD risk score versus the control group, linear contrasts will be specified and estimated to compare the treatment groups on the change in CVD risk scores at 6-months follow-up relative to baseline values at a test wise significance level of .05 and CI estimation at 95%.

Data Management

Overview

All technologies to be used in this study, including the AWS web hosting platform, PATH website, Twilio, SR Fax, ActiGraph GT3X, Fitbit, and Withings apps were reviewed and approved by Emory University's Enterprise Information Security Team. The entire data collection infrastructure, including the REDCap and PATH platforms, were tested by the study team before it was deployed for data collection. Data will be stored on a password-protected computer with access limited to the staff members who monitor participants' adherence and safety, and the data management team. Access to the master list of participant names and ID numbers will be limited to the staff members who conduct the screening and intervention procedures as they need to interact with these individuals on a name basis. The staff members who do not interact with participants are blinded to name and treatment assignment. The primary outcomes will be shared in scientific conferences and peer-reviewed publications. Investigators seeking to use the deidentified data will sign a data user agreement with Emory University.

Plans to Monitor the Data to Ensure Safety of Participants and Data Integrity

A data safety and monitoring plan will be implemented to ensure the safety of all participants involved in the study and to ensure the validity and integrity of the collected data. The PI and biostatistician (in conjunction with the project coordinators and staff members), will be responsible for the execution of this plan under the oversight of a safety officer and the institutional review board (IRB). The safety officer will act in an advisory capacity to the PI and the National Institutes of Health program director. All adverse events will be documented in REDCap and reported in publications. Major adverse events will be reported to IRB following established protocols. To posttrial care or compensation for harm will be provided. The SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) checklist is provided in Multimedia Appendix 2.

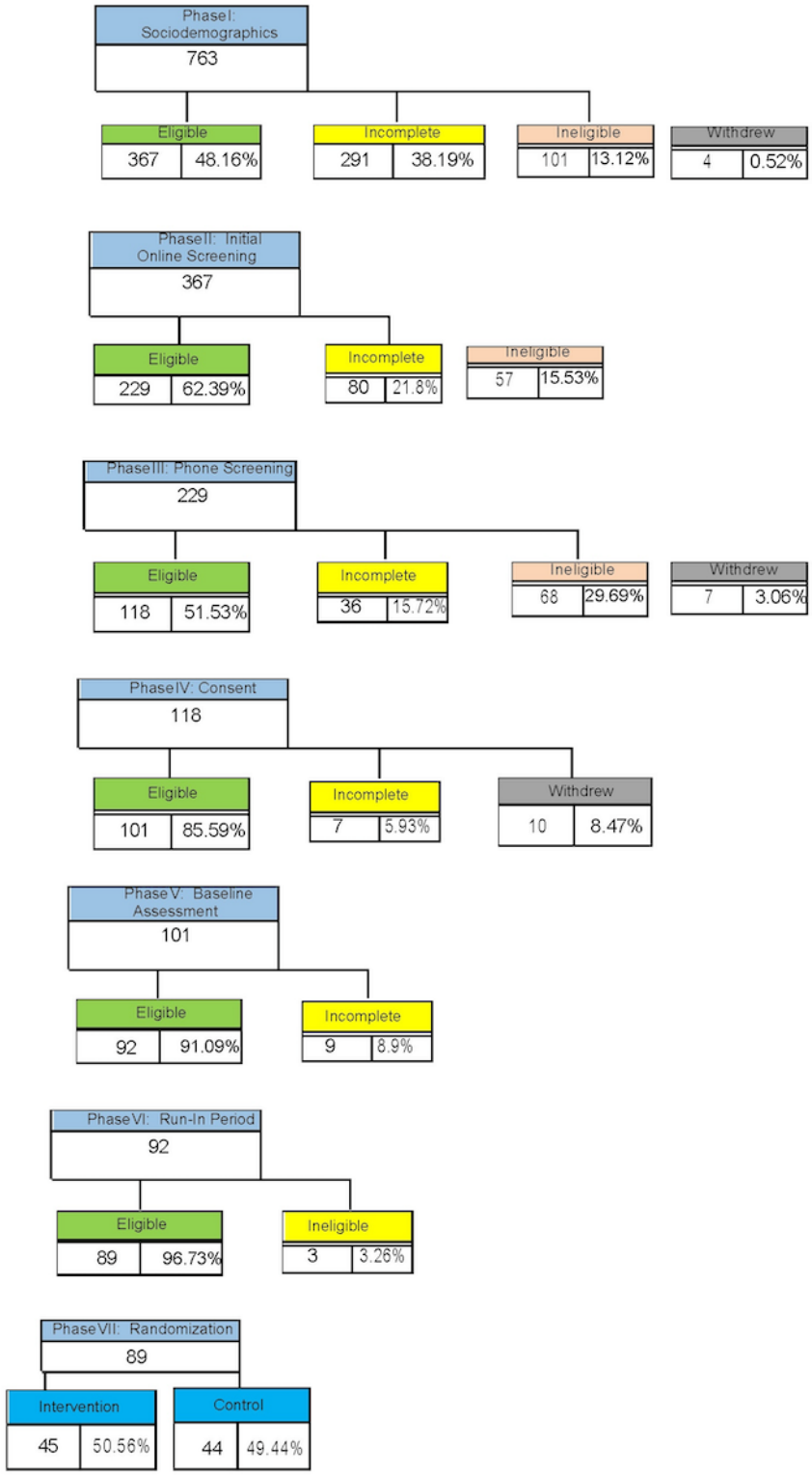
Ethical Considerations

The Emory IRB approved the study protocol before beginning the study (IRB approval #STUDY00005168). Written informed consent is obtained from all participants before participation in study procedures. Data is collected using the encrypted and password-protected REDCap and PATH platforms. Identifiable data is only stored in REDCap and is deidentified before being exported for analysis. Confidentiality will be ensured by the use of a simple ID number, which is not encoded to denote other variables. Participants received US $100 compensation and were allowed to keep their Fitbit tracker and Smart Scale for their participation in the study.

Results

We screened 763 individuals for eligibility and 89 participants were enrolled and randomized to the intervention (45/504, 50.6%) and control arms (44/504, 49.4%). The average age was 48.7 (SD 12.17) years, and most participants were female (81/504, 90.1%), Black (45/504, 50.6%), and non-Hispanic (83/504, 93.3%). No systematic differences in baseline characteristics were observed between the study arms. The 6-month intervention is currently underway, and the completion of follow-up data collection is expected in February 2025, with results to be published in the Spring of 2025. Figure 2 presents the CONSORT (Consolidated Standards of Reporting Trials) flow diagram with the screening, enrollment, and randomization details.

Figure 2. The CONSORT flow diagram.



Discussion

Anticipated Findings

The significance of addressing physical inactivity in adults with obesity cannot be overstated. The PATH intervention is testing a novel strategy for addressing the multifaceted barriers to PA among adults with obesity. Our study protocol is grounded in the understanding that traditional PA programs often fail to engage this population because they do not address their unique barriers to PA including stigma, poor fitness, low self-efficacy, unmet weight loss expectations, and limited access to relatable exercise programs [10,15]. By engaging users via tailored workout videos, online coaching, and digital self-monitoring tools, the PATH intervention offers a scalable, participant-centered, and highly accessible solution to address barriers to PA engagement among individuals with obesity. The weight-neutral messaging included in PATH programming is

intentionally designed to help participants focus on getting active without being discouraged by limited weight loss progress.

Preliminary evidence from formative studies suggests that the PATH intervention is promising in promoting PA engagement and adherence among adults with obesity [18]. The integration of personalized online coaching with a highly accessible and user-friendly web-based platform addresses key limitations of previous web-based and mobile health (mHealth) PA interventions, which often lacked the individualized support necessary to sustain long-term behavior change [10,14,16]. Our approach in this RCT aligns with that used in recent studies that have highlighted the importance of combining technology with human interaction to promote engagement and adherence in PA programs [14,18]. Moreover, the use of validated smart digital tools (eg, Fitbit tracker, Withings scale, and BP monitor) that are interfaced with the user-facing dashboard on PATH facilitates near–real-time accurate monitoring of multiple cardiovascular health indicators without increasing participant burden. These tools enable the coaches to offer timely feedback and appropriate support during online coaching sessions, helping the participants maintain PA engagement over time.

If successful in promoting PA adherence, the PATH intervention could provide a practical, scalable option that health care providers can recommend to patients who struggle with PA adherence, especially those with obesity. Because PA has been shown to reduce the risk of CVD even without weight loss [8], the PATH intervention has the potential to play a critical role in improving health outcomes in this high-risk population. The program's weight-neutral messaging encourages the participants to focus on being active with the goal of achieving cardiovascular health benefits, even if no weight loss is attained. This careful messaging is intended to mitigate unmet weight loss expectations, which are a major impediment to long-term adherence to PA in this high-risk population [12].

Understanding the mechanisms of action underlying the efficacy of PATH is highly significant. In this study, we are examining factors such as self-efficacy, social support, and outcome expectations to gain more insights into how the PATH intervention facilitates behavior change. These data will inform further refinement and optimization of the PATH platform. The next phase of optimization could leverage novel digital health technologies such as artificial intelligence for enhanced personalization to further improve the engagement and efficacy of the PATH intervention. This presents a promising opportunity for providing a more tailored and engaging experience for users, which aligns with the growing trend of technology-enhanced preventive health solutions.

This study has a few limitations that are worth acknowledging. The relatively small sample size may limit the generalizability of findings, and our eligibility criteria may favor participants with higher levels of digital literacy and access to technology. Future research should focus on addressing these limitations by conducting larger-scale trials that evaluate long-term efficacy and sustainability of PA adherence, with proactive strategies to reach populations with limited digital access. Our next logical step will be to conduct a full-scale RCT which will be adequately powered to examine if the PATH intervention can increase long-term PA and cardiometabolic health in adults with obesity. After large-scale efficacy trials, comparative effectiveness studies may be needed to determine how PATH performs relative to other web-based, in-person, or hybrid PA interventions to identify the most effective strategies for promoting PA adherence in adults with obesity. In addition, evaluating the cost-effectiveness of PATH compared to traditional PA programs or other web-based or mHealth interventions is also necessary to examine its value as a sustainable solution in real-world settings.

Moreover, future research should explore how the PATH platform can be further tailored to meet the needs of specific subgroups, such as older adults, individuals from diverse cultural backgrounds, or those with comorbidities like diabetes or hypertension. This will enhance the intervention's relevance and effectiveness for a broader range of individuals. Then, future studies can explore how the PATH intervention can be availed to health care systems to facilitate seamless referral of sedentary high-risk patients by clinicians, making PATH a more practical tool for promoting PA in routine clinical practice. Currently, there are very few options for structured PA programs that health care providers can refer their patients to beyond physical therapy.

Conclusion

In conclusion, the PATH intervention offers a promising, evidence-based approach to overcoming the barriers that have hindered previous PA programs for adults with obesity. For instance, most of the existing supervised PA programs, such as cardiac rehabilitation are usually short-term and address recovery to a baseline–rather than long-term maintenance of health-enhancing PA. By incorporating user preferences, human support, and a flexible, scalable web-based platform, the PATH intervention is poised to significantly improve PA adherence and reduce the risk of CVD in this high-risk population. If the PATH program proves to be efficacious in promoting PA among individuals with obesity, it could be an option for referral at the end of cardiac rehabilitation to promote and maintain a regular PA regimen. The findings from this RCT will contribute valuable insights to the field of research focusing on behavioral interventions to manage obesity, with potential implications for reducing the burden of obesity-related diseases. This aligns with the broader goal of preventive health care models that emphasize lifestyle modification as a cornerstone for managing chronic diseases [12,65].

Acknowledgments

The study was supported by National Heart, Lung, and Blood Institute (NHLBI; grant R56 HL164737). Research reported in this publication was supported by the NHLBI of the National Institutes of Health (award 7R56HL164737-02, see Multimedia Appendix 3).

Conflicts of Interest

None declared.

Multimedia Appendix 1
The Informed Consent.
[PDF File (Adobe PDF File), 516 KB - resprot_v14i1e67972_app1.pdf]

Multimedia Appendix 2
The SPIRIT checklist.
[DOCX File , 46 KB - resprot_v14i1e67972_app2.docx]

Multimedia Appendix 3
Peer-review report from the Lifestyle Change and Behavioral Health Study Section (National Institutes of Health, USA).
[PDF File (Adobe PDF File), 103 KB - resprot_v14i1e67972_app3.pdf]

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Abbreviations

API: application programming interface
BP: blood pressure
CONSORT: Consolidated Standards of Reporting Trials
CVD: cardiovascular disease
FITT-VP: frequency, intensity, type, time, volume, and progression
HbA1c: hemoglobin A1c
HDL: high-density lipoprotein
HIPAA: Health Insurance Portability and Accountability Act
IL: interleukin
IRB: institutional review board
ITT: intent-to-treat
LDL: low-density lipoprotein
MCP-1: monocyte chemoattractant protein 1
MET: metabolic equivalent
mHealth: mobile health
MVPA: moderate to vigorous physical activity
PA: physical activity
PAR-Q+: PA readiness questionnaire
PATH: Physical Activity for the Heart
PI: principal investigator
RCT: randomized controlled trial
REDCap: Research Electronic Data Capture
RPE: rating of perceived exertion
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials
TNF-α: tumor necrosis factor alpha
VO2 maximum: maximum rate of oxygen consumption during incremental exercise

Edited by A Schwartz; submitted 25.10.24; this is a non–peer-reviewed article;accepted 14.02.25; published 18.03.25.

Please cite as:
Kariuki J, Burke L, Erickson K, Sereika S, Paul S, Cheng J, Biza H, Abdirahman A, Wilbraham K, Milton H, Brown C, Sells M, Osei Baah F, Wells J, Chandler R, Barone Gibbs B
Acceptability and Preliminary Efficacy of a Novel Web-Based Physical Activity for the Heart (PATH) Intervention Designed to Promote Physical Activity in Adults With Obesity: Protocol for a Pilot Randomized Controlled Trial
JMIR Res Protoc 2025;14:e67972
URL: https://www.researchprotocols.org/2025/1/e67972
doi:10.2196/67972
PMID:

Protocol

Theory-Based Social Media Intervention for Nonmedical Use of Prescription Opioids in Young Adults: Protocol for a Randomized Controlled Trial

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Abstract

Background: The nonmedical use of prescription opioids (NMUPO) in young adults in the United States is concerning and is robustly influenced by many psychosocial factors. Given the advantages of flexibility, wide coverage, and real-time responses and assessment, using social media appears to be a promising and innovative approach to delivering psychosocial intervention to young adults. However, few theory-based social media interventions are available for NMUPO targeting this at-risk population.

Objective: Guided by the information-motivation-behavioral skills model, the proposed research aims to address critical gaps by theoretically exploring psychosocial content associated with NMUPO among young adults via formative assessment. These findings will then be used to develop and evaluate the feasibility and preliminary efficacy of a peer-led social media intervention to reduce NMUPO among young adults.

Methods: The proposed study will comprise serial research activities. First, formative research will be conducted through semistructured interviews among 30 young adults engaged in NMUPO. Qualitative data will be synthesized using a pragmatic approach for identifying psychosocial content associated with NMUPO. Second, qualitative findings will be used for developing a peer-led social media intervention to reduce NMUPO among young adults by integrating promising psychotherapy principles and incorporating them with well-trained recovery coaches. Third, the social media intervention will be evaluated through a 12-week randomized controlled trial among 70 young adults (n=35, 50% in the intervention group and control group) engaged in NMUPO via mixed methods, including pre- and postintervention surveys, social media paradata (eg, time-series reactions to posts) collection, and ecological momentary assessment during the intervention. The control group will not receive an intervention but will complete the pre- and postintervention surveys. The primary outcomes will be feasibility, usability, and acceptability, while the secondary outcomes will be psychosocial and behavioral measures, such as past–3-month NMUPO, intention, psychological distress, self-efficacy, resilience, and coping strategies.

Results: The proposed study was funded in May 2024. Social media campaigns have received responses from a total of 379 individuals, with 24 (6.3%) identified as eligible. As of February 10, 2025, we have completed formative interviews with 8 eligible participants.

Conclusions: The proposed study will be one of the first efforts to develop and deliver a theory-based peer-led intervention on social media, incorporating empirical findings on the psychosocial mechanism of NMUPO. The findings of the proposed study

will provide valuable insights into opioid risk reduction for young adults through an innovative approach. If the tested trial is found to be feasible, the proposed study will contribute to future scaled-up and fully powered psychosocial interventions among young adults and other key populations at risk for NMUPO.

Trial Registration: ClincialTrials.gov NCT06469749; https://clinicaltrials.gov/study/NCT06469749

International Registered Report Identifier (IRRID): DERR1-10.2196/65847

(JMIR Res Protoc 2025;14:e65847) doi:10.2196/65847

KEYWORDS

nonmedical use of prescription opioids; opioid misuse; young adults; social media; psychosocial intervention; randomized controlled trial; mixed methods

Introduction

Background

The nonmedical use of prescription opioids (NMUPO) is a critical public health concern in the United States, and young adults are particularly susceptible to this behavior. NMUPO refers to the aberrant use of prescription opioids in a manner other than as prescribed [1-3]. Substance use literature has paid increasing attention to NMUPO owing to its adverse consequences. National US data have shown a substantial increase of opioid-related overdose deaths, from <5000 in 1999 to >100,000 in 2023 [4,5]. NMUPO has also led to extensive medical costs in the United States (US $78.5 billion annually) [6]. Young adults (aged between 18 and 25 y) are at a high risk for NMUPO. In 2019, 5.5% of young adults in the United States engaged in past-year NMUPO, compared to 2.3% to 3.5% for other age groups. This rate was even higher among those who were not enrolled in college (6.3%) [7]. Besides the risk of overdose and dependence, NMUPO is associated with other negative outcomes, including health-jeopardizing behaviors (eg, driving under the influence), sexual risk behaviors, and suicide attempts [1,8-11]. In response to this issue, many US jurisdictions have launched initiatives to monitor prescription opioids [12]. Despite an obvious reduction in the prescribing rate (eg, 47% in 2019 to 38% in 2023) [12], NMUPO-related deaths remain high (>100,000 in 2023). Notably, NMUPO is strongly linked with the initiation of heroin and synthetic opioid use (eg, fentanyl) in young adults, posing a substantial risk for the development of substance use disorder (SUD) and overdose [13]. Hence, interventions targeting young adults are urgently needed to address NMUPO, and those should be delivered beyond the college population [14].

Interventions for NMUPO in young adults should take psychosocial factors into account. NMUPO literature has identified several important psychosocial factors associated with NMUPO in young adults, including perceived stress (eg, academic strain and traumatic stress), psychiatric distress (eg, depression and anxiety), perception of risk, peer and family influences, and sensation seeking [15-18]. Tam and his colleagues' previous research on NMUPO in college students has indicated several additional factors that reduce risk for NMUPO, such as psychological resilience, positive coping, outcome expectancies, and self-esteem [10,19-21]. Importantly, psychosocial factors robustly contribute to NMUPO. A meta-analysis study revealed that pooled effect sizes of psychosocial factors on NMUPO (odds ratios 2.14-2.45) were higher than those of somatic symptoms (odds ratio 0.81-1.76), which are traditionally viewed as major NMUPO determinants [22]. These findings indicate that interventions should be guided by a structured framework between psychosocial factors and health actions for NMUPO.

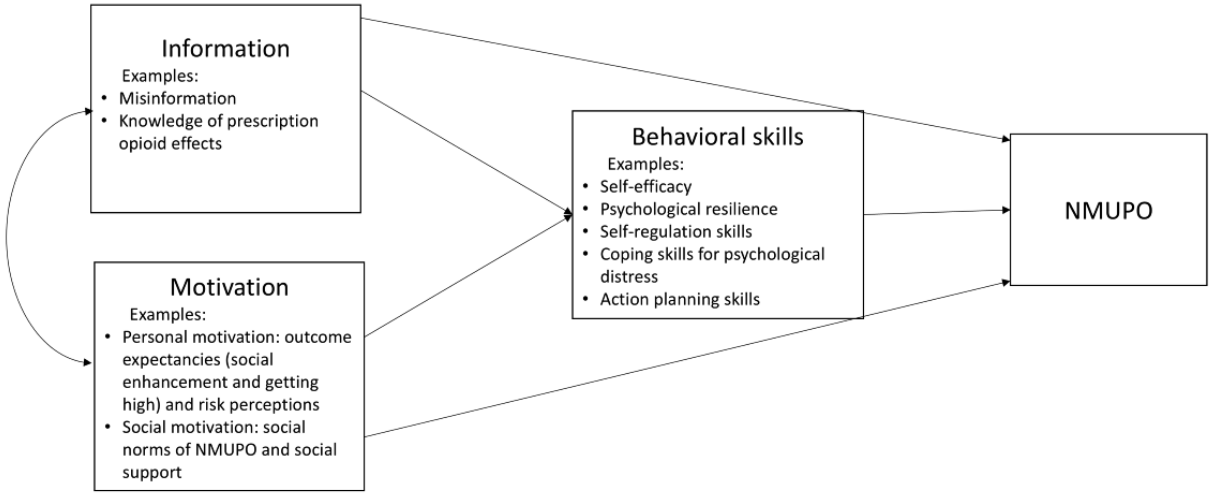
There are a handful of interventions that have been recently developed to address psychosocial aspects of NMUPO in young populations [23-25]. Although these programs have shown some efficacy, they encounter numerous challenges. First, most programs have been adapted from existing substance use interventions that were not originally designed for NMUPO. For example, some content specific to opioids (eg, the risk for overdose and pain relief expectancy) are absent from these programs, yet these factors significantly contribute to health action related to NMUPO. Second, most programs were delivered in schools and failed to target young adults who did not attend college or were difficult to reach. Third, the flexibility of these interventions was limited because they were delivered by professionals in an in-person setting. Furthermore, literature on substance misuse prevention in young adults has revealed several drawbacks to the in-person context, such as limited trust and fear of being stigmatized [26]. These challenges highlight the critical need for an innovative intervention that is based on psychosocial theory, tailored to the NMUPO context, and flexible in real-world settings.

Psychosocial Theoretical Framework for an NMUPO Intervention

To guide an intervention addressing psychosocial aspects of NMUPO, a theoretical framework (Figure 1) was developed based on the information-motivation-behavioral skills (IMB) model [27]. The IMB model has been applauded for its strength in considering a straightforward path diagram for health behavior changes [28]. This model emphasizes that health behavior changes are driven by 3 arrays of psychosocial constructs—information, motivation, and behavioral skills. Information refers to knowledge contributing to a prerequisite for enacting the changes (eg, misinformation of opioids). Motivation includes 2 belief components: personal motivation (eg, outcome expectancies and risk perceptions) and social motivation (eg, social norms and support). Behavioral skills stand for cognitive capacities (eg, self-efficacy and resilience) and behavioral skill sets necessary for adopting the changes (eg, coping or self-regulation skills) or for managing barriers (eg, stress management) [27,28]. Information and motivation can directly affect the target behavior as well as indirectly affect it

through the acquisition of adjacent behavioral skills. Such a well-structured framework offers clear guidance for intervention practices and suggests that intervention delivery could benefit from targeting information and motivation factors in the initial sessions, along with enhancing the role of behavioral skill training gradually in the intervention. For instance, initial efforts ought to address misinformation and outcome expectancies of substance use, and, as the intervention progresses, sessions should facilitate action by helping participants develop planning strategies and coping skills. Indeed, existing evidence has shown the efficacy of IMB-guided interventions in reducing substance use (ie, tobacco and illicit drugs) [29-32]. Thus, the IMB model is an ideal theoretical choice for developing an intervention for NMUPO.

Figure 1. Theoretical framework for the proposed study. NMUPO: nonmedical use of prescription opioids.



Social Media as a Promising Platform for an NMUPO Intervention Targeting Young Adults

The rapid development of social media technologies provides a novel tool for substance use interventions. Increasing substance use literature has highlighted the significant potential of social media, in which individuals can obtain substance use knowledge, communicate their experiences and thoughts of substance use problems, and seek out social support from peers with similar problems through available networks or groups [33,34]. It is worth noting that social media offers distinct merits in addressing existing challenges in interventions for NMUPO in young adults. First, recent research has validated the use of social media to reach people who engage in NMUPO from multiple venues across the United States [35,36]. Ubiquitous connectivity enables interventions to deliver content remotely to young adults who are not enrolled in college and, therefore, not able to access traditional models of education on safe substance use. Second, social media allows interactive posts in multiple formats (eg, texts, images, polls, and videos) and with customized functions (eg, internet-based goal setting tools and notifications) without time restrictions. This can facilitate exposure to intervention content at the time when participants choose to engage [37]. Third, social media technologies are applicable to timely measurements, such as ecological momentary assessment (EMA) and paradata (eg, auxiliary data of engagement [frequencies of shares, comments, and "likes," etc] analyses) [38,39], which allow tracking of intervention usability and acceptability on specific modules in real time. Extant literature has shown that EMA has been applied in intervention research for substance use reduction and psychosocial improvements [40]. Fifth, social media is extremely popular among young adults. The latest national data indicate that 72% of US adults use social media, most of whom are young adults (84%) who use it daily (70%) [41].

Another notable feature of social media is that it is significantly favorable for the peer role model, which has been a robust intervention approach for reducing substance use, particularly among young adults [42]. Existing evidence has demonstrated that social media interventions are effective in promoting behavior change for stigmatizing behaviors, including substance use, with perceived peer influence and support playing an important role in the change [43]. Accordingly, emerging peer-led intervention programs have been initiated on popular social media platforms among young adults (ie, Instagram [Meta Platforms, Inc], Facebook [Meta Platforms, Inc], Snapchat [Snap Inc], and Twitter [subsequently rebranded X; X Corp]) and have indicated good feasibility and preliminary efficacy in reducing various substance use behaviors (eg, risky drinking, cigarette use, and cannabis use) [37,42-47]. Notably, promising findings have also been reported for NMUPO reduction. Young et al [45] conducted a pilot study of a peer-led trial on Facebook for patients with chronic pain, who were randomly assigned to the peer-led intervention group or the control group (with no peer leaders) The preliminary results suggested higher engagement and more discussion on NMUPO and coping in the intervention group than in the control group. Taken together, the advantage for the peer role model with other promising aspects, social media appears to be a promising platform for NMUPO intervention among young adults, and such programs would be strongly powered by psychosocial theory–guided content and peer-led modules.

The Aims of This Study

Overview

This study proposes to develop and pilot-test a theory-guided, peer-led social media intervention on Instagram as well as examine its feasibility and preliminary efficacy among young adults engaged in recent NMUPO via a randomized controlled trial (RCT). The assessments will use mixed methods to collect various types of data, including qualitative assessment of semistructured interviews; psychometric measures in pre- and postintervention surveys; real-time paradata on social media platforms; and brief, timely measures in EMA surveys during the intervention. The specific aims are mentioned below.

Aim 1

Aim 1 involves conducting a formative study to inform a theory-based social media intervention for NMUPO among young adults in the United States. By collaborating with 4 peer leaders trained as "recovery coaches," the proposed study will recruit 30 young US adults (aged 18-25 y) who engage in NMUPO from social media (eg, Instagram) and conduct in-depth semistructured interviews to explore psychosocial content associated with NMUPO. The interviews will be guided by the IMB model.

Aim 2

Aim 2 involves developing a theory-based social intervention to reduce NMUPO among young adults. The intervention will be developed upon findings from the formative study and based on several promising strategies (eg, peer support group, ambivalence resolving techniques, interactive training modules, internet-based goal setting, and video modeling). It will be delivered via Instagram private groups by peer leaders, with close supervision provided by experts and clinicians in the fields of health psychology and addiction medicine.

Aim 3

Aim 3 involves testing the feasibility and preliminary efficacy of the theory-based social media intervention with a randomized controlled design for NMUPO among young adults. Participants who engage in recent NMUPO will be randomly assigned to 1 of the 2 parallel groups, including the intervention group (35/70, 50%) and control group (35/70, 50%), using a 1:1 allocation ratio. The intervention will be evaluated in terms of feasibility, usability, acceptability, engagement, dose, and preliminary efficacy using mixed methods (eg, surveys, EMA, paradata, and semistructured interviews). During the intervention, EMA (a prompt every 2 days) will assess the acceptability and usability of individual modules. Preliminary efficacy will be tested on behavioral outcomes (ie, past-month NMUPO) and psychosocial factors (eg, outcome expectancy, self-efficacy, action or coping planning, resilience, and psychiatric symptoms).

Methods

Research Settings and Participants

Research Platforms

The proposed formative and intervention study will be conducted on Instagram, which is a popular social media platform for young US adults (71% use) [41,48] and home to many support groups for substance use prevention and reduction [49,50]. Recruitment sites will expand to Snapchat and Facebook (>65% use) [41], which are identified as useful recruitment sources for substance use prevention in young US adults [51,52]. As a pilot study for a cross-platform trial, the module prototypes will be developed based on Instagram features available on other platforms (eg, live streaming, voting polls, group chatting, and multimedia posting). Recent interventions developed on these features indicated efficacy on behavioral changes, including drug use [37,45,46,53-56].

Peer Leaders

The study will engage 4 peer leaders who are serving in recovery programs at substance use–related associations or communities for young adults (ie, Gamecock Recovery at the University of South Carolina). The study takes advantage of this model in various aspects, including recruitment and intervention development or delivery. Eligible leaders will be those who are (1) aged between 18 and 25 years, (2) formally trained as a recovery coach (>40 h), (3) have had successful recovery from opioid misuse or opioid use disorder, and (4) use social media (eg, Instagram, Facebook, and Snapchat) on a daily basis. The health psychologist and addiction treatment experts and doctoral-level clinical psychology trainees at the Integrated Care for Recovery (I-CaRe) Training Center at the University of South Carolina will provide training and ongoing support for the peer leaders. e-gift cards will be provided to compensate for their time (US $2 for each recruitment; US $30/h for intervention).

Participants and Recruitment

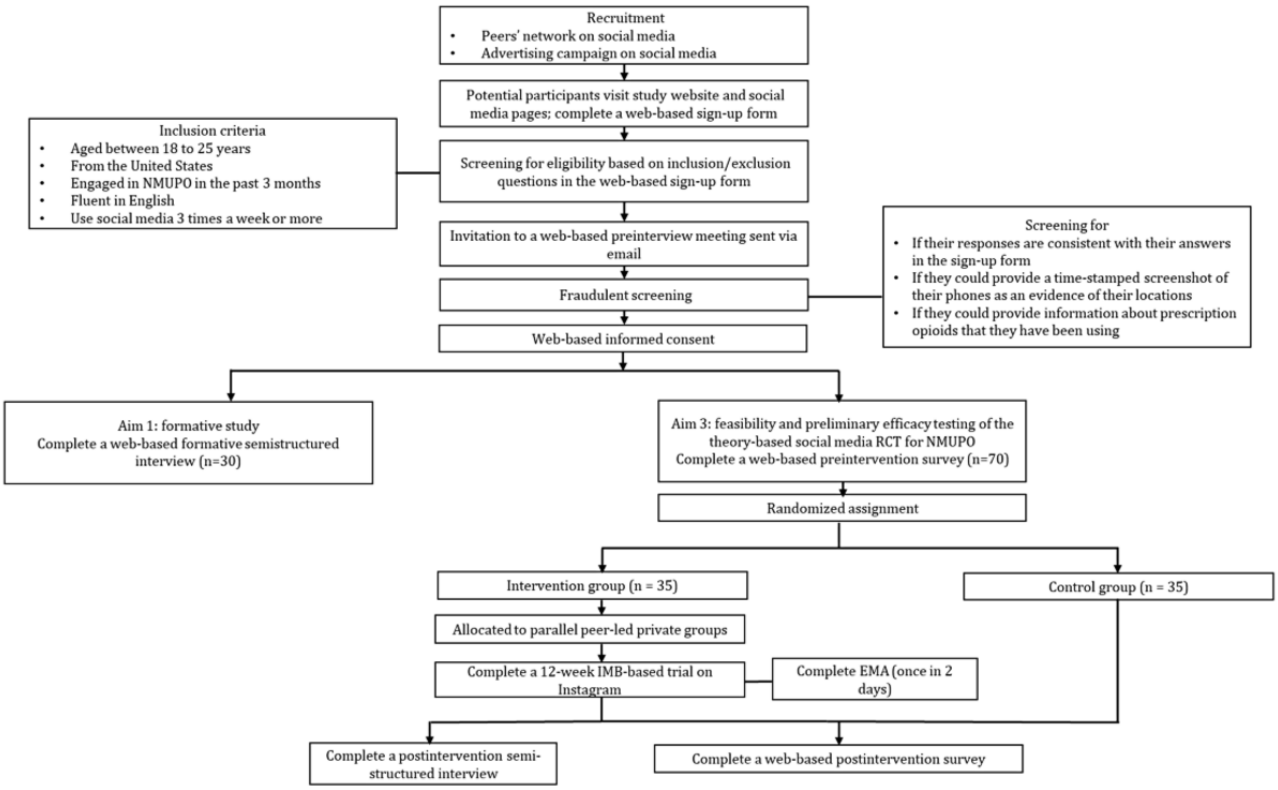
Participants for the formative study and intervention trial will be those who meet the following inclusion criteria: (1) aged between 18 and 25 years, (2) US residents, (3) engaged in NMUPO in the past 3 months, and (4) using Instagram at least 3 times a week in the past 3 months. NMUPO refers to the occurrence of the following behaviors (1 time or more): (1) taking a prescription opioid without a prescription, (2) taking more doses than prescribed, and (3) using opioid for a nonmedical reason (eg, getting high) [1-3]. Individuals will be excluded if they report (1) receiving substance use interventions in the past 3 months, (2) being diagnosed with SUD, or (3) not being proficient in English. We anticipate a total sample size of 100, with 30 for the formative study and 70 for the intervention trial.

The entire recruitment procedure is presented in Figure 2. Recruitment will be conducted using two strategies: (1) peer outreach and (2) advertising campaigns. For the peer outreach approach, peer leaders will distribute recruitment advertisements via online social networking (eg, posting advertisements on their social media accounts and inviting subscribers to repost the advertisements). Peers can also send direct invitations to young adults who they personally know to be eligible for the study. For advertising campaign approaches, we will target the accounts (on Instagram or Facebook) of colleges, local young adult communities (eg, trade unions), and substance use support groups. Upon approval from their group administrators, we will post advertisements in the groups. In addition, we will develop

targeted advertising using Ads Manager (Meta Platforms, Inc) [57]. The advertisements will display research-relevant images, hashtags, and headings, which are tailored to engaging content for young adults. To ensure appropriateness, the advertisements will be reviewed by a community advisory board. The advertisements for aim 3 will be improved in line with formative research. The Ads Manager will also determine the range of the advertisement campaign in terms of age, time, and locations (ie, the United States). The designed advertisements will be delivered in various formats dependent on the platforms, such as linear posts within personal feeds on Instagram, news feeds on Facebook, and stories on Snapchat. To ensure representativeness, recruitment will be stratified based on key demographics (eg, gender, race or ethnicity, and education) in line with the latest US national data on NMUPO [58]. The advertisements will navigate potential participants to a web-based sign-up survey on REDCap (Research Electronic Data Capture; Vanderbilt University), which is a secured web-based platform monitored by the University of South Carolina. The prescreening survey will include questions in terms of age, past–3-month NMUPO (National Institute on Drug Abuse [NIDA]–Modified Alcohol, Smoking and Substance Involvement Screening Test [59]), US residency, use of social media, and SUD diagnosis or treatment history. Participants who are identified as eligible will provide their preferred contact method (eg, Zoom [Zoom Communications, Inc]) in the survey for a brief preinterview online meeting with the study team for a fraudulent screening. Such a screening will be conducted by checking for inconsistencies in their responses, requesting time-stamped screenshots to prove their locations, and asking for information (eg, brand names) of prescription opioids that they have been using. Eligible participants with no fraud responses will then be invited to complete web-based informed consent. Young adults enrolled in the study will be provided with instructions for interviews (aim 1) or intervention (aim 3).

Our recruitment approaches are considered feasible according to existing data. Feasibility research examined the advertising campaign approach on Facebook to reach young adults engaged in NMUPO, showing that it successfully recruited 689 participants over 2 weeks (91% past-year misuse) [35]. The US national data indicate that the majority of young people with NMUPO do not have SUDs (2801/3257, 85.9%) [60]. Previous substance use studies indicated retention rates of 75% to 93% among young adults reached by social media [46,53,61].

Figure 2. CONSORT (Consolidated Standards of Reporting Trials) flowchart of the proposed study. EMA: ecological momentary assessment; IMB: information-motivation-behavioral skills; NMUPO: nonmedical use of prescription opioids; RCT: randomized controlled trial.



Study Design and Procedures

Aim 1: Formative Study

Young adults who are social media users (eg, Instagram and Facebook) and indicate NMUPO will be invited to web-based 60-minute individual semistructured in-depth interviews. The interview guide will be based on the IMB model and aim to (1) identify NMUPO patterns (eg, drug classes and individual behaviors), (2) understand psychosocial factors contributing to reducing NMUPO, (3) extract vivid examples related to psychosocial content, (4) identify planning processes and coping skills facilitating the change, (5) assess the feasibility and acceptability of social media to manage NMUPO, and (6) review recruitment advertisements. This will provide the foundational knowledge and materials to develop specific content (eg, video and posts) for the intervention. The interviewers will be trained research assistants from the fields of psychology or public

health. As suggested by the guideline of qualitative research [62], the sample size will be 30 young adults.

Interviews will be audio recorded, transcribed, and coded using a pragmatic approach. The framework analysis [63] will be performed via a deductive process, including five key steps: (1) familiarizing the data, (2) developing a coding scheme, (3) condensing and structuring the data, (4) rearranging the coded data and comparing patterns, and (5) mapping and interpretation [64]. A codebook will be developed based on step 2 as a guide for coding. Coding disagreements will be resolved through group discussion. Data analysis will be conducted on NVivo (version 11.0; Lumivero). Interrater reliability will be assessed throughout the coding process with a goal of ≥0.80 [65].

Aim 2: Intervention Development

Intervention Strategies

The intervention will apply various principles in psychotherapy. The intervention materials (texts, videos, and images) and activities will be developed using the findings from the formative study. To address particular factors in the IMB model, it will be based on peer support for behavioral change, motivational interviewing (MI) [66], cognitive behavioral therapy (CBT) [67], and solution-focused therapy (SFT) [68], which have been widely applied in substance use interventions [69-71]. Peer support is promising for facilitating social support and skill coaching [72]. MI is used to resolve cognitive ambivalence (eg, positive expectancies of substance use vs the benefits of making change), which is particularly beneficial for promoting motivation [73]. CBT is widely applied to distress management by reframing negative thoughts and facilitating adaptive coping [74]. SFT emphasizes a focus on problem-solving and is favorable for setting concrete goals (action planning) [75,76]. This content and these activities will be packed in different modules.

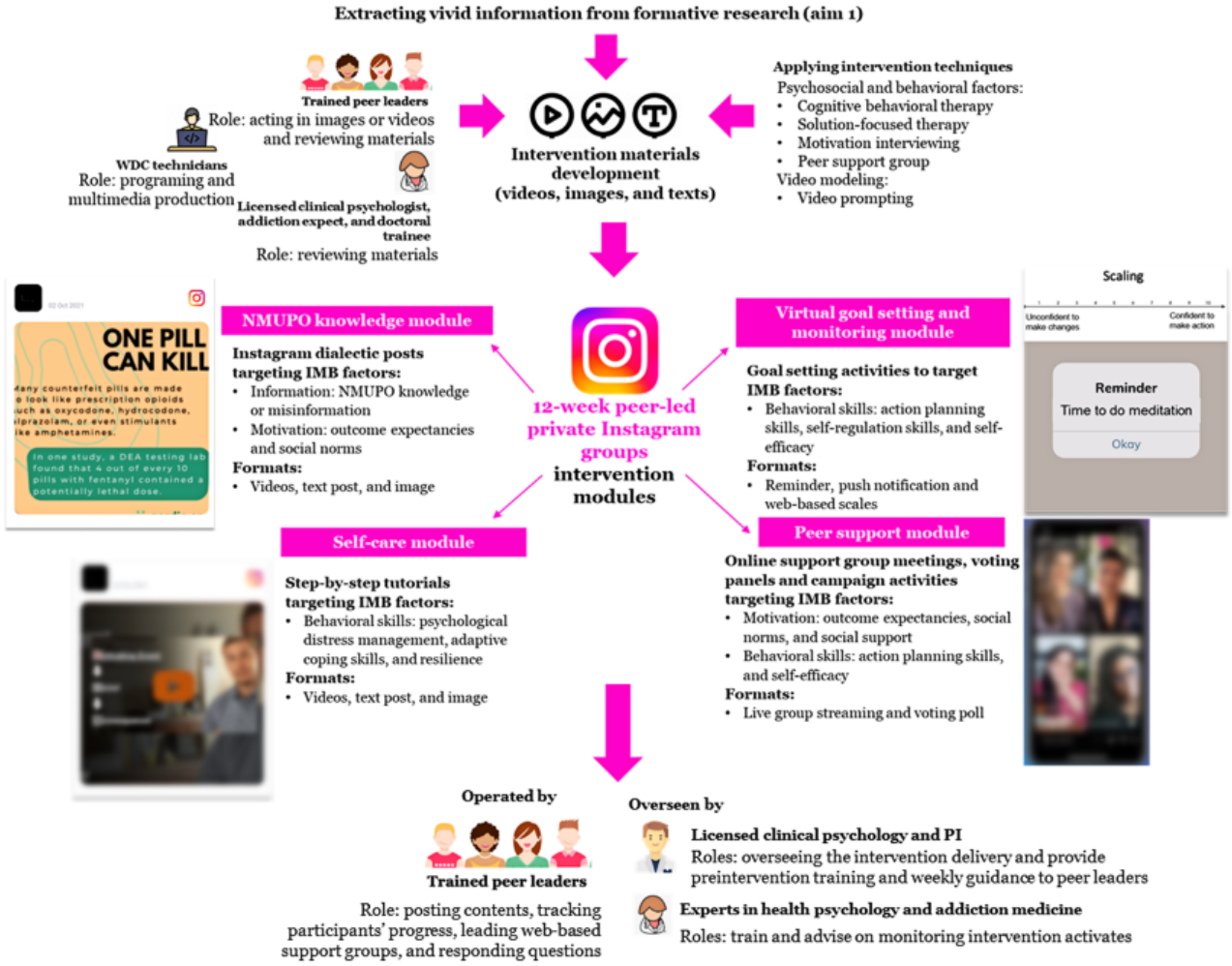
Incorporating inputs from peer leaders, the video content will follow a video prompting strategy [77]. Videos will feature peer leaders and involve breaking tutorials into steps, allowing young adults to learn and rehearse cognitive and behavioral skills in a sequential fashion. For example, guided by CBT, a peer leader may lead participants may lead participants to reflect on the context, thoughts, and consequences, related to their last experience of NMUPO, and then practice adaptive responses (eg, positive reframing and replacement behaviors). Video prompting has been effective for skill coaching in young adults [78].

Intervention Components

Overview

The proposed intervention components are guided by the IMB-based conceptual framework (Figure 1), with each component targeting specific factors derived from 3 psychosocial constructs (ie, information, motivation, and behavioral skills). As outlined in the framework, the pacing of intervention is structured to prioritize addressing information and motivation factors during the initial phases, while later sessions progressively promote behavioral skill training that contributes to psychological distress management and NMUPO reduction. Incorporating Instagram functions, the intervention platform is proposed to consist of four intervention modules, including (1) NMUPO knowledge module, (2) self-care module, (3) internet-based goal setting or monitoring module, and (4) peer support module (Figure 3). These are planned, and final content will be informed by or modified in line with the formative research. The research team will work closely with the community advisory board and peer leaders to ensure appropriate content and language. The intervention will last 12 weeks according to previous social media trials (typically 8-12 wk) [37,44,79-86]. Clinicians will review the intervention materials and ensure the scope is appropriate. Content will be prompted daily as suggested by the IMB model (eg, initially focus on information and motivation factors and gradually enhance the role of behavioral skills).

Figure 3. Planned intervention modules and strategies. I-CaRe Training Center: Integrated Care for Recovery Training Center; IMB: information-motivation-behavioral skills; NMUPO: nonmedical use of prescription opioids; PI: principal investigator; WDC: Web Development & Communication.



NMUPO Knowledge Module

A self-paced psychoeducation module will be developed targeting information and motivation factors. This module will provide the latest information about prescription opioids (eg, illicit manufacture and the role of fentanyl, naloxone, and xylazine) and the harms of NMUPO, introduce the benefits of use reduction, and clarify misconceptions. Each component will display vivid stories drawn from the formative study and delivered via multiple formats, including images, videos, and text. Participants can react to the posts by leaving comments or by liking the posts. The majority of the content will be based on MI strategies (eg, ambivalence resolution). This media campaign strategy, combined with prevention education, has been identified as an essential approach for reducing NMUPO in young adults [25].

Self-Care Module

This module will provide tutorial materials on behavioral skills for managing psychological distress and identifying strengths to make changes. Material formats (videos, texts, and images), duration, and content will be determined by the findings from the formative study. For example, serial 3-minute tutorial videos will introduce CBT strategies for reframing negative thoughts (eg, "I'm a total failure") and exploring intrapersonal or interpersonal strengths (eg, resilience). Tutorials will be step-by-step based, allowing participants to role-play and rehearse, presented with vivid examples extracted from the formative research (aim 1). Such a self-guided CBT component has proven effective in reducing psychiatric distress [87].

Internet-Based Goal Setting or Monitoring Module

This module aims to enhance action planning skills to reduce NMUPO. Specifically, it will assist young adults with setting personalized goals associated with NMUPO reduction and tracking progress toward meeting the goal. Web-based activities will be developed using SFT strategies. For example, the video will guide using scaling questions, which help participants identify their confidence levels to stop NMUPO and make a realistic plan based on it. Participants will then be instructed to explore barriers and their corresponding coping strategies for moving up the scale. Peer leaders will track their progress and provide support via online support group meetings. In addition, tutorials will instruct participants to set daily reminders or notifications on their devices (eg, mobile phone) to monitor the progress. This virtual self-monitoring has been a promising strategy to manage psychiatric distress and substance use [88].

Peer Support Module

This module will provide interpersonal activities for discussing NMUPO, sharing strategies, monitoring progress, providing social support, and increasing self-efficacy to take action, with themes based on the aim 1 findings. Activities include weekly (30 min) online support groups, discussion polls, and campaign activities. Online support groups are live video meetings led by peer leaders and assisted by doctoral-level clinical psychology trainees at the I-CaRe Training Center, who will be overseen by a licensed clinical psychologist and principal investigator (PI), under supervision from experts in health psychology and addiction medicine (SH and AHL). Each meeting will discuss personal practices related to content in that week. Peer leaders will use techniques (eg, active listening, insights, and interpretation) [26] to facilitate cohesion and provide feedback. Discussion polls will be voting activities (eg, selecting adaptive coping skills), aiming to stimulate discussions. Campaign activities will be held weekly with target-orientated themes (eg, "#healthy coping challenge") to boost posting. Participants will be encouraged to leave comments and peer leaders will promptly provide feedback.

Intervention Encouragement and Monitoring

Several strategies that are shown to be useful for enhancing engagement will be used [82,84,89-92]: (1) reminder notifications (via Instagram or emails); (2) prompt replies to participants' messages; and (3) biweekly prize draws of US $25 gift cards for those who post, attend meetings, and reply on the panels. The intervention will be overseen by PI and a licensed clinical psychologist at the I-CaRe Training Center, under supervision from experts in addiction medicine and psychotherapy for SUD. They will provide preintervention training (eg, skills in MI or CBT techniques and findings from aim 1) and weekly guidance to peer leaders. They will also advise on referrals to link participants to licensed mental and behavioral health professionals in their states of residence if necessary. The doctoral-level psychology trainees at I-CaRe Training Center will support intervention delivery by (1) ensuring conversations are intervention related and banning inappropriate content; (2) promptly replying to participants' comments; and (3) monitoring participants' safety (eg, emotional reactions to the posts and in the online group meetings) and offering referrals for outside psychological services, if needed. They will also be responsible for reporting adverse events to the PI if observed.

Aim 3: Intervention Feasibility and Preliminary Efficacy Evaluation Study

RCT Design

The intervention modules will be tested through an RCT design using mixed methods in 70 young adults who engage in NMUPO [93]. The primary purpose is to determine acceptability, usability, feasibility, and initial efficacy. Participants reached by peer leaders or advertisements on social media will be navigated to a screening survey on REDCap and scheduling a meeting with the research team for informed consent. Participants will be required to comply with the user safety agreement. Participants will be randomly assigned to the parallel intervention (35/70, 50%) or control group (35/70, 50%) using computer-generated random numbers. Participants are blinded to the randomized assignments. Intervention group will be guided to join Instagram peer-led private groups (n=10-15 each). Participants will be asked to provide their Instagram accounts to their assigned peer leaders for participating in intervention activities. Peer leaders will set up private and independent groups via their Instagram accounts and will send direct invitations to their assigned participants to join groups. Once group membership is confirmed, peer leaders will post intervention materials and lead group activities according to the plan as developed in aim 2. Private groups will synchronously deliver intervention packages over 12 weeks. To ensure confidentiality, participants will be assigned unique study IDs, which will be used for data collection and intervention activities. The intervention group will participate in data collection through multiple formats, including Instagram paradata, pre- and postintervention surveys, EMA surveys, and postintervention semistructured interviews.

The control group will not engage in any intervention activities but will complete the pre- and postintervention surveys.

Web-Based Pre- and Postintervention Surveys

The web-based pre- and postintervention surveys will be developed and administered on REDCap [94] to measure demographic variables as well as psychosocial and behavioral factors outlined in the IMB-based conceptual framework. Factors include NMUPO behaviors (past–3-month NMUPO) and information- and motivation-related factors (ie, NMUPO knowledge, NMUPO risk perception, outcome expectancies, self-efficacy, psychological distress, resilience, and other substance use). Web-based surveys will be conducted among participants in both the intervention and control groups. Participants will receive survey links via inbox messages to the Instagram accounts they provide for the study. The preintervention survey will be sent 2 weeks before the intervention (baseline), and the postintervention survey will be sent in the week immediately following the intervention (12-week follow-up). The survey will be self-administered and take approximately 20 to 30 minutes to complete. If participants cannot complete the surveys at one time, they can save their responses, and the platform will generate a code that allows them to resume the survey within the same week. The survey will also provide forward and back buttons, allowing participants to review and change their responses before they submit their surveys. Study IDs and filling time will be collected for determining duplicate entries. e-gift cards will be provided for the completion of surveys (baseline and 12 weeks; US $30 each).

Use of EMA

EMA will be used through brief evening surveys to screen the prompt acceptability and usability (the Usefulness, Satisfaction, and Ease of use questionnaire) [95] and the dose of particular modules in the intervention group. The EMA survey will be conducted once every 2 days during the intervention. The daily EMA is widely used in behavioral trials [39]. Data will be collected via a 20-second survey on a smartphone app (ExpiWell), which is user-friendly and customizable for EMA development and implementation [96]. A prompt will be sent

at the moment for assessment and tailored for the intervention materials in the past 2 days. A reminder will be provided if no response is made in 30 minutes. For safety purposes, if an EMA occurs during an incompatible activity (eg, driving), participants will be instructed to ignore or postpone the prompt.

Postintervention Semistructured Interviews

At week 12, participants will join semistructured interviews measuring (1) feasibility, usability, and acceptability and (2) reactions to the content, format, concepts, visual presentation, assessments (survey and EMA) and adaptation to other platforms. The interview guide will be based on mobile health (mHealth) studies [97]. The interview will be audio recorded and take approximately 60 minutes via an online meeting application (eg, Zoom).

Measures

Mixed Methods Measures for Primary Outcomes: Intervention Feasibility Outcomes

Multiple forms of data will be collected within 12 weeks during the intervention for the intervention feasibility evaluation.

Feasibility, Acceptability, and Usability

Mixed methods will be used. Acceptability will be assessed using EMA on Likert items that rate how helpful the module is (1=not at all to 5=extremely). Usability will be measured using EMA on the Usefulness, Satisfaction, and Ease of use questionnaire [95], which assesses perceived usefulness, satisfaction, and ease of use for the module. At week 12, participants will join semistructured interviews measuring (1) feasibility, usability, and acceptability and (2) reactions to the content, format, concepts, visual presentation, assessments (survey and EMA), and adaptation to other platforms. The interview guide will be based on mHealth studies [97].

Engagement

Paradata on participants' interactions with specific modules will be collected, including their frequency of reactions (ie, comments, "likes," questions, and replies on specific posts) and personal posts to Instagram groups [37]. Retention will be assessed by calculating the percentage of participants engaging in the group at varying time points. Data will be collected in real time.

Dose of Intervention

Participants' engagement in particular intervention modules will be measured in EMA surveys as guided by dose operationalization for mHealth interventions [98]. Dose for specific modules will be assessed in three domains (1 yes or no item each): (1) intervention actions (if viewing a post), (2) participant actions (if practicing a skill or completing an assignment), and (3) behavioral target actions (if adopting skills outside of the intervention).

Web-Based Surveys for Demographic Variables and Secondary Outcomes: Psychosocial and Behavioral Outcomes

The web-based surveys will measure demographic factors and psychosocial and behavioral factors outlined in the IMB-based conceptual model (Figure 2).

Demographic Characteristics

In the baseline preintervention survey, participants will be asked to report their background information regarding gender (ie, man, woman, transgender, or other), race or ethnicity (eg, White or African American or Black), age (y), socioeconomic status, education, family or household characteristics, and physical health status (Patient Health Questionnaire-15) [99].

NMUPO Measurement

The past–3-month NMUPO will be measured using relevant items from the Tobacco, Alcohol, Prescription medication, and other Substance use tool [100]. The scale includes 2 sections, with a screener followed by a brief assessment. The screener contains 1 item asking the frequency of NMUPO (ie, used just for feeling, more than prescribed, or without a prescription) with 5 response options (daily or almost daily, weekly, monthly, less than monthly, or never). Participants with a response other than "never" will be led to the brief assessment, including 3 dichotomous questions regarding their level of use, dependence, and concern from others related to the past–3-month NMUPO. The sum score of the brief assessment will be calculated, with a higher score indicating a greater level of NMUPO.

NMUPO Knowledge

Information about NMUPO and relevant topics, such as misconceptions, the role of fentanyl, naloxone, and xylazine, will be assessed using the NMUPO knowledge scale [61]. This scale will be developed according to the measure in POP4Teens and the formative study. This scale is proposed to include 15 statements related to opioids or NMUPO. Participants will be asked to determine if a statement is true or not (0=false and 1=true). Responses will then be rated by the research team, with higher scores indicating better knowledge of NMUPO.

Outcome Expectancies

Beliefs on positive or negative consequences of engaging in NMUPO will be assessed using a scale adapted from the Behaviors, Expectancies, Attitudes, and College Health Questionnaire [101]. A total of 50 items will be scored on a 5-point Likert-type scale ranging from 0 (not at all) to 4 (very often or always), with higher sum scores standing for the greater level of expectancies. The scale consists of 8 dimensions related to specific expectancies of opioids, including pain reduction, tension reduction, academic preference, emotion enhancement, social enhancement, guilt and dependence, cognitive impairment, and physical discomfort.

NMUPO Risk Perception

Perceived susceptibility and severity of engaging in NMUPO will be assessed using the Perceived Risk Scale for Prescription Drug Abuse [102]. This scale includes 5 items with 4 rating options (1="strongly disagree" and 4="strongly agree"). The

sum score will be generated, with a higher score indicating a greater level of perception risk for NMUPO.

Action Self-Efficacy and Coping Self-Efficacy

Perceived control on making actions to stop or reduce NMUPO or confidence on coping with barriers against the actions will be assessed using an adapted version of the Self-Efficacy Scale [103]. A total of 6 items will be rated on a 5-point Likert scale (1=strongly disagree and 5=strongly agree) and can be organized into 2 subscales (coping self-efficacy and action self-efficacy) with 3 items each. The sum scores will be generated for each subscale, with higher scores indicating greater levels of self-efficacy.

Psychological Distress

Depression and anxiety symptoms in the past 2 weeks will be assessed using the Patient Health Questionnaire-9 [104] and Generalized Anxiety Disorder-7 [105], respectively. The Patient Health Questionnaire-9 is composed of 9 items asking the frequency of depressive mood experiences (eg, “feeling down, depressed, and hopeless”), while the Generalized Anxiety Disorder-7 comprises 7 items assessing the frequency of feelings of nervousness or worry (eg, “not being able to stop or control worrying”). Two scales have 4 response options ranging from 0 (not at all) to 4 (nearly every day). Sum scores for 2 scales will be generated, with higher scores indicating greater levels of depression or anxiety.

Resilience

The Connor-Davidson Resilience Scale will be used for assessing psychological resilience [106]. This scale has 25 items asking about personal capacities in response to stress, including tenacity, tolerance of negative affect, positive acceptance of change, and positive view of adversities. Items will be rated on a 5-point scale (1=not at all and 5=nearly all the time). The sum score will be generated, with a higher score indicating a greater level of resilience.

Other Substance Use

The engagement in the use of alcohol, illicit drugs, and cigarettes in the past 3 months will be assessed using the NIDA-Modified Alcohol, Smoking and Substance Involvement Screening Test [59]. The scale includes 12 dichotomous items (0=no and 1=yes) asking if a participant has engaged in using or misusing any of 12 individual substances.

Data Analysis

The intervention trial will use multiple data analytic methods according to the format of the data.

Qualitative Analyses

Postintervention interviews will be audio recorded, transcribed, and coded using a pragmatic approach. The framework analysis [63] will be performed via a deductive process, including five key steps: (1) familiarizing the data, (2) developing a coding scheme, (3) condensing and structuring the data, (4) rearranging the coded data and comparing patterns, and (5) mapping and interpretating [64]. A codebook will be developed based on step 2 as a guide for coding. Coding disagreements will be resolved through group discussion. Data analysis will be conducted by the PI and graduate assistants on NVivo (version 11.0). Interrater reliability will be assessed throughout the coding process with a goal of ≥0.80 [65]. Analyses for postintervention interviews will synthesize the comments on feasibility, acceptability, and usability of the intervention, as well as summarize suggestions for improvements.

Quantitative Analyses

Bivariate Analyses

Data of web-based surveys (ie, before and after intervention) will be screened for missing data, outliers, and normality. If data are not missing (completely) at random or have a high missing rate (>5%), multiple imputation will be used [107]. Transformations will be conducted if violating normality (square root for moderate skew or log for greater skew). Attrition tests will be used (ie, chi-square tests and ANOVA) on demographics and outcomes at baseline. Descriptive statistics will be reported on primary (feasibility outcomes) and secondary outcomes (psychosocial and behavioral outcomes).

Multivariate Analyses

Preliminary outcomes from baseline and 12 week will be tested using repeated measures analysis of covariance, controlling for demographics. EMA data will be tested using multilevel modeling (ie random-coefficient regression model) to examine intervention usability and acceptability, capable of incorporating tests of time-serial characteristics, including linear trend over time and cyclicity. Before multilevel modeling, unconditional means models will be tested for between- and within-participant variation in each measure and determination of appropriate within-person error covariance structure [108].

Mixed Method Analysis

Qualitative and quantitative data on feasibility will be triangulated with a complementary proposition [109], in which the qualitative findings will provide in-depth understanding for the quantitative results in terms of intervention feasibility outcomes.

Power Analysis

The primary aim is to evaluate the feasibility, acceptability, and usability of the intervention to support a future large-scale RCT. According to the guidance for pilot intervention studies [110], it is suggested a minimum sample of 30 per group for the feasibility evaluation. In terms of the aim for the preliminary efficacy evaluation (ie, secondary outcomes of psychosocial and behavioral factors associated with NMUPO), we estimate an effect size according to a previous review on digital interventions for illicit drug use [111] and found small-to-medium effect sizes (Cohen d=–0.17 to –0.34) with a 6-month follow-up assessment. G-power analysis [112] estimated a sample size of 10 to 35 per arm for an RCT (repeated measures analysis of covariance). According to previous mHealth trials for substance use with retention rates ranging from 75% to 93% [46,53,61], a sample of 70 appears to be feasible and provides adequate power for proposed analytic plans. Despite a small sample size, this is appropriate for the aim of developmental research.

Project Timeline

A detailed study timeline is shown in Table 1.

Table 1. The project timeline.

	Year 1	Year 2	Year 3	Year 4	Year 5
Phase 1: formative study (aim 1)	✓	✓			
Literature review and assessment development (ie, surveys and semistructured interviews)	✓				
IRB[a] submission	✓				
Peer leader recruitment, participant recruitment and assessment, and community advisory board establishment	✓				
Transcription and data analysis or extraction		✓			
Phase 2: intervention development (aim 2)		✓	✓		
Development of multimedia files or features based on data from formative research		✓			
Establishment of IMB[b]-based intervention module packages		✓	✓		
Development of prototype for social media groups and pages (ie, Instagram [Meta Platforms, Inc])			✓		
Peer leaders' and administrators' training (doctoral clinical psychology trainees)			✓		
Phase 3: intervention feasibility and preliminary efficacy evaluation study (aim 3)			✓	✓	
Participant recruitment, preintervention assessment, and randomized controlled trial assignment			✓		
Delivery of intervention			✓		
EMA[c] surveys and paradata collection			✓		
Postintervention assessment and interviews				✓	
Data analysis				✓	
Revisions based on participants' feedback				✓	
Dissemination and disclosure of research findings				✓	✓
Preparation and submission a research proposal for a large-scale intervention effectiveness evaluation with a randomized controlled trial design				✓	✓

[a]IRB: institutional review board.

[b]IMB: information-motivation-behavioral skills.

[c]EMA: ecological momentary assessment.

Ethical Considerations

All data (ie, qualitative and quantitative) and materials (including video, images, and comments) collected or generated in the proposed study are deidentified and stored on a password-protected drive to ensure confidentiality. Intervention materials will be only delivered in private Instagram groups, which are not accessible to public users. Before their participation, all participants are provided with informed consent that explains the study's purposes, voluntary nature, and confidentiality. Participants are allowed to withdraw from the study at any time. Participants will receive e-gift cards for the completion of formative interviews (US $50) and each intervention assessment (preintervention and postintervention; US $30 each). The prorated incentive will be given according to the completion of EMA during the intervention period (eg, US $25 e-gift card for a 100% completion; US $15 for a 67% completion). Biweekly random prize draws of US $25 gift cards for these who post, attend meetings, and reply on the panels. At the end of the intervention, US $60 e-gift cards will be provided to participants who complete 90% of tasks during the intervention.

As a multiphase study, the protocol is reviewed by the research ethics boards in a sequential manner. A protocol for a formative interview study (aim 1) has been submitted to relevant institutional boards for review. Detailed information on the ethical approval and recruitment progress is provided in the subsequent sections. The protocol has been developed and reviewed in accordance with the SPIRIT (Standard Protocol Items: Recommendations for Intervention Trials checklist; Multimedia Appendix 1). The protocol of the formative study (aim 1) has been approved by the Institutional Review Board for Human Research at the University of South Carolina (#Pro00135306).

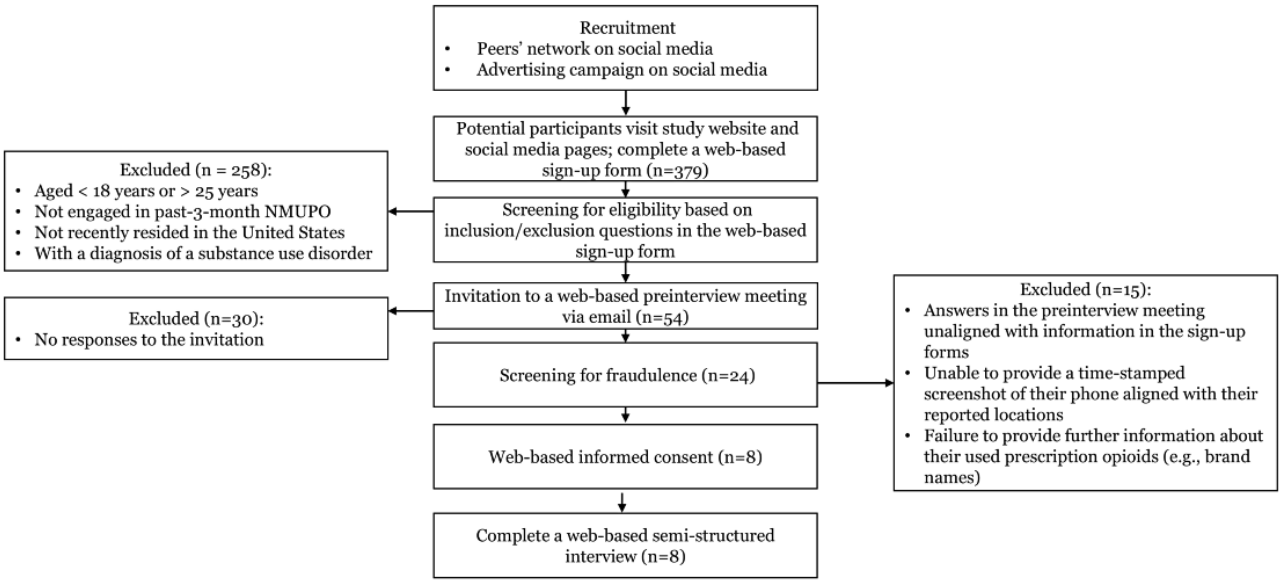
Results

The protocol was funded in May 2024 by the NIDA under the award number 1K01DA058768-01A1. The research team has

developed a social media campaign (eg, Facebook and Instagram) to facilitate recruitment for formative qualitative interviews. As of February 10, 2025, the study has received 379 responses, with 24 (6.3%) completing screening interviews. In total, 8 participants who are identified as eligible for the study have consented and completed formative interviews (Figure 4).

Formative interviews (aim 1) are expected to be completed by May 2025. The completion of formative qualitative analyses and intervention module development (aim 2) is anticipated by May 2027. A protocol for an intervention study (aim 3) will be submitted to the Institute Review Board for Human Research for review in early 2027. Upon receipt of an approval, the recruitment of the RCT will be initiated in late 2027, and the intervention will be conducted in early 2028. The intervention feasibility and preliminary efficacy (aim 3) will be finalized by the middle of 2028. Data analyses and manuscript development of the intervention will be completed by the end of 2029.

Figure 4. Recruitment progress for the formative study (aim 1) as of February 10. NMUPO: nonmedical use of prescription opioids.



Discussion

Anticipated Findings

In response to the growing evidence on psychosocial aspects of opioid addiction and relevant disorder concerns in the United States, this proposed study aims to apply a psychosocial theoretical framework and peer role model techniques to develop and implement an evidence-based intervention for reducing NMUPO risk in young US adults. The intervention will be established through a serial research activity, from a formative semistructured in-depth interview study to feasibility evaluation of a 12-week interactive peer-led trial. By leveraging the merits of social media, the proposed intervention study will be powered by adopting innovative approaches, including a tailored recruitment strategy (eg, paid advertisement campaigns), intervention delivery that transcends time and space constraints, and the application of mixed methods and time-series assessments (eg, paradata and EMA measures). As one of the first attempts to deliver peer-led interventions on social media specifically targeting NMUPO, the findings from this mixed methods design will offer valuable insights into the use of innovative approaches for reducing opioid risk among young adults. In line with previous intervention studies for NMUPO on social media [45], we anticipate that our intervention will yield high feasibility outcomes. In particular, the mixed methods assessments for the intervention group will demonstrate (1) high feasibility, acceptability, and usability on all intervention modules among young adults across 12 weeks and (2) high engagement, especially for the modules in the interactive formats, such as discussion polls and live streaming group meetings. We also anticipate significant preliminary intervention efficacy on the NMUPO-related and psychosocial behavior outcomes. Compared to the control group, the intervention will report (1) decreases in past–3-month NMUPO and other substance use (eg, alcohol, illicit drugs, and cigarettes), (2) decreases in psychological distress, (3) changes in outcome expectancies (eg, increased physical discomfort and decreased pain reduction), (4) increases in NMUPO knowledge and NMUPO risk perception, and (5) increases in resilience and self-efficacy (ie, action and coping).

Notably, the proposed intervention will be developed and implemented based on qualitative findings on the psychosocial mechanism of NMUPO, incorporating tailored psychotherapy strategies, such as CBT, MI, and peer role models. As highlighted in recent research, NMUPO in young adults is robustly driven by psychosocial factors, with influences comparable to biological and medical factors, which are traditionally viewed as prominent determinants [22]. However, scant theory- and evidence-based intervention programs have been designed to empower psychosocial skills for young US adults, especially for those who have engaged in NMUPO but do not develop addiction or SUDs. As a pilot trial, our feasibility evaluation will contribute to emerging practices of opioid use disorder prevention within social media settings, particularly through the implementation of peer-led groups [45,46]. In addition, preliminary efficacy on psychosocial measures will contribute to the growing literature on psychosocial aspects of NMUPO and offer clinical evidence for using psychosocial

intervention to manage the risk of opioid misuse in the young population. The success of the proposed trial should underscore the potential of leveraging social media as a feasible tool for delivering secondary prevention programs targeted at group-based psychosocial skill training for young people at high risk of SUD.

The proposed study has several methodological limitations. First, the generalization of our findings will be limited by the convenient sampling approach. Second, because most evaluations in this study will be based on self-reported measures, results could be subject to response bias (eg, social desirability and recall bias). Third, our EMAs could impose additional burdens on participants due to the frequent prompts for assessments in real time. Fourth, our efficacy findings could be limited in assessing long-term effects given a pre- and postevaluation design. Fifth, since the planned content for all peer-led groups will be identical and delivered concurrently, our analyses could not examine the efficacy of specific intervention modules. Sixth, given a program will be delivered on Instagram, our findings will be limited to Instagram users, and the format and presentation of the intervention content will be constrained by the platform's available features and functionality. Seventh, our peer leaders could also have limitations. They are recruited solely from local agencies within a single state (South Carolina). In addition, although they will be supported by clinicians (eg, licensed clinical psychologists and physicians in addiction medicine), their service may be subject to disparities in the quality of support. To address those, our future plan is to conduct a scaled-up cross-platform social media RCT study with a design of the multiphase optimization strategy and longitudinal measures. The intervention will be provided by a team of peer leaders, comprising recovery coaches with expertise in opioid misuse from various states across the United States.

The proposed intervention might encounter several potential challenges related to social media, including inefficient recruitment (eg, scams) and intervention delivery affected by the policy changes to social media platforms. Several contingency plans will be used if these occur. To address recruitment challenges, the eligibility of participants will be thoroughly evaluated by a 2-step approach. Young adults who have signed up for participation via social media will be navigated to complete a screening survey regarding their age, current NMUPO, history of SUDs, and their preferred online meeting methods. The research team will then contact the participants by their preferred methods and evaluate their eligibility in person. In addition, the recruitment plan will be supplemented by additional in-person approaches, including a snowball strategy (ie, allowing participants to invite eligible peers), and an outreach approach (ie, advertising at local young adult communities, colleges, and associations). To address the policy challenges to social media, the research team will transfer multimedia files to a publicly available but password-secured platform (eg, Discord [Discord Inc]), which also allows member reactions, and implement all interactive activities (eg, live streaming) via alternative social media applications (eg, WhatsApp [Meta Platforms]).

Guided by a theoretical framework, the proposed intervention study is dedicated to reducing NMUPO behaviors and the risk for opioid-related addiction and disorders by empowering psychosocial competencies among young adults via the application of social media. The proposed program is informed by substantial literature on NMUPO in young adults and formative qualitative findings of psychosocial mechanisms associated with NMUPO behavior management. Findings from rigorous methods are anticipated to inform a future scaled-up RCT study to optimize intervention content and effectiveness of a fully powered cross-platform social media intervention.

Study Dissemination

To promote the academic and social benefits of the proposed intervention study, several strategies will be used to disseminate the study findings. First, the findings will be published in international and national scientific journals and presented at national and international scientific meetings or conferences held by SUD research institutes. Second, the access to the deidentified data will be available for registered users through our selected data repository, the Interuniversity Consortium for Political and Social Research, with high security standards. Third, documentation and support materials regarding the intervention will be available at ClinicalTrials.gov and compatible with its protocol registration data elements. Fourth, we will capitalize on social media and professional networks that can increase the research and accessibility of findings, such as webinars, files, and videos available on websites and publicly available channels (eg, YouTube [Google LLC]), to increase the visibility and impact of the scientific publications and presentations. We hope that the anticipated success of the proposed intervention will prompt policy attempts for prescription drug intervention and treatments. The lessons learned from the proposed study and the intervention strategies tested can be scaled up to reduce NMUPO risk in young adults and other high-risk populations.

Acknowledgments

This protocol reported in this paper was supported by the National Institute on Drug Abuse (1K01DA058768-01). The content solely reflects the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Data Availability

The (deidentified) datasets generated or analyzed during this study will be available in the Data Sharing for Demographic Research data repository hosted at the Interuniversity Consortium Political and Social Research.

Authors' Contributions

CCT is the principal investigator of this project and led the study design as well as manuscript development. AHL, SH, SDY, and XL contributed significantly to the conception and design of the study. SDY and XL contributed significantly to the editing of the manuscript. All authors reviewed and provided comments to improve the manuscript and final approval of the manuscript.

Conflicts of Interest

SY is an advisor to digital health startups and a consultant to SBIRs grant to help opioid use disorder researchers. The remaining authors have no conflict of interest to declare.

Multimedia Appendix 1
SPIRIT (Standard Protocol Items: Recommendations for Intervention Trials) checklist for the proposed study.
[PDF File (Adobe PDF File), 75 KB - resprot_v14i1e65847_app1.pdf]

Multimedia Appendix 2
Peer-review report from the IPTA–Interventions to Prevent and Treat Addictions Study Section, National Institute on Drug Abuse (National Institutes of Health, USA).
[PDF File (Adobe PDF File), 164 KB - resprot_v14i1e65847_app2.pdf]

Multimedia Appendix 3
CONSORT-eHEALTH checklist (V 1.6.1).
[PDF File (Adobe PDF File), 312 KB - resprot_v14i1e65847_app3.pdf]

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Abbreviations

CBT: cognitive behavioral therapy
EMA: ecological momentary assessment
I-CaRe: Integrated Care for Recovery
IMB: information-motivation-behavioral skills
mHealth: mobile health
MI: motivational interviewing
NIDA: National Institute on Drug Abuse
NMUPO: nonmedical use of prescription opioids
PI: principal investigator
RCT: randomized controlled trial
REDCap: Research Electronic Data Capture
SFT: solution-focused therapy
SPIRIT: Standard Protocol Items: Recommendations for Intervention Trials
SUD: substance use disorder

Edited by A Schwartz; submitted 27.08.24; this is a non–peer-reviewed article;accepted 18.02.25; published 26.03.25.

Please cite as:
Tam CC, Young SD, Harrison S, Li X, Litwin AH
Theory-Based Social Media Intervention for Nonmedical Use of Prescription Opioids in Young Adults: Protocol for a Randomized Controlled Trial
JMIR Res Protoc 2025;14:e65847
URL: https://www.researchprotocols.org/2025/1/e65847
doi:10.2196/65847
PMID:

Protocol

Assessment of Health System Readiness and Quality of Dementia Services in Peru: Protocol for a Qualitative Study With Stakeholder Interviews and Documentation Review

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Abstract

Background: Dementia is a global health priority with significant challenges due to its complex nature and increasing prevalence. Health systems worldwide struggle to address chronic conditions like dementia, often providing fragmented care. However, information about how health systems respond to the needs of people with dementia and their carers, and the quality of care provided, is scarce in low- and middle-income countries.

Objective: This study aims to assess the quality of the health system to provide diagnosis and care for people with dementia and their carers in Peru. In order to do this, the study will explore the response of the Peruvian health system to people with dementia and their carers, and explore the experiences of people with dementia of receiving their diagnosis, management, and quality of care for this condition.

Methods: This study is part of a research program called “IMPACT Salud: Innovations using Mhealth for people with dementia and Co-morbidities,” aimed at strengthening health systems to provide care for people with dementia and their carers. The study has a descriptive, cross-sectional design that uses a qualitative methodology, including stakeholder interviews and documentation review, and consists of 2 substudies, a health system assessment (HSA) and an exploration of the patient journey. The first substudy uses an HSA methodology suitable for low- and middle-income countries, conducting 160 structured interviews with 12 different stakeholder types across 3 levels of the health system (micro, meso, and macro) in 4 Peruvian regions, each with distinct geographical and urbanization profiles. The second substudy uses a patient journey methodology, which involves conducting 40 in-depth interviews with people with dementia, carers, and health care workers from the same 4 regions. The insights into the people with dementia patient and caregiver experience within the health system from the interviews will be used to produce a

patient journey map. The analysis will be guided by the high-quality health system framework, and the findings from the HSA and patient journey will be structured using the domains included in the framework through the lens of quality of services.

Results: Data collection began in March 2024. As of the end of September 2024, a total of 156 interviews from the HSA and 38 interviews from the patient journey study have been conducted across 4 regions.

Conclusions: This study will provide a national, multilevel insight into the current operation of the Peruvian health system, including an analysis of the quality of services provided with regard to dementia diagnosis, management, and care from the perspectives of stakeholders, patients, and their carers.

International Registered Report Identifier (IRRID): DERR1-10.2196/60296

(JMIR Res Protoc 2025;14:e60296) doi:10.2196/60296

KEYWORDS

dementia; health system readiness; caregiver; comorbidities; Peru; study protocol; quality of care; comorbidity; patient journey; mHealth

Introduction

Background

Health systems worldwide face the challenge of addressing chronic conditions, which in low- and middle-income countries (LMICs) is exacerbated due to resource scarcity. LMICs often respond to diseases in isolation through vertical programs [1]. A global and integrated response to chronic conditions is needed to provide high-quality care for individuals with complex conditions [2]. Dementia is one such chronic condition, characterized as a complex disorder involving psychosocial dysfunction and vulnerability due to brain disease [3]. Dementia is a generic term that describes progressive cognitive and behavioral decline severe enough to interfere with daily life and independent function [4] and is a global health priority given its enormous human and economic costs.

Globally, the number of people with dementia is increasing. According to the World Health Organization, there are approximately 50 million people with dementia, projected to reach 75 million by 2030 [4]. Studies indicate that women are more likely to develop dementia than men [5]. Furthermore, around 60% of people with dementia live in LMICs, which are aging rapidly and have limited capacity to support them [5]. In Peru, in 2022, the Ministry of Health (MoH) attended to 13,066 people with Alzheimer disease and other dementias [6].

Health systems in LMICs are not well equipped to address dementia, often resulting in inadequate or nonexistent care. Specific challenges for the health systems and people with dementia include developing effective diagnostic services, managing cognitive and behavioral decline, handling multiple comorbidities, caregiver burden, widespread stigma, and lack of awareness about dementia. The concept of tracer conditions can help facilitate understanding the complexity of health systems and the challenges LMICs face [7,8]. Using tracers in health systems research is based on the premise that focusing on carefully selected health problems allows for the identification of weaknesses within the system and facilitates more direct insight of its performance [7,8].

Dementia affects multiple aspects of individual and family well-being, serving as an indicator of multimorbidity in both people with dementia and their carers. People with dementia have twice the number of chronic physical and mental conditions compared to those without dementia [9,10]. Dementia shares risk factors with many other common chronic diseases, including health-related behaviors (eg, unhealthy diet, smoking, and physical inactivity), as well as obesity, hypertension, diabetes, depression, and social isolation. Together, these factors account for 35% or more of the population-attributable risk (proportion of new cases of dementia due to the noted exposures). In Latin America and the Caribbean, this percentage can reach 56%, due to a combination of cultural, political, and economic factors [11].

In a broader context, addressing dementia does not mean working with a disease in isolation but rather a broader set of system-wide responses, both within and outside health care delivery structures, which can in turn contribute to achieving global goals such as Universal Health Coverage and the Sustainable Development Goals [12-16]. Abundant literature has pointed out significant deficiencies in protection systems that are relevant for addressing dementia. In Peru, despite having a specific law that addresses dementia (law no. 30795: Law for the Prevention and Treatment of Alzheimer's Disease and Other Dementias) [17], people with dementia are affected by the fragmented health care systems, shortage of human resources, limited specialized services, minimal or nonexistent long-term care, and a siloed approach to addressing diseases and health conditions.

In the vast majority of cases [18-22], support available for individuals with chronic conditions in Peru, including dementia, comes from family members, predominantly women [23], who commonly lack access to information and primary or specialized dementia care services. A study across various LMICs identified high psychological stress and caregiver burden, particularly among female carers of people with dementia [24]. Studies, such as those by Papastavrou, recognize caregiving for people with dementia as highly stressful for families, potentially leading to depression, panic disorder, anxiety, or substance use like psychotropic drugs, alcohol, and nicotine.

To date, few studies have addressed dementia in South America. Notably, the 2023 Pan American Health Organization report [25] indicates that only Chile has a national dementia plan, with underreporting in LMICs potentially reaching 90%. The 10/66 Dementia Research Group study [25] highlights the high cost

of dementia for health systems and the negative mental health impacts on women in LMICs, who are often primary caregivers for people with dementia [26]. This underscores the need for further research on dementia diagnosis and care in LMICs and for directing it effectively toward impactful decision-making. This landscape highlights the urgent need for improved dementia diagnosis strategies in Peru and LMICs, considering the unique challenges posed by limited resources, illiteracy rates, and caregiver burden. Task-shifting approaches recommended by the World Health Organization could help bridge the gap in dementia care [4]. Additionally, addressing the social and economic impacts of dementia requires a multifaceted approach, involving collaboration between health care providers, policy makers, and community organizations. To understand the potential for such improvements on dementia diagnosis and care in Peru, a thorough exploration is needed of the existing health system and the problems that people with dementia and their carers face in daily life from a multistakeholder perspective. For these reasons, this study aims to assess the readiness to diagnose and treat dementia, as well as the quality of dementia services, in the Peruvian health system from the perspective of various stakeholders.

The study has 2 overarching objectives, which are addressed by 2 parallel substudies, respectively: a health system assessment (HSA) and an exploration of the patient journey within the health system.

Substudy 1: HSA

The HSA aims to understand the diagnosis and treatment needs of people with dementia and their carers in Peru and resources available for this, including the readiness of the health system to implement innovative mobile health (mHealth) tools for the screening and diagnosis of dementia. It will address the following research questions (Textbox 1).

Textbox 1. Research questions.

- What is the existing capacity of health workers to provide care to people with dementia and what is the quality of this care?
- What are the preconceived barriers and enablers for engaging with interventions using mobile health (mHealth) technology?
- What are the main system barriers and facilitators for the uptake of mHealth tools for supporting people with dementia and carer dyads?

Substudy 2: Patient Journey

This substudy aims to understand the journey of people with dementia to being diagnosed and receiving management for dementia and to identify opportunities to improve the diagnosis and management of dementia for people with dementia. It will address the following research questions (Textbox 2).

Textbox 2. Research questions.

- What are the experiences and challenges of providing care and unmet needs of people with dementia, their carers, and health workers?
- What are the most common barriers and facilitators to being diagnosed with dementia from the perspective of people with dementia, their carers, and health workers?
- What are the most common barriers and facilitators to receive or provide treatment and management of dementia from the perspective of people with dementia, their carers, and health workers?

Methods

Context

The IMPACT Salud research program comprises 4 distinct work packages (see Table 1), which have the overarching goal of strengthening the health system in Peru through sustainable, integrated, community-delivered, technology-enabled innovations. The expected outcomes of the overall program include improving access to diagnosis of dementia and development of a feasible and acceptable mHealth intervention for people with dementia and their carers. The first work package, the focus of this protocol manuscript, is a descriptive cross-sectional qualitative study, consisting of an HSA and an exploration of the patient journey through interviews and documentation review in order to inform future work packages of the program. The HSA will collect information on the structure and organization of the Peruvian health system, the political environment, financing, data collection and information systems, availability and affordability of medications and tests, barriers to diagnosis and treatment, service delivery in prevention and management issues, training and capacity to provide care, medical technologies and infrastructure, and perceptions of and experience with using mHealth technology.

Table 1. Work packages that comprise IMPACT Salud.

Work packages	Objective
1	Evaluate health system readiness to diagnose, treat, and support people with dementia and carers
2	Develop and implement a mobile health–enabled system for the diagnosis of dementia
3	Determine the feasibility of an intervention to treat and support people with dementia and their carers
4	Assess the economic burden of dementia and related comorbidities in Peru and estimate the costs of rolling out the diagnosis tool at a national level

This information will be collected from diverse stakeholders from different institutions, including not only health services provision, eg, civil society and municipalities, among others, but also from policy and practice documentation. The patient journey study will complement the information gathered from the HSA from a more centered perspective of people with dementia and their carers. The insights into the experiences of both people with dementia and carers within the health system will inform the development of a journey map that visualizes these experiences. The findings from the HSA and patient journey will inform other work packages of the program and will allow for the identification of opportunities for using mHealth technology for dementia diagnosis improvement and management intervention.

Setting

Study Regions

The IMPACT Salud program is working across 4 sites in Peru (see Table 2). These include Lima, the nation's capital with over 10 million inhabitants [27], situated along the central coast. Lima holds significant importance as the country's primary city, burdened with the highest incidence of noncommunicable diseases [28]. Notable for its social disparity and cultural heterogeneity, Lima is a dynamic research locale. The second city, Huancayo, has over half a million residents [29] and is positioned in the central highlands at an elevation of 3200 meters above sea level. A pivotal hub for the economic growth of the central region, Huancayo attracts migrants from the jungle and southern highlands, primarily engaged in providing diverse services for citizens and agricultural activities. The third city, Iquitos, serves as the primary urban center in the jungle, hosting almost half a million inhabitants [30]. Characterized by diverse indigenous populations, Iquitos can only be accessed via river and air transport, resulting in an economy marked by high transportation costs. Lastly, Tumbes, located in Peru's northern most region with 265,844 residents [31], operates as a border economy due to its proximity to Ecuador. With a warm, rainy climate, Tumbes is currently experiencing heavy rainfall attributed to the “El Niño-Southern Oscillation” climatic phenomenon.

Table 2. Characteristics of the study sites or locations. Source: Instituto Nacional de Estadística e Informática (INEI)-2017—Repositorio Único Nacional de Información en Salud (REUNIS) [27-30].

Sites	Population, n	Region	Illiteracy rate in the department (15+), %	Completed high school in the department (15+), %	Most spoken language in the department	Quintile of dementia care in Peru
Lima (Metropolitan)	8,894,412	Coast	2	50.2	Spanish	1
Huancayo	545,615	Highlands (Andes)	5.3	45.5	Spanish	3
Iquitos—Maynas	149,773	Amazon Jungle	5.4	50.1	Spanish	1
Tumbes	2,154,962	Coast	4.1	48.3	Spanish	4

Health Care System

The Peruvian health care system is fragmented and complex, with health care provision and financing depending on multiple public and private entities under the oversight of the MoH. Within this fragmentation, the 2 main public health care providers are the MoH and the Social Security System (EsSalud), the last one depending financially on the Ministry of Labour and Employment Promotion [32].

This study will primarily work with the MoH, which serves 74.5% of the population [33]. Since 2007, there has been a coordinated and decentralized health system [34], which has resulted in the creation of regional health directorates and management for each region that, independently, are responsible for implementing MoH's regulations.

For the purpose of this research, we categorize the health system into 3 levels: micro, meso, and macro. The micro level encompasses primary health care services, along with any supplementary systems or organizations at the local level. The meso level includes secondary health care services and regional directorates. Finally, the macro level encompasses tertiary health care services, national directorates of the MoH, and specialized bodies.

Design

The HSA follows a Rapid Assessment Protocol (RAPIA) methodology for data collection, targeting access to care for individuals with chronic diseases in LMICs [35]. The RAPIA framework is being used for its structured approach to data collection, designed to generate information from both primary and secondary sources, including structured interviews with participants across various levels of the health system within the 4 representative regions. The interview questions were adapted to gather information on dementia, modifying the focus on medications and emphasizing inquiries about the care provided to people with dementia by their caregivers. Key attributes of this methodology include its patient-centric focus, cost-effectiveness, and provision of valuable insights for decision-makers. The rapid assessment methodology is implemented via structured interviews following a standardized questionnaire, supplemented with a review of secondary sources of information (eg, policies and national statistics), to explore 11 themes related to the Peruvian health system across the 3 levels of the health system (macro, meso, and micro). This framework will facilitate the understanding of the needs and available resources for patients with dementia and their carers. Similarly, to understand the experiences of people with dementia in receiving their diagnosis and the subsequent management of their condition, we will use the “patient journey” methodology.

This approach is used by health care managers to identify gaps in the touchpoints between the health care system and the patient throughout the care process, such as the admission process, physical care, and appointment reminders [36]. In LMICs, "patient journeys" for noncommunicable diseases provide valuable insights for decision makers aiming to prioritize interventions and optimize disease management [36]. To carry out the "patient journey," we will conduct in-depth qualitative interviews with individuals with dementia, their caregivers, and health care professionals. This follows an example of a study on understanding poststroke care management [37]. Based on the patient journey interviews, a patient journey map will be developed to visualize the experience of people with dementia, carers, and health care workers within the health care system.

Participants and Selection Criteria

Overview

Table 3 details the different types of participants across the 2 substudies and the criteria used for purposive selection of participants. In the HSA, 14 types of key actors are participating across the macro [4], meso [3], and micro [7] levels. The patient journey involves 3 types of key actors: people with dementia, their carers, and health care workers. The aim is to achieve a comprehensive coverage of health care system stakeholders pertinent to the theme of dementia.

Table 3. Key actors and inclusion criteria.

Level	Target institution and key stakeholder role	Inclusion criteria
Substudy 1		
Macro	• (1) Ministry of Health (eg, Mental Health Strategy, Non-Communicable Diseases Strategy, Integrated Health Insurance (SIS) Department, Planning and resources) • (2) Ministry of Financing (eg, Presupuesto por Resultados) • (3) Social Security (EsSalud) • (4) Ministry of Women and Vulnerable Populations • (5) Key opinion leaders (eg, nongovernmental organization representatives, representatives of health organizations)	• 18 years of age or older • Occupy the specified role in the Peruvian provinces of Lima, Huancayo, Iquitos, or Tumbes
Meso	• (6) Regional directorates of health • (7) Health workers of mental health public hospitals, general hospitals, and specialized memory clinics (eg, including psychologists and therapists) • (8) Nursing homes run by District Municipalities	• 18 years of age or older • Occupy the specified role in the Peruvian provinces of Lima, Huancayo, Iquitos, or Tumbes
Micro	• (9) Grass-root organizations and elderly community centers (Centro del Adulto Mayor) • (10) Community leaders and community health workers • (11) Health care workers (eg, physician, nurses, technicians, pharmacies) from primary health care facilities and community primary mental health care facilities (Centro de Salud Mental Comunitario)	• 18 years of age or older • Occupy the specified role in the Peruvian provinces of Lima, Huancayo, Iquitos, or Tumbes

Micro	• (12) People with dementia and carers	• Only for people with dementia; people with a mild dementia diagnosis who meet the following criteria:
		  • Status of dementia: people will be asked for a self-reported diagnosis of dementia. Where this is not possible, the carer will be asked to confirm. This diagnosis had to be performed by a physician in a health facility.
		  • Level of functionality: the Pfeffer Functional Activities Questionnaire (PFAQ), Spanish version, will be applied with potential participants (n=31); participants must score below 6 to participate.
		  • People with dementia should also have at least one chronic comorbidity, such as hypertension, diabetes, depression, and anxiety, among others.
		• Carers: people who are formal or informal carers, including family members that are responsible for taking care of the people with dementia. They need to have been with the people with dementia in the process of diagnosis and management and are self-recognized as carers of the people with dementia. We will also include carers of people with severe stages of dementia

Substudy 2		
N/A[a]	• (1) People with dementia	Same as substudy 1
N/A	• (2) Carers	Same as substudy 1
N/A	• (3) Health care workers	General health practitioners and neurologists

[a]N/A: not applicable.

Sampling Method

Across the HSA and patient journey substudies, we aim to include 200 participants in total across the 4 sites through purposive sampling to recruit the required range of stakeholders across the health system. The inclusion criteria are detailed in Table 3, and the target sample size is provided in Table 4. These numbers will allow for gathering sufficient information from all regions to understand differences across the 4 settings and levels. For recruitment of people with dementia, there are specific inclusion criteria related to the stage of dementia and level of functionality. A community mapping exercise was conducted in each region to identify relevant organizations and groups from which to recruit potential participants. The purposive sampling was focused on identifying participants who represented each stakeholder type across each level of the health system as outlined in Table 4 and continued until all stakeholder types had been recruited.

Table 4. Sample size.

	Huancayo	Iquitos	Lima	Tumbes	Total
Substudy 1					
Macro[a]	—	—	—	—	20
Meso	15	15	15	15	60
Micro	20	20	20	20	80
Substudy 2					
People with dementia and carers	6	6	6	6	24
Health care workers	4	4	4	4	16

[a]The precise breakdown of participants is unclear for the 4 provinces.

Fieldwork Team

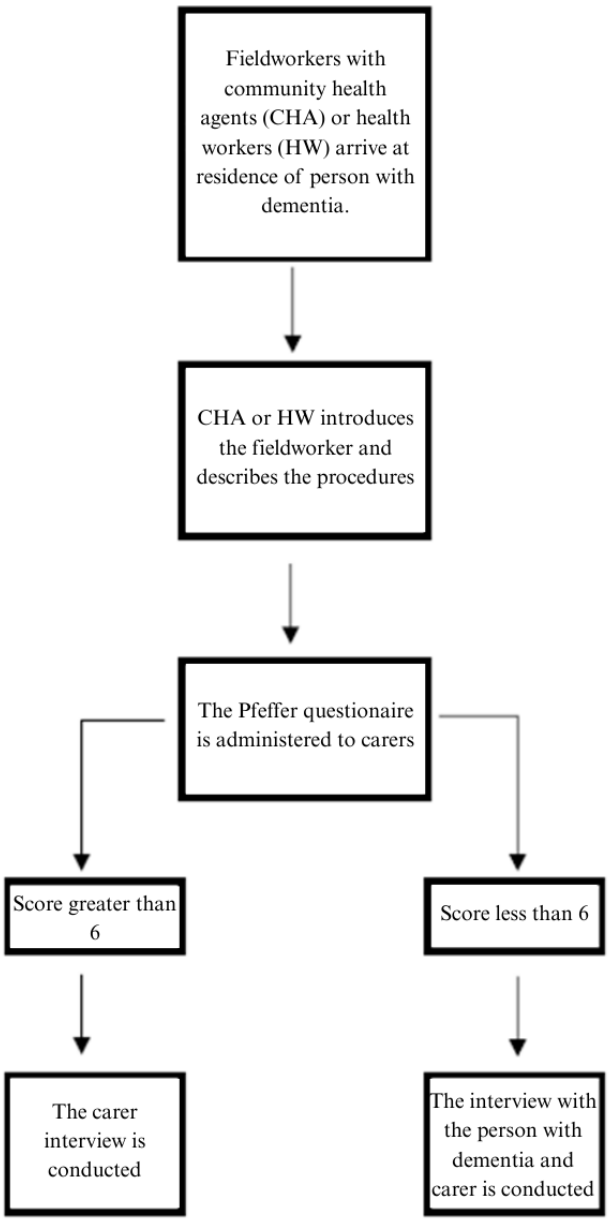
Field workers in each site were selected for their expertise in conducting qualitative interviews, their health care sector experience, and residency in the designated city of work. A total of 11 field workers have been engaged, with 9 assigned to micro- and meso-level interviews and 2 for the macro-level. A dedicated team of 2 or 3 researchers has been formed for each site, alongside a coordinator. Fieldwork team members attended 2 comprehensive training sessions, combining in-person and virtual formats. Training topics encompassed participant recruitment protocols, ethical considerations in elderly populations and dementia care, implementation of informed consent and assent procedures, an introduction to dementia from biomedical perspectives, and familiarization with the data collection materials. Upon completion of training, field workers received an operational manual detailing standardized operating procedures for data collection.

Data Collection Procedures

The study received institutional support from MoH and follows a staggered data collection approach. The process commences with higher management levels progressively authorizing interviews at operational tiers such as first-level health centers. Identification of persons with dementia (diagnosed by a health center) and their carers is facilitated through community health agents, health care center workers, and health care facility administrations. They introduce the fieldwork staff, who then administer the Pfeffer Functional Activities Questionnaire [38,39] to assess the people with dementia's functional abilities for daily activities and their possibility to participate in the interview. Scores below 6, indicating no clear impairment of functional activities, prompt interviews with both the caregiver and the person with dementia. In such cases, an informed assent is sought from the person with dementia, with informed consent obtained from the carer in their representative capacity. Figure 1 summarizes the procedure for conducting interviews with people with dementia. For other actors, specific informed consent procedures are followed prior to initiating data collection. Detailed information regarding recruitment can be found in Multimedia Appendix 1.

For the HSA, interview information will be recorded in notes on a printed version of the interview questionnaire and captured with handheld recorders. These notes will then be entered into the REDCap (Research Electronic Data Capture; Vanderbilt University) software, developed by Vanderbilt University. In this case, interviews will not be transcribed; only the recordings will be used as backup. This is due to the format of the RAPIA methodology, which advocates for a rapid analysis of information, prioritizing the perspectives of various actors rather than delving deeply into them; hence, a detailed analysis of the testimony is not necessary. On the other hand, for the patient journey, the interviews will be recorded and subsequently transcribed verbatim and coded in an Excel spreadsheet. Following coding, the information will be shared in order to seek its validation at a meeting with people with dementia and careers who were interviewed.

Figure 1. Procedure for conducting interviews with people with dementia.



Data Collection Materials

Questionnaires with closed and open-ended questions will be used to perform the structured interviews conducted in the HSA. These instruments were originally designed to assess health systems with regard to access to insulin [35]; subsequently, they have been applied for exploring chronic diseases and neglected tropical diseases [1]. Drawing from these previous experiences, they have been adapted for this study, with questions amended or added to capture information on several key thematic areas to assess the readiness of the Peruvian health system for diagnosing and managing dementia. These thematic areas are informed by the RAPIA guidelines mentioned earlier and are outlined in more detail in Table 5, including sections and topics of the structured interview questionnaire; an example of the structured questionnaire is also provided in Multimedia Appendix 2. As per the RAPIA guidelines, interview data will be supplemented with a document review of relevant technical standards, laws, regulations, national plans, care protocols, clinical guidelines, and other materials that are publicly available. In the patient journey, we will use semistructured interview guidelines for the in-depth interviews with people with dementia, carers, and health care workers. The guidelines will explore topics to understand the diagnosis and management process of dementia and identify opportunities for improvement. The interview guide is structured into 3 stages: prediagnosis, diagnosis, and treatment [40]; an example is provided in Multimedia Appendix 3. In these stages, the number of interactions with health care personnel, the time between appointments, the emotions associated with the encounters, among others, will be collected.

Table 5. Sections and topics of the questionnaire in the health system assessment.

Type of data	Components
General information	• Place and date • Contact information • Demographic information • Workplace and time • Occupational category
Health system structure and organization	• Units or departments responsible for people with dementia • Preparation of health personnel • Preparation to attend comorbidities • Services and organizations centered in people with dementia
Relevant policies	• Public policies and relevant policies for people with dementia
Financial issues	• Sufficient funding for prevention, diagnosis, and treatment in people with dementia • Barriers or difficulties for find funding for people with dementia • Programs or financial contributions for people with dementia and careers
Data collection and information systems	• Date registration for people with dementia • Statistic information available about people with dementia and comorbidities
Service delivery in prevention and management	• Knowledge of the available tests for people with dementia • Medications for people with dementia • Peruvian political medication for people with dementia • Knowledge of the available medication for people with dementia • Barriers or difficulties in the access of medication, tests and technology for people with dementia
Barriers for diagnosis	• Current barriers to dementia assessment • Current barriers to dementia attention • Current barriers of dementia care
Training and capacity to provide care	• Training, knowledge and capacity of health care workers in the provision and management of dementia care
Medical technology	• Infrastructure to support internet access • Infrastructure to support use of mHealth
Perceptions of and experience with using mHealth technology	• Knowledge of the tools for the dementia diagnosis • Opinion about mobile applications for disease diagnosis

Analysis Procedure

The analysis of substudy 1 HSA will follow a deductive process using coding reliability thematic analysis [41], with the aid of a structured codebook to index the information collected within the domains proposed by the high-quality health system (HQHS) framework developed by Kruk. The HQHS framework was designed to take into account the challenges of LMICs and allows for a comprehensive evaluation of service quality beyond mere access, emphasizing patient-centered care and trust in health care systems. The framework will allow us to organize and structure the results of our substudies in order to create an overall overview of the health system and the quality of services provided to people with dementia and their carers. The relevance of using this framework lies in its ability to integrate general aspects, such as access to health care centers and the number of consultations, with the patient's perception of the service's utility when describing service quality. In contrast, the analysis of the patient journey in substudy 2 will be inductive, following a framework analysis approach [42]. Analyses for both substudies will be carried out in parallel until the final phase, at which point they will be integrated to enhance the HQHS framework. The detailed analytical procedures are outlined below.

Substudy 1 will follow a 3-step process, conducted initially by 2 researchers working together on data from one site first to agree on understanding of codes and then moving to work independently on interviews from the additional sites subsequent to this. Throughout the process, the team overseeing the study will meet regularly to discuss the coding of data into the various categories and thematic areas in order to confirm understandings and address any disagreements in data coding placement (Textbox 3).

Substudy 2 will consist of 4 phases (Textbox 4).

The findings will be reported in accordance with the checklist proposed by the COREQ (Consolidated Criteria for Reporting Qualitative Research) reporting guidelines for qualitative studies [43].

Textbox 3. Phases of the analysis for substudy 1.

- First, the data from the structured interviews and document review will be coded into the 11 themes proposed by Rapid Assessment Protocol (RAPIA; Table 5), where each theme will be structured according to the interviewees and the regions they represent.
- Next, the data from stakeholders as coded into the RAPIA themes will be cross-referenced with the components and subcomponents of the high-quality health system framework.
- The final step will involve integrating relevant information from substudy 2 into this matrix.

Textbox 4. Phases of the analysis for substudy 2.

- The first phase will involve developing an analytical framework based on codes derived from initial familiarization with the data. This familiarization process will consist of 4 meetings (one meeting per site) in which 3 researchers will listen to the interview transcripts and propose categories for analysis. The categories resulting from the first meeting will be used in the subsequent meetings, where their relevance will be evaluated.
- The second phase will involve coding all the data into the identified codes.
- The third phase will consist of summarizing data from the codes into overarching categories that represent key milestones identified as significant within the patient experience, as well as those identified by their carers and health care workers.
- These overarching category summaries will serve as the foundation for creating a patient journey map to visualize the data and for describing the subcomponents and components of the high-quality health system framework as identified in substudy 1.
- The draft patient journey map will be presented to a subsample of substudy 2 participants in each region to sense check the understanding of their experiences and inform a final version of the map and to feedback into the refinement of the overall analysis.

Ethical Considerations

The research protocol, data collection materials, and consent were initially reviewed and approved by the institutional review board (IRB) at Universidad Peruana Cayetano Heredia (UPCH) on July 20, 2023 (IRB number 209080). Subsequent amendments were approved by UPCH on October 30, 2023, and May 13, 2024, and an extension was granted on June 18, 2024, allowing data collection until June 2025. The protocol and consent forms were also approved by the Imperial College Research Ethics Committee (IRB number 6784708) on February 29, 2024, with a further amendment approved on June 11, 2024. The study will be conducted in accordance with the recommendations for physicians involved in research on human subjects adopted by the 18th World Medical Assembly, Helsinki 1964, and later revisions. Participation in the interviews will be completely voluntary; potential participants will be provided with information about what taking part will involve, and signed consent will be sought for each participant prior to collecting any data.

All invited participants have the option to decline the invitation or withdraw from the study at any time. No monetary or material compensation has been provided, other than a brochure containing general information about dementia. All collected data will be anonymized prior to analysis, in order to protect confidentiality.

In addition to the considerations mentioned earlier, specific measures to ensure ethical safeguards and to abide by local legislation will be taken in the cases of people with dementia and their carers. Assent and dissent will be respected from people with dementia, verbally or nonverbally. Also, carers who function as proxy decision makers will also be consulted about consent when the potential participant has not been able to give full consent.

Results

The IMPACT Salud program was funded in October of 2022, but the study was launched in Peru in November 2023. In the meantime, ethical approval and pilots were conducted before the implementation of both substudies. The pilot study took place from July to September 2023. The implementation of both substudies began in March 2024. As of September 30, 2024, 192 individuals have been interviewed as part of the HSA and the patient journey study from the cities of Iquitos, Huancayo, Tumbes, and Lima. Transcription and data systematization in REDCap will occur simultaneously with the administration of questionnaires and interviews. The analysis phase is scheduled to take place from October 2024 to January 2025.

Discussion

Principal Findings

This study, with its focus on both HSA and understanding the patient journey, will generate comprehensive insights into how dementia is diagnosed and managed across the diversity of the Peruvian health care system. The findings will be organized in 3 core themes from the HQHS framework, such as the process of care, quality impacts, and foundations. It is anticipated that this will reveal areas of strength in dementia care as well as areas where there are issues with quality of provision or lacking provision. This might include, for example, structural issues with financial resourcing, training of health care workers, or the existence of standardized policies and protocols. It is anticipated that there may be divergence between the experiences of stakeholders at different levels of the health system, as well as across the different regions in which the study is being conducted. Furthermore, the study will reveal insights into the facilitators and barriers to using mHealth technology in Peru for supporting better diagnosis and management of dementia.

To date, few studies have holistically addressed dementia in South America. This work aims to serve as the foundational step in a series of studies across LMICs, particularly in Latin America, assessing health care system readiness to effectively diagnose, manage and provide care for people experiencing dementia and chronic comorbidities. As the burden of dementia and associated conditions rises among older populations in LMICs [44-46], there is a dearth of data on health care system preparedness. Additionally, the study will also address the needs of other work packages as part of the IMPACT Salud program (see Table 1).

It is important to note that using health care system evaluations from high-income nations for public health decisions in LMICs is cautioned against due to considerable disparities in home care systems, health care professional readiness, belief and health literacy, technology and infrastructure availability, as well as the political stability essential for sustained quality care. As such, this research endeavors to provide updated insights into the intricate workings of health care systems in Peru, potentially driving reforms in the health care sector. Furthermore, it aims to foster alignment among stakeholders and amplify the impact of reforms on dementia patients' lives. A notable antecedent of health care systems' responses to dementia is the STRIDE project that engages 7 countries (Mexico, Brazil, India, Indonesia, Jamaica, Kenya, and South Africa) [47]. There is one publication of this study in Mexico, and STRIDE, like IMPACT Salud, involves actors from civil society, such as the Alzheimer's Association of Mexico, its allied associations, and researchers. However, STRIDE does not directly include the participation of patients and carers as project participants, as its goal is to improve the implementation of public policies rather than gathering the needs and experiences of people with dementia in the health care system [48]. A comparative analysis of findings between these projects is planned, aiming to elucidate differences and similarities. The results of this research also aim to provide input for the development of Comprehensive Care Guidelines for individuals with Alzheimer disease and other dementias, a task that the MoH has pending since its proposal in the 2018 regulation of the Law for the Prevention and Treatment of Alzheimer's Disease and Other Dementias [17].

Also, the study has a particular focus on carers due to the significant impact of caring for a person with dementia on their mental health. Carers are 4 times more likely to experience depression and 3 times more likely to experience anxiety [49,50]. For these reasons, it is important to explore the needs of carers and possible opportunities to better support them and reduce any burden they experience. The intervention that will be adapted [51] in work package 3 of the IMPACT Salud program (Table 1) will have carers as its focus, aiming to provide guidance and tools with the aim of improving the quality of life of people with dementia and the mental health and quality of life of their carers.

Study Strengths and Limitations

The RAPIA methodology offers a diverse, multilevel, and national perspective to assess the health system, in this case having dementia as a tracer condition in Peru. While the patient journey complements this by providing insights from a patient-centered perspective about the health care system's functionality.

The HQHS framework will enable the analysis to be organized to identify structural issues (such as access, political support, and availability of qualified health care personnel), as well as relative or subjective issues contingent upon each dementia patient, caregiver, and health care provider (such as trust and service quality).

The decision of using a combination of methodological approaches is based on their focus on the end user of the health system, namely persons with dementia and their carers. Furthermore, the RAPIA methodology has the quality of being flexible to the context, allowing the addition of topics to the interview and new questions to the questionnaire [35]. Finally, the methods offer replicability benefits for researchers and health system specialists in terms of time and costs to implement.

The approach proposed in this study involves examining the macro view while also taking into account the daily lives of people living with dementia. By staying focused on these, we aim to propose solutions in the health system that have a tangible impact on people's lives. The study includes 4 sites with diverse characteristics in terms of population size, ecosystem, mother tongue, and number of people with dementia attended by MINSA; this will allow comparing the quality of the health system and experiences of people with dementia and carers, as well as opportunities in 4 highly diverse contexts within Peru.

While the study has adopted existing robust methodologies for HSA and understanding patient experience, there are potential limitations with applying these in practice. To date, the study has faced difficulties in recruiting dementia patients who meet the inclusion criteria. Our data so far indicate that most patients seek diagnosis late, resulting in worse cognitive decline than expected (a score of less than 6 on the Pfeffer functional test). This issue is compounded by the view of dementia as a normal part of aging, which discourages symptomatic individuals from seeking health care. We have partially addressed this by conducting more interviews with carers in cases where patients themselves do not meet the inclusion criteria.

Furthermore, while the setting for the research includes 4 sites with diverse characteristics to represent the various sociodemographics and cultures of Peru, this is not exhaustive, and there may be factors related to the diagnosis and management of dementia that remain unidentified by this study.

Additionally, the HQHS framework has been used previously with a survey to share information from some domains or subdomains [52]. However, there is not much published research using this framework with qualitative data, so there may be some challenges faced with this during the analysis phase.

Conclusions

This study will provide a national, multilevel insight into the current operation of the Peruvian health system, including an analysis of the quality of services provided. The findings will be structured in 3 core themes from the HQHS framework (process of care, quality impacts, and foundations) in order to

share information about dementia diagnosis, management, and care from the perspectives of stakeholders, patients, and their carers.

Dissemination

The dissemination strategy of the IMPACT Salud program is focused on sharing the study findings with a wide variety of audiences, including the patient and carer community, health care providers, and policy makers. A variety of dissemination formats are planned, including online and in-person meetings and webinars, policy briefs and briefing notes, social media, and news communication and scientific formats including peer-reviewed journals and conferences. We will also use the project web page [53] to share information for these different audiences in a friendly format.

Acknowledgments

This study is funded by the UK National Institute for Health Research (NIHR) Global Health Policy and Systems Research Programme (grant number NIHR150287). The views expressed are those of the authors and not necessarily those of the National Health Service, the NIHR, or the Department of Health and Social Care. The funder had no role in the design or conduct of the study; review or approval of the manuscript; or decision to submit the manuscript for publication. JH and GM work at The Centre for Development, Evaluation, Complexity and Implementation in Public Health Improvement (DECIPHer), which is funded by the Welsh Government, through Health and Care Research Wales.

Data Availability

The datasets generated or analyzed during this study will initially be available in anonymized format from the study investigators (MLP, JH, SCF, and CB) upon reasonable request, in accordance with participants' informed consent and IRB requirements. No publicly accessible repository is currently used for data sharing, but this will be developed as part of the IMPACT Salud study and more information will be available on the study website [53] in due course.

Authors' Contributions

JH, MLP, CB, JJM, and MGL worked in the first version of the protocol. FTS, MLP, JH, and DRV worked to prepare the first draft of the protocol for publication. All authors reviewed the questionnaires for the HSA and the journey map as well as reviewed and approved the current protocol. Members of the IMPACT Salud Study Group: Cecilia Anza Ramirez; María Verónica Belón Hercilla; Julio Leonardo Albitres Flores; Mariela Margarita Villegas Chavez; Javier Eduardo Sanchez Calderon; Kelly Milagros Tello Lizarraga; Lee White; Ángeles Cano Cárdenas; Matías Vega; Ioana Dobre; Martina Cesarina Edith Guillermo Roman; Pablo Fonseca; Marco Da Re

Conflicts of Interest

None declared.

Multimedia Appendix 1
Study manual detailing recruitment procedures.
[PDF File (Adobe PDF File), 95 KB - resprot_v14i1e60296_app1.pdf]

Multimedia Appendix 2
HSA (health system assessment) questionnaire example - health workers and patient caregiver.
[PDF File (Adobe PDF File), 389 KB - resprot_v14i1e60296_app2.pdf]

Multimedia Appendix 3
Patient Journey Interview Guide Example - Caregiver.
[PDF File (Adobe PDF File), 171 KB - resprot_v14i1e60296_app3.pdf]

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Abbreviations

COREQ: Consolidated Criteria for Reporting Qualitative Research
HQHS: high-quality health system
HSA: health system assessment
IRB: institutional review board
LMICs: low- and middle-income countries
mHealth: mobile health
MoH: Ministry of Health
RAPIA: Rapid Assessment Protocol
REDCap: Research Electronic Data Capture
UPCH: Universidad Peruana Cayetano Heredia

Edited by A Schwartz; submitted 09.05.24; peer-reviewed by J Zhang; comments to author 25.09.24; revised version received 19.11.24; accepted 20.01.25; published 21.03.25.

Please cite as:
Lazo-Porras M, Tateishi-Serruto FJ, Butler C, Cuba-Fuentes MS, Rossini-Vilchez D, Perez-Leon S, Lúcar-Flores M, Miranda JJ, Bernabe-Ortiz A, Diez-Canseco F, Moore G, Landeiro F, Cardenas MK, Vera Tudela JC, White L, Calvo RA, Whiteley W, Hawkins J, IMPACT Salud Study Group
Assessment of Health System Readiness and Quality of Dementia Services in Peru: Protocol for a Qualitative Study With Stakeholder Interviews and Documentation Review
JMIR Res Protoc 2025;14:e60296
URL: https://www.researchprotocols.org/2025/1/e60296
doi:10.2196/60296
PMID:

Publisher:
JMIR Publications
130 Queens Quay East.
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Phone: (+1) 416-583-2040
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